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Ciclesonide Nasal Spray
In Allergic Rhinitis

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Contents

Abstract

- Ciclesonide nasal spray delivers the corticosteroid ciclesonide as a hypotonic spray via a metered-dose manual pump.
- Systemic exposure to ciclesonide and its active metabolite desisobutyryl-ciclesonide is low after intranasal administration. High protein binding (≈99%) and rapid first-pass clearance further reduce systemic exposure to the drug.
- In well designed trials, intranasal ciclesonide 200 μg once daily for 2–4 weeks was more effective than placebo in terms of improving nasal symptoms in adolescents and adults with moderate to severe seasonal allergic rhinitis. Quality of life measures were statistically significantly improved in ciclesonide relative to placebo recipients during the first 2 weeks of therapy.
- Similarly, in adolescents and adults with moderately severe perennial allergic rhinitis, ciclesonide 200 μg once daily was more effective than placebo in terms of reducing nasal symptoms in well designed trials of 6 weeks' and 1 year's duration. Improvements relative to placebo in quality of life measures were not considered clinically relevant.
- Ciclesonide nasal spray was generally well tolerated in these clinical trials; most adverse events were mild to moderate in intensity.

Features and properties of ciclesonide nasal spray (Omnaris™)	
Featured Indication	
Seasonal (SAR) or perennial allergic rhinitis	
Mechanism of action	
Ciclesonide (CIC), a corticosteroid administered as an inactive parent compound, is cleaved by nasal epithelial esterases to desisobutyryl-CIC (des-CIC), which has anti-inflammatory activity	
Dosage and administration	
Dose	200 μg (two 50 μg actuations in each nostril)
Route of administration	Intranasal
Frequency	Once daily
Systemic exposure	
In healthy adult volunteers and adult patients with SAR after intranasal CIC ≤800 μg/day for 14 days	Serum levels of CIC and des-CIC were below the lower limit of quantification for most samples
In healthy adult volunteers after oral CIC 6.9 mg single dose	Median systemic bioavailability of des-CIC relative to that after 0.64 mg intravenous CIC was <1%
Most frequent treatment-emergent adverse events after 1 year of therapy (incidence ≥5%)	
Upper respiratory tract infection, nasopharyngitis, epistaxis, pharyngolaryngeal pain, sinusitis, headache	

Allergic rhinitis is one of the most common chronic diseases in the US.[1,2] Although not life-threatening, it has a significant impact on health-related quality of life and is associated with a substantial financial burden in terms of direct and indirect costs.[1] Moreover, patients with co-morbid asthma and allergic rhinitis may have worse asthma outcomes than those with asthma alone and optimal treatment of allergic rhinitis may improve asthma symptoms.[1,3]

Several pharmacological options are available for therapy; the choice of treatment is determined by the severity and symptoms of the condition.[3] Intranasal corticosteroids, such as budesonide, fluticasone propionate and fluticasone furoate, are currently the most effective treatment options for allergic rhinitis, and treatment guidelines recommend their use in the management of patients with moderate to severe intermittent (seasonal [SAR]) and mild to severe persistent (perennial [PAR]) allergic rhinitis.[2,3] They are recommended as a first-line treatment option for patients with nasal congestion and if symptoms are frequent or persistent.[2,3] The effectiveness of intranasal corticosteroids may be attributed to the high concentrations of medication that can be achieved at receptor sites in the nasal mucosa, with minimal risk of systemic adverse effects.[2] In addition, the formulation of the agent may influence the efficacy, tolerability, patient preference and adherence to therapy.[4]

Ciclesonide nasal spray (Omnaris™)[1] is delivered as a hypotonic spray via a metered-dose manual pump and each actuation delivers 50 μg of the drug.[5] This review focuses on the use of ciclesonide nasal spray in adolescents and adults with SAR or PAR.

