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Intranasal Ciclesonide for Treatment of Allergic Rhinitis in Children and Adolescents

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Ciclesonide nasal spray was first approved by the Food and Drug Administration (FDA) on October 20, 2006 as a hypotonic aqueous suspension (Omnaris®; Sunovion Pharmaceuticals, Inc.).¹⁻⁴ It is currently indicated for the treatment of seasonal allergic rhinitis in adults and children 6 years of age and older, as well as perennial allergic rhinitis in adults and adolescents 12 years of age and older. Since its introduction, ciclesonide has become one of the most popular treatment options for allergic rhinitis, a condition affecting as much as 20% of the US population.

On January 20, 2012, the FDA approved a second ciclesonide intranasal product, Zetonna® from the same manufacturer.⁵ This new formulation utilizes a hydrofluoroalkane (HFA) propellant which dispenses the drug in a fine dry mist. The resulting aerosol spray produces less run-off of the drug down the throat or out of the nose following administration, which may provide more accurate drug delivery and improved patient acceptance.

Mechanism of Action/Pharmacokinetics

Ciclesonide is a prodrug that is hydrolyzed to an active metabolite, desisobutyryl-ciclesonide (des-ciclesonide) by intracellular esterases in the upper and lower airways. Esterification of ciclesonide has been demonstrated in human nasal, bronchial, and alveolar type II epithelial cells. While the parent compound is detectable for up to 2 hours after administration, the metabolite is responsible for the majority of the clinical effect. Des-ciclesonide possesses an affinity for glucocorticoid receptors roughly 100-fold higher than that of the parent compound. Binding at these receptors produces an array of anti-inflammatory effects, including reduction in histamine, eicosanoid, leukotriene, and cytokine release. Intracellular concentrations of des-ciclesonide are maintained in the airways for up to 24 hours as the result of reversible fatty acid conjugation in pulmonary tissues, which serves as a reservoir for des-ciclesonide and allows once daily dosing.¹⁻⁷

There is minimal oral absorption of ciclesonide and des-ciclesonide after intranasal administration, resulting in a bioavailability of less than 1%. Des-ciclesonide is highly protein bound (99%). As a result of these properties, intranasal administration of the aqueous ciclesonide spray produces negligible serum concentrations of the parent compound, although some patients will have low, but measurable, concentrations of des-ciclesonide.^{1,2,7}

In a study of 30 healthy adults, administration of a 300 mcg aqueous ciclesonide dose produced a serum des-ciclesonide concentration greater than 10 ng/L (the lower limit of detection) in only five subjects.⁷ The highest des-ciclesonide concentration documented was 26.7 ng/L. Administration of the ciclesonide HFA aerosol using a 300 mcg dose produced a mean maximum des-ciclesonide concentration of 59.1 ng/L. For comparison, the authors evaluated concentrations in subjects receiving an orally inhaled 320 mcg dose from a ciclesonide HFA metered dose inhaler (MDI). These data suggest that the systemic exposure to des-ciclesonide after use of the aqueous intranasal spray is approximately 40-fold lower than use of the MDI, while systemic exposure after use of the HFA intranasal spray is 10-fold lower.

A study of children 6 to 11 years of age receiving the aqueous ciclesonide spray on a daily basis, demonstrated that all had des-ciclesonide concentrations less than 45 ng/L, except for one value of 64.5 ng/L. In a 6-week study of children 2-5 years of age, daily administration of 25, 100, or 200 mcg ciclesonide produced detectable des-ciclesonide concentrations in 13%, 22%, and 41% of the children, respectively.³

Concentrations of des-ciclesonide were recently assessed in a Phase I pharmacokinetics, pharmacodynamics, safety, and tolerability study of ciclesonide HFA intranasal aerosol in 36 adults.⁸ The blinded 3-period crossover study included 18 healthy subjects and 18 with perennial allergic rhinitis. Subjects received

ciclesonide HFA at a dose of either 148 mcg or 282 mcg, or placebo, once daily for 2 weeks. As with the aqueous suspension, systemic exposure to des-ciclesonide was low, with a mean serum concentration of 25.98 ng/L for the 148 mcg dose and 35.84 ng/L for the 282 mcg dose.

