

NEW DRUG UPDATE

Drug Name:	ciclesonide
Trade Name (Manufacturer):	Zetonna™ (Nycomed GMBH)
Form:	Aerosol, nasal
Strength:	37 mcg per actuation, 6.1 g canister contains 60 actuations
FDA Approval:	January 20, 2012
Market Availability:	Not yet available
FDA Approval Classification:	Standard review: New formulation
Classification:	Specific Therapeutic Class (HIC3): Nasal Anti-inflammatory Steroids (Q7P)

Indication¹: Ciclesonide (Zetonna) is indicated for treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

Contraindications/Warnings: The only specific contraindication associated with the use of Zetonna nasal aerosol is known hypersensitivity to ciclesonide or any of the ingredients of zetonna nasal aerosol (additional ingredients are hydrofluoroalkane and ethanol). Hypersensitivity with symptoms such as angioedema; with swelling of the lips, tongue and pharynx; has been reported following administration of ciclesonide. Epistaxis and nasal ulceration, nasal septal perforation, localized *Candida albicans* infections of the nose and pharynx, and impaired wound healing are possible local nasal effects of ciclesonide nasal aerosol. Spraying Zetonna nasal aerosol directly onto the nasal septum should be avoided. Use of the product should be avoided in patients with recent septal perforation, recent nasal erosion or ulcers, and recent nasal surgery or trauma. Patients should be monitored for signs of nasal mucosa adverse effects and Zetonna nasal aerosol discontinued if erosions, ulcerations, or perforations occur. Glaucoma and cataracts, immunosuppression, and hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction are possible systemic adverse reactions. Patients susceptible to these reactions such as those with history of these or related conditions should be closely monitored while using the product. Existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex could be worsened by use of Zetonna nasal aerosol. If the medication must be discontinued, procedure consistent with that for discontinuing oral steroid therapy should be used.

Drug Interactions: Ciclesonide, a non-halogenated glucocorticoid, is a pro-drug enzymatically hydrolyzed to the pharmacologically active metabolite, des-ciclesonide. Des-ciclesonide, as suggested in in vitro and clinical pharmacology studies, has no potential for metabolic drug interactions or interactions based on protein-binding. Co-administration of orally inhaled ciclesonide and oral ketoconazole, a cytochrome P450 3A4 potent inhibitor, increased the AUC of des-ciclesonide by about 3.6-fold at steady state, in a drug interaction study, while levels of ciclesonide remained unchanged. The moderate inhibitor of cytochrome P450 3A4, erythromycin, had no effect on pharmacokinetics of either des-ciclesonide or erythromycin, following oral inhalation of ciclesonide.

Common Adverse Effects: The most common adverse reactions (\geq two percent incidence) with Zetonna nasal aerosol are nasal discomfort (3.2 percent), headache (3.1 percent) and nose bleeds (2.9 percent).

Special Populations:

Pediatrics: Safety and effectiveness in pediatric patients 11 years of age and younger have not been established.

Pregnancy: Pregnancy Category C.

Geriatrics: Sufficient numbers of patients age 65 and older were not included in clinical trials to determine whether their response is different from younger patients. Neither have differences in responses between elderly and younger patients been identified by other clinical experience. As generally recommended, dose selection for an elderly patient should be made cautiously due to their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or medication therapy.

Renal Impairment: Trials in patients with renal impairment were not conducted since renal excretion accounts for ≤ 20 percent of des-ciclesonide elimination.

Hepatic Impairment: Dose adjustment in liver impairment is not necessary.

Dosages: The recommended dose of Zetonna nasal aerosol, formulated with a hydrofluoroalkane (HFA) propellant, for allergic rhinitis in adults and adolescents 12 years of age and older, is one actuation per nostril once daily (37 mcg per actuation). The maximum total daily dosage should not exceed one actuation in each nostril (74 mcg per day). Zetonna nasal aerosol delivers ciclesonide as a fine dry mist in a small volume to the nose via a pressurized, metered-dose aerosol canister and actuator, which is fitted with a dose indicator. It is to be administered by the intranasal route only. Prior to initial use, Zetonna nasal aerosol must be primed by actuating three times. It must be primed in this same fashion if not used within ten consecutive days.

Clinical Trials: A literature search was performed using “ciclesonide nasal spray”, “Zetonna” and “Omnaris”. Due to a paucity of data in the literature, clinical trials that are placebo-controlled have been included.