1. Pharmacodynamic Profile

This section provides a brief overview of the pharmacodynamic properties of ciclesonide nasal spray, with the discussion focusing on data pertaining to allergic rhinitis. Some data are available from the US prescribing information[5] and the US FDA medical review of ciclesonide.[6]

- Ciclesonide, a nonhalogenated glucocorticoid, is an inactive parent ester compound (see section 2). The active molecule is the metabolite desisobutyryl-ciclesonide (des-CIC).[7] Both ciclesonide and des-CIC have low systemic bioavailability (see section 2). The binding affinity of des-CIC to human glucocorticoid receptors is 100- to 120-fold higher than that of ciclesonide.[8,9]
- The relative receptor binding affinity (RRA) of des-CIC is 1200 (relative to that of the reference agent dexamethasone [RRA = 100]) compared with 2300, 1800, 1345 and 935 for mometasone furoate, fluticasone propionate, beclometasone monopropionate and budesonide, respectively.[9]
- While the exact mode of action of des-CIC is not known, corticosteroids affect many of the cells (e.g. mast cells, eosinophils and lymphocytes) and mediators involved in allergic inflammation (e.g. histamine and cytokines).[5]
- An anti-inflammatory effect (decrease in intracellular adhesion molecule-1 expression) was demonstrated within 3 hours of addition of ciclesonide to pro-inflammatory cytokine-activated human bronchial epithelial cell cultures *in vitro*, and was retained for 48 hours.[10] Levels of granulocyte macrophage-colony stimulating factor and interleukin (IL)-8 were also reduced. The effect appeared to be proportional to the level of activation of the bronchial cells.[10]
- Both ciclesonide and des-CIC inhibited the release of the pro-inflammatory cytokines IL-4 and IL-5 from, and the proliferation of, activated rodent and human immune cells *in vitro*; des-CIC was generally as potent as budesonide and was 1.3- to 8.0-fold more potent than ciclesonide.[11]
- *In vivo*, ciclesonide inhibited bradykinin-induced mucosal leakage into the trachea, and ciclesonide and des-CIC inhibited antigen-induced accumulation of eosinophils, tumour necrosis factor (TNF)-α and total protein into the broncheolar lavage fluid in rats; budesonide showed generally similar ac-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

tivity.[11] Fluticasone propionate, on the other hand, was more potent than ciclesonide in terms of suppressing eosinophilia (7.2- to 7.9-fold) and lung oedema (9-fold) in rats.[8] Equidose systemic effects (adrenal and thymic involution and the decrease in bodyweight gain) were lower (6- to 44-fold) with ciclesonide than with budesonide or fluticasone propionate.[8,11]