Systemically absorbed des-ciclesonide undergoes further metabolism via hepatic CYP3A4, and to a lesser degree by CYP2D6. The metabolites are then excreted in the bile, with less than 20% of an intranasal dose cleared renally. The elimination half-life in adults is 3.5 hours. Dosage adjustment in patients with liver or kidney impairment is not considered necessary.¹⁻⁴

Clinical Studies

The efficacy and safety of aqueous ciclesonide intranasal spray has been demonstrated in a number of randomized controlled trials involving adults and adolescents.^{3,9,10} In premarketing studies, aqueous ciclesonide spray produced significant reductions in total nasal symptom scores (TNSS), a composite endpoint encompassing scores for sneezing, nasal discharge, itching, and congestion. These scores are often defined as reflective, representing the patient's assessment of symptoms over the previous 12 hours, or instantaneous, representing symptoms present at the time of documentation.

In a premarketing seasonal allergic rhinitis trial conducted in 324 adults and adolescents, patients received either 200 mcg ciclesonide or placebo once daily for 4 weeks. The change in reflective TNSS from baseline to the end of the trial was significantly greater in the patients receiving ciclesonide (-2.40 in the treatment group and -1.50 in the controls, $p < 0.001$). The change in instantaneous TNSS was also significant (-1.87 in the treatment group versus -1.03 in the controls, $p < 0.001$). In a 6-week perennial allergic rhinitis trial, the same dosing scheme produced similar results. The change in reflective TNSS was -2.51 in the treated patients compared to -1.89 in the controls ($p < 0.001$). The change in instantaneous TNSS was -1.99 in the treatment group compared to -1.46 for the controls ($p = 0.004$).

Two randomized, blinded, placebo-controlled studies of the aqueous spray were conducted by the manufacturer in children 6 to 11 years of age.³ Both demonstrated efficacy similar to that achieved in adolescents and adults. A total of 1,282 children were enrolled into either the 2-week dose-ranging study of children with seasonal allergic rhinitis or a 12-week study of children with perennial allergic rhinitis. In the 2-week dose-ranging study, ciclesonide 200 mcg once daily produced a significantly greater

improvement in reflective TNSS compared to placebo (-2.46 versus -2.07, $p = 0.04$), but the 100 mcg dose did not (-2.38 versus -2.07, $p = 0.103$). In the 12-week trial, the changes in TNSS with ciclesonide were not significantly different than that with placebo, although there was a trend towards improvement with the 200 mcg dose.

To date, ciclesonide HFA intranasal aerosol has only been tested in adolescents and adults. In 2010, Ratner and colleagues conducted a manufacturer-sponsored randomized placebo-controlled trial of ciclesonide HFA for the treatment of seasonal allergic rhinitis.¹¹ A total of 707 patients were randomized to treatment with either a 80 mcg or 160 mcg ciclesonide dose, or placebo, once daily for 2 weeks. The percentage reduction in reflective TNSS from baseline was 15.1% and 16% in the 80 mcg and 160 mcg groups, significantly greater than the 3.7% reduction in the controls ($p < 0.01$). Reductions in instantaneous TNSS were 14.3% and 15.4% for the two treatment groups and 6.8% in the controls ($p < 0.001$). Ocular symptoms were also reduced (15.7% and 15%, compared to 6.8% in the controls, $p < 0.001$). There were no differences in the frequency of adverse effects.

