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Behçet disease as a cause of hearing loss: A prospective, placebo-controlled study of 29 patients

Ozgur Kemal, MD; Yucel Anadolu, MD; Ayse Boyvat, MD; Ahmet Tatarağası, AuD

Abstract

We conducted a prospective, placebo-controlled study to determine the incidence and severity of inner ear involvement and hearing loss in patients with Behçet disease. Our study population was made up of 29 patients with Behçet disease and 28 healthy controls. Audiometric pure-tone thresholds and transient evoked otoacoustic emission (TEOAE) levels were determined in both groups. The main outcome measures were pure-tone audiometry (PTA) levels and TEOAE levels in the two groups. PTA detected a sensorineural hearing loss in 10 of the 29 patients (34.5%). The difference in audiometric findings between the two groups was statistically significant at 1, 2, 4, and 8 kHz ($p \leq 0.0498$). A comparison of TEOAE levels revealed that the difference in sound-to-noise ratio between the two groups was not significant at 1, 1.5, 2, and 3 kHz, but it was significant in 4 kHz ($p = 0.02$), and the difference in reproducibility between the two groups was significant at 2 and 4 kHz ($p \leq 0.03$). We conclude that all patients with Behçet disease should be screened for hearing impairment and subsequently treated if an impairment is discovered.

Introduction

Behçet disease is a multisystem vascular inflammatory disease of unknown origin. This entity was first described by Dr. Hulusi Behçet in 1937 as a clinical triad of aphthous ulceration, genital ulceration, and iridocyclitis.[1] The presentation of disease is not limited to these three signs. It is a disorder that may involve many areas, including the central nervous system (CNS), gastrointestinal tract, lungs, skin, veins, and arteries.

The International Study Group for Behçet's Disease has recommended that recurrent oral ulceration be a prerequisite for a definitive diagnosis, together with two of the following: genital ulcers, skin lesions, eye lesions, and skin hypersensitivity reaction (pathergy test).[2] The presence of other signs—such as arthritis or involvement of the CNS or the gastrointestinal or vascular system—represents minor criteria that may support the diagnosis.[2]

Hearing loss is also common in Behçet disease. In this study, we aimed to compare the incidence of hearing loss, the degree of hearing loss, and the nature of inner ear involvement in Behçet disease patients and healthy controls.

Patients and methods

We reviewed the cases of 1,000 patients with Behçet disease to identify those who met the inclusion criteria for our study. We identified 29 such patients—18 men and 11 women, aged 22 to 51 years (mean: 37.8). We also recruited a control group of 28 individuals without Behçet disease—14 men and 14 women, aged 20 to 48 years (mean: 31.8). There were no significant differences between the two groups in terms of sex and age (table 1). There is no Institutional Review Board at our hospital, but we did obtain proper informed consent from all participants in keeping with the mandate of the Declaration of Helsinki.

All patients fulfilled the International Study Group's diagnostic criteria for Behçet disease.[2] Patients with a history of recurrent otitis, cranial trauma, ototoxic drug use, any condition related to inner ear damage, and any

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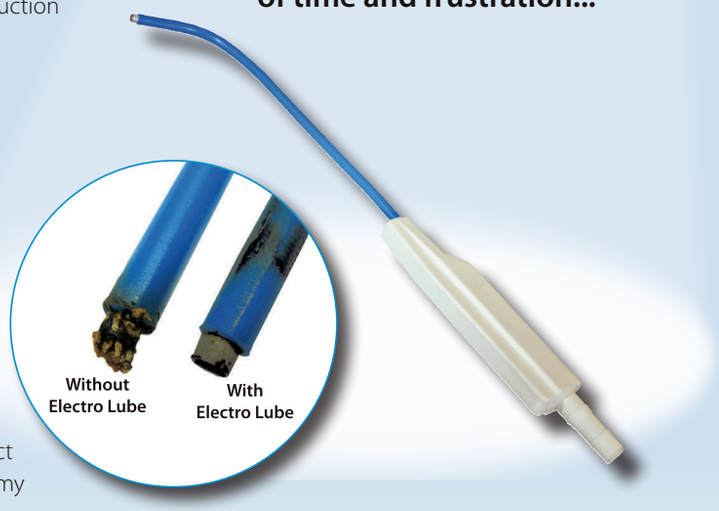
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Table 1. Distribution of sex and age in the two groups

Demographic variable	Behçet patients (n = 29)	Controls (n = 28)
Sex, n (%)		
Men	18 (62.1)	14 (50.0)
Women	11 (37.9)	14 (50.0)
Age, yr		
Range	22 to 51	20 to 48
Mean ± SD	37.8 ± 8.9	31.8 ± 6.2

Table 2. Clinical findings in the Behçet group

Finding	n (%)
Oral ulcers	29 (100)
Genital ulcers	27 (93.1)
Positive pathergy test	27 (93.1)
Eye involvement	7 (24.1)
Skin lesions	4 (13.8)

otologic or neurologic disease unrelated to Behçet disease were excluded from the study. All patients and controls underwent an ENT examination, and those who had an acute or chronic ear infection or a perforated tympanic membrane were excluded.