- The clinical onset of action of ciclesonide, as assessed by the time to reach a significant difference between ciclesonide 200 μg (single dose[6] or once daily for ≤6 weeks[12,13]) and placebo recipients in instantaneous Total Nasal Symptom Score (iTNSS), ranged from 1 hour in an environmental exposure chamber study (n = 502)[6] to ≥12 hours in another environmental exposure chamber study (n = 420)[6] and in clinical trials (n = 327[12] and 471[13]) in adults with SAR[6,12] or PAR.[13]
- Clinical symptoms of allergic rhinitis are improved by intranasal ciclesonide.[14] Ciclesonide 400 μg once daily for 7 days significantly ($p < 0.05$) improved rhinal airflow from day 5 and reduced nasal obstruction from day 2 relative to placebo following intranasal allergen provocation in 24 patients (median age 28 years).[14] Moreover, in larger clinical trials, ciclesonide 200 μg once daily improved nasal symptoms in patients with SAR or PAR (see section 3).
- Ciclesonide and des-CIC have high protein binding (see section 2), which results in low systemic concentrations of the pharmacologically active unbound drug, thereby limiting its systemic effects mediated via glucocorticoid receptor binding.[15,16]
- Moreover, the plasma and lung tissue concentrations of free des-CIC were 53- and 156-fold lower than the plasma and lung tissue concentrations of total des-CIC.[17] In comparison, the plasma and lung tissue concentrations of free budesonide were 13- and 25-fold lower than the plasma and lung tissue concentrations of total budesonide. These results suggest that ciclesonide may have less pulmonary effects than corticosteroids with relatively lower protein binding such as budesonide.[17]
- Intranasal ciclesonide (50–800 μg/day for 2 weeks) did not appear to affect 24-hour urinary free cortisol or plasma cortisol levels in a trial in 48 healthy volunteers and asymptomatic patients with SAR.[18] Similar results were observed in a long-term (1-year) clinical trial in patients with PAR (see section 4).
- Coadministration of intranasal ciclesonide with inhaled corticosteroids did not have an additive inhibitory effect on the hypothalamus-pituitary-adrenal axis in patients with PAR.[19,20] Following 43 days of therapy, mean plasma cortisol and 24-hour urinary free cortisol levels were similar in beclometasone dipropionate 320 μg twice daily plus ciclesonide 200 μg once daily compared with beclometasone dipropionate monotherapy recipients,[19] and in fluticasone propionate/salmeterol 500 μg/50 μg twice daily plus ciclesonide 200 μg once daily compared with fluticasone propionate/salmeterol monotherapy recipients[20] in randomized, double-blind trials (n = 111[19] and 150[20]).

2. Pharmacokinetic Profile

The pharmacokinetic properties of intranasal ciclesonide were evaluated in a 14-day, randomized, double-blind, placebo-controlled trial in asymptomatic adult patients with SAR who received ciclesonide 800 μg/day (n = 8) and in healthy adult volunteers who received 50–800 μg/day (n = 40).[18] Serum ciclesonide and des-CIC were measured using liquid chromatography with tandem mass spectrometry detection.[18] In addition, a randomized, crossover, radiolabelling study evaluated the pharmacokinetics of single-dose 6.9 mg oral and 0.64 mg intravenous ciclesonide in six healthy volunteers.[21] Some data are also available from the US manufacturer's prescribing information.[5]

- Ciclesonide is enzymatically cleaved by endogenous esterases (carboxylesterases and cholinesterases) in human nasal epithelial cells to release its active primary metabolite des-CIC,[7] which, in turn, undergoes reversible fatty acid conjugation. In *in vitro* studies, after addition of ciclesonide to human nasal epithelial cells, des-CIC and fatty acid conjugates of des-CIC were retained in the cells for up to 24 hours. Ciclesonide concentrations fell 93-fold during this period (mostly in the first 3 hours), while

the concentrations of des-CIC remained constant and the concentrations of des-CIC fatty acid conjugates, which may revert to the active metabolite, increased.[7]

- In a rabbit model, a hypotonic formulation of ciclesonide (current formulation of the nasal spray) provided higher ($p < 0.05$) persistence of ciclesonide in the nasal cavity (as assessed by the concentration of des-CIC) and less (≈1.5-fold) oesophageal run-off compared with a isotonic formulation 30–120 minutes after administration of a 200 μg dose via a pumping device developed for humans.[22]

- Serum ciclesonide concentrations after intranasal ciclesonide ≤800 μg/day were below the lower limit of quantification (25 pg/mL) in patients with SAR and in all except two healthy volunteers (with concentrations of <50 pg/mL).[18] The levels of des-CIC were also below the lower limit of quantification (10 pg/mL) in most samples, with levels undetectable for dosages ≤200 μg/day.[5,18]

- Gastrointestinal absorption of oral ciclesonide is low. Serum concentrations of ciclesonide were undetectable and the median systemic bioavailability of des-CIC was <1% in healthy volunteers after a single 6.9-mg oral dose of radiolabelled ciclesonide.[21]