An additional ciclesonide HFA study by these investigators was published earlier this year, using the product that is now on the market.¹² Adults and adolescents with allergic rhinitis were randomized to receive a ciclesonide HFA dose of either 74 or 148 mcg or placebo once daily for 2 weeks. As in the previous study, patients were assessed by comparing baseline and treatment instantaneous and reflective TNSS and ocular symptom scores. Both treatment groups produced significant improvement in reflective TNSS (a mean change of -1.04 and -1.02 for the 74 and 148 mcg groups respectively, $p < 0.001$ compared to placebo) and instantaneous TNSS (mean change -0.90 and -0.83, $p < 0.001$ compared to placebo). Only the lower dose group showed a statistically significant improvement in ocular symptoms ($p = 0.0124$). The incidence of adverse effects was similar among the groups.

The manufacturer has also conducted a 26-week trial of ciclesonide HFA in adults and adolescents with allergic rhinitis using the same methodology as in the previous study.⁵ A total of 472 subjects with seasonal allergic rhinitis were enrolled. As in the previous studies, there was a significantly greater mean change from baseline reflective TNSS in the treated patients than in those given placebo (-1.5 versus -0.5, $p < 0.001$), as well as the instantaneous TNSS (-1.3 versus -0.5, $p < 0.001$). The decrease in ocular symptom scores was also significant (-0.8 versus -0.2, $p = 0.001$). Similar results were seen in the

471 subjects with perennial allergic rhinitis. Mean change for the treatment group was significantly greater in reflective TNSS (-2 compared to -1.3, $p < 0.001$) and instantaneous TNSS (-1.8 compared to -1.2, $p < 0.001$).

Warnings and Precautions

All corticosteroids pose the risk for suppressing adrenal function. The effect of intranasal administration of ciclesonide on adrenal function has been assessed in several studies, using a variety of methodologies. In a 12-week placebo-controlled dose-ranging study conducted by the manufacturer in children 6 to 11 years of age, ciclesonide administration produced no significant change in mean morning plasma cortisol values.³ The groups receiving 100 mcg and 200 mcg had a small increase in their values (0.12 mcg/dL and 0.35 mcg/dL), while the lowest dose, 25 mcg, produced a small decline (-0.38). In a 6-week study conducted in children 2 to 5 years of age, ciclesonide use was associated with a small decline in morning plasma cortisol values, with a mean change from baseline -0.12, -0.36, and -1.04 mcg/dL for the 25 mcg, 100 mcg, and 200 mcg doses, respectively.

Additional long-term studies, up to 1 year in length, support the finding that ciclesonide and its metabolite do not alter serum cortisol levels.^{1,2} Based on these findings, the risk for significant adrenal suppression with intranasal ciclesonide appears unlikely, but the precautions regarding potential immunosuppression are still provided in the prescribing information.³⁻⁵

Ciclesonide should not be used in patients with tuberculosis, as well as any form of untreated fungal, viral, parasitic, or bacterial infections. All patients using intranasal corticosteroids should be aware of the risk for epistaxis, nasopharyngeal pain, nasal septal perforation, impaired wound healing at the site of administration, or localized Candida infections in the nose and pharynx. Epistaxis and nasopharyngeal pain have been associated with the use of higher ciclesonide doses, a longer duration of use, or an incorrect administration technique. Patients using an intranasal spray consistently for periods more than 1-2 months should be aware of the need for periodic examination of the nose and throat. Although intranasal ciclesonide has not been associated with a reduction in growth velocity, children receiving these products should be monitored for any slowing of their rate of growth.³⁻⁵

Glaucoma and cataracts have been reported in patients using inhaled or nasal corticosteroids. While not observed in ciclesonide trials, patients with a family history of these conditions or those

reporting any change in vision should be closely monitored. Hypersensitivity reactions have been reported with ciclesonide, but are rare.³⁻⁵

Adverse Effects

In pooled data from clinical trials of adults and adolescents, the most frequently reported adverse effects after use of aqueous ciclesonide spray were headache (in 6% of patients), epistaxis (4.9%), nasopharyngitis (3.7%), and ear pain (2.2%). In children 6 to 11 years of age, the findings were similar, with headache in 6.6%, nasopharyngitis in 6.6%, and pharyngolaryngeal pain in 3.4%. Studies in younger children (2 to 5 years of age) produced similar results. Other adverse effects reported after long-term use in adults and adolescents have included sinusitis, cough, bronchitis, influenza, back pain, and urinary tract infection.^{3,4}