One randomized, double-blind, parallel-group, multicenter, placebo-controlled dose-ranging trial (74 mcg, 148 mcg, and 282 mcg once daily) and three confirmatory trials (74 mcg and 148 mcg once daily) in adults and adolescents with allergic rhinitis were used to evaluate the efficacy of Zetonna nasal spray.² For the two seasonal allergic rhinitis trials, efficacy endpoints were evaluated at two weeks and for the perennial allergic rhinitis trial, efficacy endpoints were evaluated at six weeks. There were a total of 3,001 patients included in these four trials. A total of 513 patients [193 males (37.6 percent) and 320 females (62.4 percent)], of whom 65 (12.7 percent) were adolescents, were included in the dose-ranging trial. Included in the three confirmatory trials were a total of 2,488 patients (905 males and 1,583 females) of whom 170 were adolescents, ages 12 to 18 years. Patients enrolled in the trials had a history of seasonal or perennial allergic rhinitis, a positive skin test to at least one relevant allergen, active symptoms of allergic rhinitis, and were 12 to 81 years of age at study entry. The primary efficacy endpoint for the dose-ranging trial was the difference from placebo in the change from baseline of the average of morning and evening reflective total nasal symptom scores (rTNSS) averaged over the two-week treatment period. A statistically significant estimated treatment difference from placebo of 0.81 (95% CI: 0.32, 1.29); 0.9 (95% CI: 0.4, 1.39); and 0.66 (95% CI: 0.16, 1.16) for 282 mcg, 148 mcg and 74 mcg, respectively, was shown by the rTNSS. For the two confirmatory seasonal allergic rhinitis trials, the primary efficacy endpoint was measured as for the dose-ranging trial. Both trials showed similar results. Zetonna nasal aerosol, given at a dose of 74 mcg once daily, was statistically significantly different from placebo. The results

indicate that the effect was maintained over the full 24-hour dosing interval. Statistically significant decrease from baseline compared to placebo was also seen for the secondary efficacy variables, total ocular symptom score (TOSS) and the Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities [RQLQ(S)]. There was not an efficacy benefit provided by Zetonna nasal aerosol 148 mcg once daily over the 74 mcg once daily dose. For the confirmatory perennial allergic rhinitis trial, there was one 26-week placebo-controlled, double-blind trial that evaluated efficacy of two doses of Zetonna nasal aerosol (74 mcg and 148 mcg once daily) for patients with perennial allergic rhinitis. The difference from placebo in the change from baseline of the average of morning and evening rTNSS averaged over the first six weeks of treatment was the primary efficacy endpoint. Zetonna nasal aerosol 74 mcg once daily was statistically significantly different from placebo in decreasing nasal symptom scores in this trial. The results indicate that the effect was maintained over the full 24-hour dosing interval. Compared to placebo, Zetonna nasal aerosol 74 mcg did not demonstrate a clinically significant change from baseline in the overall RQLQ(S). This trial did not evaluate TOSS. An efficacy benefit was not provided by 148 mcg once daily of Zetonna nasal aerosol over a dose of 74 mcg once daily. Frequent recording of instantaneous symptom score was used to evaluate onset of action in both 2-week seasonal allergic rhinitis trials and the one 6-week perennial allergic rhinitis trial. Onset of effect was seen after 36 hours following the first dose. After initiation of dosing, maximum benefit is usually achieved within one to two weeks.

Long-term safety trials included one 26-week double-blind, placebo-controlled trial and a 26-week open-label extension trial. More frequent nasal discomfort (5.7 percent) and epistaxis (11.4 percent) were noted in the 26-week safety trial as compared to shorter (two-sixweek) clinical trials. A dose response was demonstrated by nasal mucosal/septum disorders and cough.

Other Drugs Used for Condition: Medications for use in patients with allergic rhinitis include antihistamines, decongestants, cromolyn, topical corticosteroids, anticholinergics, and leukotriene receptor antagonists.³

Place in Therapy: With the exception of systemic corticosteroids, nasal corticosteroids are the most effective single agents for controlling the spectrum of allergic rhinitis symptoms, according to the American Academy of Allergy, Asthma, and Immunology.⁴ Intranasal corticosteroids are generally not associated with systemic adverse effects in adults. Local adverse effects such as nasal irritation and bleeding may occur but incidence is minimized if patients are carefully instructed in the use of drugs in this class. Clinical trials have shown that intranasal corticosteroids are similar in efficacy and differ by patient preference and number of sprays needed per day and dosing frequency. Ciclesonide is one of several intranasal corticosteroid products and Zetonna is one of two ciclesonide intranasal products. The other ciclesonide product is Omnaris™ nasal spray. There are no comparative trials between Zetonna and Omnaris. Omnaris is formulated as a hypotonic aqueous suspension to be delivered by a metered-dose manual-pump spray and has the additional age indication for treatment of nasal symptoms of seasonal allergic rhinitis in children six years of age and older. Omnaris is dosed two sprays (50 mcg per spray) per nostril once daily (200 mcg total daily dose). The maximum recommended Omnaris total daily dose is 200 mcg.⁵ Zetonna would seem to offer an additional formulation that can be delivered by fewer sprays and may be preferred by some patients but would offer little clinical advantage.

Suggested Utilization Management:

Anticipated Therapeutic Class Review (TCR) Placement	Intranasal Rhinitis Agents
Clinical Edit	None
Quantity Limit	1 inhaler per month
Duration of Approval	1 year
Drug to Disease Hard Edit	No
Retro-DUR	Indication and dosage
Provider Profiling	No

References:

¹ Zetonna [package insert]. Sunovion Pharmaceuticals; Marlborough, MA; January 2012.

² Zetonna [package insert]. Sunovion Pharmaceuticals; Marlborough, MA; January 2012.

³ 2011 Diagnosis and Treatment of Respiratory Illness in Children and Adults guideline. <http://www.icsi.org> Accessed February 24, 2012.

⁴ <http://www.aaaai.org/professionals/resources/pdf/rhinitis2008.pdf> Accessed February 24, 2012.

⁵ Omnaris [package insert]. Sunovion Pharmaceuticals; Marlborough, MA; October 2011.