- The volumes of distribution of ciclesonide and des-CIC were ≈2.9 and ≈12.1 L/kg after intravenous ciclesonide 800 μg (recipient population not reported).[5] An *in vitro* protein binding study showed that ≈99% of ciclesonide and des-CIC is bound to human plasma proteins, largely albumin and α_1-acid glycoprotein, with no apparent saturation of binding.[15]

- The biologically active metabolite des-CIC undergoes hepatic metabolism to additional metabolites largely by the cytochrome P450 (CYP) isoenzyme 3A4 and to a lesser extent by CYP2D6.[5,23] Oral ciclesonide and des-CIC undergo almost complete first-pass metabolism, a contributing factor to the low serum levels.[21] Ciclesonide may be metabolized to other potentially active and as yet unidentified metabolites; only 19.3% of the radioactivity in the plasma was accounted for by ciclesonide and des-CIC.[5]

- Systemically administered ciclesonide is eliminated as metabolites, mainly in bile, via the faeces (70–80%), with the remainder eliminated in urine.[5,21] Elimination is complete within 80–120 hours of administration.[5,21] The terminal elimination half-lives of ciclesonide and des-CIC were 0.38 and 3.5 hours following single-dose intravenous ciclesonide 0.64 mg.[21] The clearance rates of ciclesonide and des-CIC were ≈152 and ≈228 L/h after intravenous ciclesonide 800 μg.[5]

- The pharmacokinetic properties of intranasal ciclesonide have not been evaluated in special patient populations because of low serum levels of the drug and its active metabolite.[5] However, des-CIC pharmacokinetics were not affected by bodyweight, age, race and gender in a population pharmacokinetic analysis of patients receiving inhaled ciclesonide; dosage adjustment for patients with liver impairment is not required.[5,24]

- Des-CIC does not appear to induce or inhibit the metabolism of drugs metabolized by CYP isoenzymes *in vitro*.[5] Warfarin and salicylic acid did not affect plasma protein binding of des-CIC *in vitro*.[15] Coadministration of inhaled ciclesonide and the potent CYP3A4 inhibitor ketoconazole increased exposure to des-CIC by ≈3.6-fold at steady state; ciclesonide levels remained unchanged.[5] Coadministration of inhaled ciclesonide and oral erythromycin, a CYP3A4 inhibitor, did not affect the pharmacokinetics of either drug in 18 healthy volunteers.[25]

3. Therapeutic Efficacy

The efficacy of intranasal ciclesonide versus placebo was evaluated in four fully published randomized, double-blind, multicentre trials in adolescents and adults with SAR or PAR.[12,13,26,27] Of these, two trials of 2[26] and 4[12] weeks' duration assessed patients (aged 18–65[26] and ≥12 years[12]) with SAR, and two trials of 6 weeks'[13] and 1 year's[27] duration assessed patients (aged ≥12 years) with PAR. The 1-year long-term trial was designed primarily to assess safety of the drug and efficacy assessments were a secondary objective.[27]

One study of patients with SAR was a dose-ranging study in which patients self-administered intranasal ciclesonide 25, 50, 100 or 200 μg/day or placebo (half dose in each nostril).[26] In all other studies, patients received intranasal ciclesonide 200 μg once daily in the morning as two 50 μg actuations per nostril.[12,13,27] All studies had a 7- to 14-day baseline period prior to initiating therapy.

The primary efficacy outcomes were the least-squares mean change from baseline in the sum of morning and evening patient-assessed reflective TNSS (rTNSS) at 2 weeks,[26] and the least-squares mean change from baseline in the average of morning and evening patient-assessed rTNSS over the first 2 weeks[12] or over 6 weeks.[13] The rTNSS was defined as the sum of the scores of four nasal symptoms (runny nose, itchy nose, sneezing and nasal congestion) evaluated by the patients twice daily on a severity scale ranging from 0 (no signs or symptoms) to 3 (severe signs or symptoms).[12,13,26]