Adverse effects have been similar with the ciclesonide HFA aerosol.^{5,7,11} In pooled data from the pre-marketing clinical trials enrolling 884 adults and adolescents, the most frequently reported adverse effects were nasal discomfort (in 3.2% of patients), headache (3.1%), and epistaxis (2.9%).⁷ Approximately 1% of patients enrolled in these trials discontinued because of adverse effects. Two subjects enrolled in a short-term study experienced nasal perforation. There were no cases of nasal perforation in the 26-week long term blinded study, but there were four cases of nasal septal ulcerations in the 26-week open-label extension following it.

Drug Interactions

Administration of oral ketoconazole, a potent CYP3A4 inhibitor, increased the AUC of the des-ciclesonide metabolite approximately 3- to 4-fold. Concentrations of the parent compound were unchanged. There was no significant effect when erythromycin, a moderate CYP3A4 inhibitor, was administered with ciclesonide.³⁻⁵

Availability

Ciclesonide aqueous suspension (Omnaris[®]) delivers a 50 mcg dose per spray in 70 microliters of fluid. It is available in a 12.5 g bottle containing 120 sprays. The bottle should be discarded after 120 doses have been administered or 4 months after it is removed from the protective foil pouch, whichever comes first. The new ciclesonide HFA nasal aerosol (Zetonna[®]) delivers a 37 mcg dose in 50 microliters of a fine particle mist. It is available in a pressurized, metered-dose aerosol canister with an actuator, containing enough drug for 60 actuations.³⁻⁵

Dosing Recommendations

Directions for using both the ciclesonide aqueous intranasal spray and the ciclesonide HFA nasal aerosol are provided with the package. Before using a new bottle of the aqueous spray, it should be shaken and primed by actuating the pump eight times. If it is not used for a period of more than 4 days, it should be shaken and primed with a single spray. The recommended dose for aqueous ciclesonide intranasal spray is two sprays per nostril once daily providing a total daily dose of 200 mcg.

When using a new canister of the ciclesonide HFA aerosol, it should be primed by actuating it 3 times. If not used for 10 consecutive days, it should be primed again. There is no need to shake the canister. If the actuator becomes separated from the canister, it should be reattached and the system should be tested by spraying it once into the air. The recommended dose for the ciclesonide HFA aerosol is one actuation (37 mcg) per nostril once daily, to provide a total daily dose of 74 mcg.³⁻⁵

It is recommended that ciclesonide be given on a regular daily basis during periods when allergy symptom control is needed. Intranasal ciclesonide should not be used in patients with recent nasal injury, ulceration, or surgery. The nasal surfaces should be fully healed before treatment is resumed. The spray or aerosol should not be aimed directly at the septum and must be kept away from the eyes.³⁻⁵

Summary

Inhaled ciclesonide is an effective tool for the management of allergic rhinitis in children and adults. Data demonstrating minimal systemic absorption and no significant impact on growth velocity support its utility in the pediatric patient population. The availability of the new ciclesonide HFA intranasal spray, while not yet approved for use in children, may be of considerable benefit in young children who resist the spray because of the run-off of the aqueous spray down the throat.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their April meeting:

1. Buprenorphine/Naloxone (Suboxone[®]) was added to the Formulary with restriction to patients maintained on it as outpatients.
2. Galsulfase (Naglazyme[®]) was added.
3. Restrictions on cabergoline, celecoxib, and modafinil were added to include use in patients maintained on these agents as outpatients.
4. The restrictions on doxercalciferol and paricalcitol were amended to patients maintained on these agents as outpatients and to the hemodialysis centers.
5. The restriction on pregabalin was amended to use by the Neurology and Pain Services and in patients maintained on it as outpatients.
6. Chloral hydrate is no longer available and was removed from the Formulary.

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