The duration of disease in the Behçet group ranged from 2 to 21 years (mean: 8.9 ± 4.1). All of the study patients had oral ulcers, and most had current or previous genital ulcers and a positive pathergy test (table 2). Eye involvement at some time during the course of the disease and skin lesions were seen in a minority of patients.

Patients and controls underwent pure-tone audiometry (PTA) at 0.25, 0.5, 1, 2, 4, and 8 kHz (AC 40 clinical audiometer; Interacoustics; Assens, Denmark) and measurement of transient evoked otoacoustic emissions (TEOAEs) at 1, 1.5, 2, 3, and 4 kHz (Otodynamics; Hatfield, U.K.).

Statistical analysis was performed with the Statistical Package for the Social Sciences software (v. 10.0; SPSS; Chicago). Baseline clinical characteristics are expressed as means with a standard deviation. The Mann-Whitney *U* test was used to evaluate the differences between the Behçet patients and the controls. A p value of <0.05 was considered to be statistically significant.

Results

PTA detected a sensorineural hearing loss at bone conduction levels (≥25 dB) in 10 Behçet patients (34.5%). The difference in audiometric findings between the Behçet patients and the controls was statistically significant at 1, 2, 4, and 8 kHz ($p \leq 0.0498$) (table 3).

Analysis of TEOAE test results revealed that the difference in sound-to-noise ratio between the two groups was not significant at 1, 1.5, 2, and 3 kHz, but it was significant at 4 kHz ($p = 0.02$), and the difference in reproducibility between the two groups was significant at 2 and 4 kHz ($p \leq 0.03$) (table 4).

Discussion

Hearing loss in Behçet disease has been researched for many years. For example, Boulassel et al reported on the relationship between this autoimmune disease and hearing loss in 2001.[3] A number of studies have concerned inner ear involvement in autoimmune diseases such as Wegener granulomatosis, polyarteritis nodosa, systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome, among others.[4-6] One common finding in all these studies is that hearing impairment exists in autoimmune diseases, usually at high frequencies.[4]

The cochlea, saccule, and posterior canal are supplied by the common cochlear artery, while the utricle and anterior and horizontal canals are supplied by the anterior vestibular artery. Outer hair cell function is affected by immunologically mediated inflammation of the common cochlear artery. The common cochlear artery serves as the blood supply to the cochlea, and

Table 3. Audiometric test results in the two groups

Frequency (kHz)	Behçet patients, dB mean ± SD	Control group, dB mean ± SD	*p* Value
0.25	16.39 ± 4.72	14.86 ± 3,88	0.19
0.5	14.46 ± 4.98	13.11 ± 3.19	0.23
1	14.04 ± 6.19	11.32 ± 3.42	0.0498
2	14.75 ± 6.55	11.01 ± 3.42	0.01
4	16.39 ± 7.86	12.71 ± 4.85	0.04
8	20.64 ± 7.53	15.57 ± 6.65	0.01

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Table 4. TEOAE test results in the two groups

Frequency (kHz)	Behçet patients mean ± SD	Control group mean ± SD	*p* Value
*SNR**			
at 1 kHz	10.448 ± 7.303	12.536 ± 4.351	0.51
at 1.5 kHz	17.207 ± 15.730	16.857 ± 6.943	0.29
at 2 kHz	15.724 ± 13.022	15.680 ± 5.136	0.31
at 3 kHz	15.034 ± 17.517	13.357 ± 3.391	0.46
at 4 kHz	9.793 ± 16.019	12.536 ± 2.252	0.02
Reproducibility			
at 1 kHz	76.793 ± 36.086	92.250 ± 8.347	0.45
at 1.5 kHz	86.034 ± 24.744	95.107 ± 5.459	0.09
at 2 kHz	84.931 ± 25.503	94.929 ± 6.912	0.03
at 3 kHz	80.034 ± 25.098	94.286 ± 5.091	0.05
at 4 kHz	69.862 ± 28.763	94.001 ± 1.971	0.001

** SNR = sound-to-noise ratio.*

otoacoustic emissions are sensitive to the measurement of cochlear function.[7]

Inner ear involvement in Behçet disease was first reported by Alajouanine et al in 1961.[8] Since then, several studies of autoimmune involvement of the inner ear have been published,[5,6] and the reported rates of hearing loss among patients with Behçet disease have ranged from 15 to 80%.[4,7-13] However, some of these previous studies did not include a control group, and many did not include monitoring inner ear involvement via measurements of otoacoustic emissions.[4,9-11,14-16]

In our study, 34.5% of the Behçet disease patients had a sensorineural hearing loss (≥25 dB hearing level in at least two frequencies), particularly at the higher frequencies. The mean hearing levels were lower in the Behçet group than in the controls at all frequencies, but only the differences at 1 kHz and higher were statistically significant. Similarly, the differences in TEOAE results were significant at the higher frequencies. Our findings demonstrate that Behçet disease is associated with inner ear involvement, especially at the higher frequencies. A similar finding was reported by Kulahli et al.[10]

It is interesting that none of the Behçet disease patients in our study expressed any complaints about their hearing. This could be attributable to their having only a mild or moderate impairment (none had a severe or profound loss) that had not caused any communication problems in daily life.