Several secondary efficacy outcomes, including patient-assessed average 24-hour rTNSS,[27] patient-assessed change in iTNSS,[12,13,26] physician-assessed overall nasal signs and symptoms severity (PANS) score,[12,13,27] and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores, were also evaluated. Analyses were based on the intent-to-treat population.[12,13,26,27]

Seasonal Allergic Rhinitis

Enrolled patients had a ≥2-year history of SAR with demonstrated sensitivity to mountain cedar pollen, which was determined by a positive skin prick test[12,26] or an *in vitro* test specific for IgE.[26] Patients had moderately severe disease,[12] or a morning or evening rTNSS of ≥8 for at least 3 days.[26]

- Patients with SAR receiving intranasal ciclesonide 200 μg once daily for 2 (n = 726)[26] or 4 (n = 327)[12] weeks showed significant improvement in nasal symptoms compared with those receiving placebo.[12,26]
- In the 2-week trial (n = 726), the sum of morning and evening rTNSS at study end (primary endpoint) was significantly and dose-dependently reduced from baseline relative to placebo in recipients of intranasal ciclesonide 200 μg/day ($p < 0.01$) and 100 μg/day ($p < 0.05$).[26] Figure 1 illustrates the estimated differences from placebo for morning and evening improvements in rTNSS and iTNSS at 2 weeks.
- Benefit with ciclesonide 200 μg/day therapy was maintained over 24 hours, as indicated by a significant ($p < 0.001$) difference from baseline in the morning pre-dose iTNSS.[5]
- A significant ($p < 0.05$) difference in rTNSS between ciclesonide 200 μg/day and placebo was observed at day 3 and between ciclesonide 100 μg/day and placebo on day 4.[26]
- In the 4-week trial (n = 327),[12] ciclesonide 200 μg/day was more ($p < 0.05$) effective than placebo in reducing nasal symptoms of allergy from the second day of treatment until study end. The

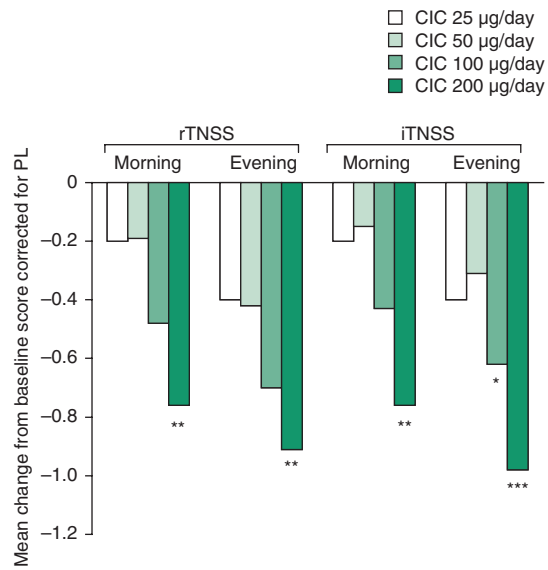

Fig. 1. Dose-dependent efficacy of ciclesonide (CIC) nasal spray in adults with moderate to severe seasonal allergic rhinitis. The figure shows the estimated least-squares mean difference from placebo (PL) in the change from baseline in morning and evening reflective Total Nasal Symptom Scores (rTNSS), and the morning and evening instantaneous TNSS (iTNSS) in the intent-to-treat cohort (n = 143–148/group).[26] Patients self-administered intranasal CIC 25, 50, 100 or 200 μg/day or placebo (half dose in each nostril) for 2 weeks in a randomized, double-blind, multicentre trial. At baseline, the least-squares mean values of the sum of morning and evening rTNSS and iTNSS were 17.8–18.8 and 16.8–18.0.[26] * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs PL.

average morning and evening rTNSS in ciclesonide and placebo recipients were improved from baseline by 2.40 and 1.50 points (27% vs 17%; $p < 0.001$) at 2 weeks and 2.69 and 1.87 points ($p < 0.001$) at 4 weeks.[12]

- Significant improvements from baseline with ciclesonide relative to placebo were also noted in average morning and evening iTNSS at 2 and 4 weeks (least squares mean treatment differences from placebo of 0.88 and 0.80; both $p < 0.001$). PANS and RQLQ scores were statistically significantly improved from baseline relative to placebo at week 2 ($p < 0.001$ and $p < 0.01$), but not at week 4 (because of large improvements in the placebo group in the last 2 weeks, which was possibly due to reduced pollen counts in this period).[12]

Perennial Allergic Rhinitis

Enrolled patients had a ≥2-year history of PAR, had previously required continuous or intermittent treatment and were expected to require therapy during study duration.[13] Patients had moderate[27] or moderately severe disease (morning or evening rTNSS score of ≥6 on at least 4 of the last 7 days of the baseline period)[13] and a demonstrated sensitivity (determined by a positive skin prick or intradermal test) to at least one allergen known to cause PAR.[13,27]

- Patients with PAR receiving intranasal ciclesonide 200 μg once daily for 6 weeks (n = 471) or 1 year (n = 663) showed significant improvement in nasal symptoms compared with those receiving placebo (figure 2).[13,27]

- After 6 weeks' therapy, there was significantly greater reduction from baseline in the average morning and evening rTNSS in ciclesonide 200 μg once daily recipients compared with placebo recipients (33% vs 24%; mean treatment difference in score 0.63; $p < 0.001$; figure 2).[13] A significantly greater reduction ($p \leq 0.01$) from baseline in this parameter in ciclesonide versus placebo recipients was observed from day 2, with the difference in effect increasing with study duration.[13]

- Ciclesonide was also associated with significantly ($p \leq 0.005$) greater reductions from baseline relative to placebo in the individual morning and evening rTNSS, and the average morning and evening iTNSS over 6 weeks of therapy.[13] In terms of individual nasal symptoms, patients receiving ciclesonide experienced significantly greater ($p \leq 0.05$) relief from nasal itching, sneezing and

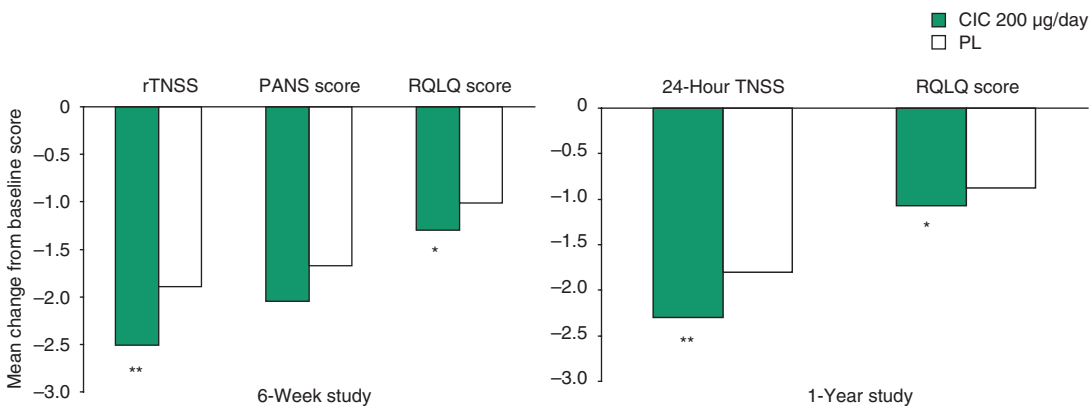

Fig. 2. Efficacy of ciclesonide (CIC) nasal spray in adolescents and adults with moderately severe perennial allergic rhinitis. The figure shows the least-squares mean change from baseline in the average of morning and evening reflective total nasal symptom scores (rTNSS; primary endpoint[13]), the 24-hour rTNSS, physician-assessed overall nasal signs and symptoms severity (PANS) scores and/or Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores after 6 weeks[13] or 1 year[27] of therapy in intent-to-treat patients. Patients received intranasal CIC 200 μg (n = 238[13] and 441[27]) or placebo (PL) [n = 233[13] and 222[27]] as two 50-μg actuations per nostril once daily in two randomized, double-blind, multicentre trials. Baseline rTNSS values were 7.6 and 7.7,[13] the mean morning 24-hour rTNSS values were 6.4 and 6.3,[27] and the RQLQ scores were 2.9 and 2.8[27] for the CIC and PL groups. * $p < 0.05$; ** $p < 0.001$ vs PL.

runny nose, but not from nasal stuffiness/congestion, than in placebo recipients.[13]

- After 1 year of therapy, a significantly greater reduction from baseline in the average 24-hour rTNSS was seen with ciclesonide 200 μg once daily than placebo (reductions of 36% vs 29%; $p < 0.001$; figure 2). A significant ($p < 0.05$) difference was observed after 1 week of therapy, which was retained thereafter until study end, suggesting that ciclesonide therapy was not associated with tachyphylaxis.[27] Patients receiving ciclesonide experienced significantly ($p < 0.05$) greater relief in all individual nasal symptoms throughout the year compared with placebo recipients.[27]
- Physicians found no significant differences between ciclesonide 200 μg once daily and placebo recipients in terms of improvements from baseline in PANS scores after 6 weeks (figure 2)[13] or 1 year (values not reported) of therapy.[27]
- Although RQLQ scores were statistically significantly ($p < 0.05$) improved from baseline in ciclesonide relative to placebo recipients by study end, the mean treatment differences of 0.29 at 6 weeks[13] and 0.19 at 1 year[27] were not considered clinically significant.[13,27]

4. Tolerability

The tolerability of intranasal ciclesonide was evaluated in adolescents and adults with SAR or PAR in the clinical trials discussed in section 3. Discussion in this section focuses on pooled data from >1000 patients with SAR or PAR participating in clinical trials of 2–6[12,13,26] weeks' duration available from the US prescribing information,[5] and data from a 1-year safety trial in patients with PAR.[27] Some data pertaining to the 1-year safety trial are also available from the US prescribing information.[5]

- Ciclesonide 200 μg once daily for 2–6 weeks was generally well tolerated in adolescents and adults with SAR or PAR. In pooled data[5] from the clinical trials,[12,13,26] the most frequent (≥2%) treatment-emergent adverse events occurring more often in ciclesonide (n = 546) than in placebo (n = 544) recipients were headache (6.0% vs 4.6%), epistaxis (4.9% vs 2.9%), nasopharyngitis (3.7% vs 3.3%) and ear pain (2.2% vs 0.6%).
- The incidences of treatment-related (11.3% vs 11.2%[13]) or likely to be treatment-related (11.0% vs 9.8%[12]) adverse events were generally similar in ciclesonide and placebo recipients at 4[12] and 6[13] weeks.
- In the 1-year safety trial, ciclesonide 200 μg once daily was generally well tolerated, with treatment-related adverse events occurring in 17.0% and 10.8% of ciclesonide and placebo recipients.[27] Likely or definitely treatment-related adverse events occurring in ≥1% of patients and more frequently in ciclesonide than placebo recipients included epistaxis (10% vs 7%), nasal discomfort (4.5% vs 4.1%) and headache (7.5% vs 5.9%).[5,27] Treatment-emergent adverse events occurring in ≥3% of ciclesonide or placebo recipients after 1-year of therapy are summarized in figure 3.[27]
- Adverse event-related withdrawal rates in the short-term trials were generally similar in ciclesonide and placebo recipients (2% vs 3%[12] and 4.2% vs 4.7%[13]); in the 1-year trial, 4.3% and 2.7% of patients withdrew from therapy because of adverse events in the ciclesonide and placebo groups.[27]
- Most adverse events were mild to moderate in severity during ≤1 year of therapy.[12,13,27] No treatment-related serious adverse events were reported in patients receiving ciclesonide in short-term trials,[12,13] and serious adverse events in the 1-year trial (3.6% vs 2.7% with placebo) were considered unrelated or unlikely to be related to treatment.[27]
- Severe adverse events occurred in 7% and 5% of ciclesonide and placebo recipients during 6 weeks of therapy; sinusitis, upper respiratory tract infection, hives, sinus headache or asthma exacerbation resulted in discontinuation of therapy in five ciclesonide recipients.[13]
- In the 1-year trial, severe adverse events occurred in 13% and 12% of ciclesonide and placebo recipients.[27] Most were not considered treatment related; nasal discomfort, nasopharyngitis and eye irritation occurred in ciclesonide (all in <1% of patients), but not placebo recipients.[27] There were

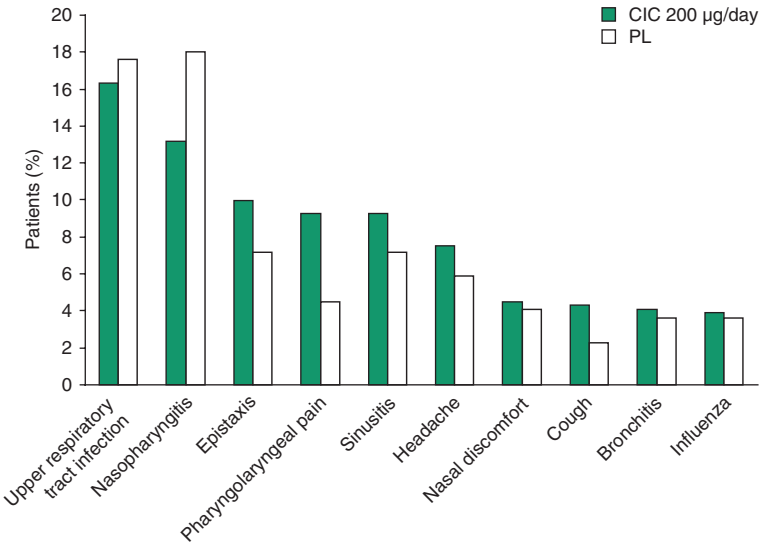

Fig. 3. Long-term tolerability profile of intranasal ciclesonide (CIC) in adolescents and adults with perennial allergic rhinitis of moderate severity. The figure shows the incidence of most common treatment-emergent adverse events (≥3%) in patients receiving CIC 200 µg (n = 441) or placebo (PL) [n = 222] once daily in a 1-year, randomized, double-blind, multicentre trial.[27]

no reports of septal perforations or ulcers with long-term ciclesonide therapy.[27]

- There were no clinically relevant changes from baseline, or differences between ciclesonide and placebo recipients, in the 24-hour urinary free cortisol or serum cortisol levels with ciclesonide therapy over 1 year (see also section 1).[27] Nor were there any clinically relevant between-group differences in intraocular pressure and lens opacities in ciclesonide and placebo recipients over this time.[27]

5. Dosage and Administration

The approved dosage of ciclesonide nasal spray is 200 µg/day administered as two 50-µg actuations in each nostril once daily in patients aged ≥6 years with SAR and in patients aged ≥12 years with PAR; exceeding the daily dosage is not recommended.[5]

For comprehensive dosage and administration guidelines, including contraindications, precautions, etc., the local manufacturer's prescribing information should be consulted.

6. Ciclesonide: Current Status in Allergic Rhinitis

Ciclesonide nasal spray is approved for use in the US in children and adults with SAR and in adolescents and adults with PAR. In several well designed clinical trials in adolescents and adults with SAR or PAR, intranasal ciclesonide was more effective than placebo in terms of reducing nasal symptoms. Ciclesonide therapy was generally well tolerated in these trials; most adverse events were mild to moderate in intensity.

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