In other studies, Soylu et al,[4] Gemignani et al,[15] and Brama and Fainaru[16] failed to find any correlation among age, inner ear involvement, and the duration of the disease. In our study, we did not find any statistically significant relationship between the duration of disease and inner ear involvement.

Many studies have been conducted in an attempt to determine the precise anatomic location responsible for hearing impairment in Behçet disease. The overall results of such studies have demonstrated cochlear (64% of cases), vestibular (28%), retrocochlear (4%), and external and middle ear (4%) disease involvement.[4,10,17] In our study, sound-to-noise ratios and reproducibility parameters indicated cochlear disease involvement. None of our patients had retrocochlear involvement, and because we did not perform vestibular testing, we are not able to speculate as to whether any of them had vestibular involvement.

The treatment of inner ear involvement in Behçet disease is generally symptomatic and individualized. The current practice is to administer combination drug therapy with a steroid, an immunosuppressant (e.g., azathioprine or cyclophosphamide), and an anticoagulant or antiaggregant.

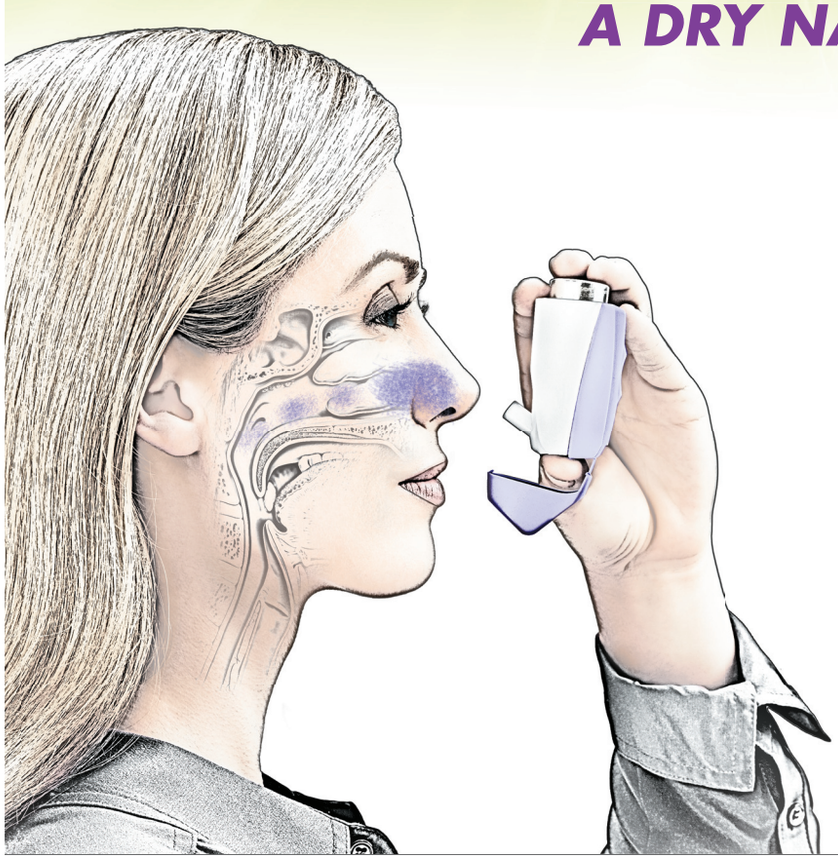
As with other investigations, our study had certain limitations. First, as mentioned, we did not perform vestibular testing. Second, our sample size was relatively small, and thus we cannot rule out the probability that the incidence of sensorineural hearing loss would have been statistically significant at *all* frequencies if we had investigated a larger number of patients.

In conclusion, this study has shown that hearing impairment and inner ear involvement are not uncommon in patients with Behçet disease. All Behçet patients should be regularly monitored by an otolaryngologist and screened with TEOAE testing if possible in order to facilitate the early diagnosis and treatment of inner ear involvement.

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  - seasonal ocular allergy symptoms in patients with seasonal allergic rhinitis[4]
  - seasonal and year-round nasal allergy symptoms[4]
- **One spray per nostril, once-daily dosing**

INDICATION: ZETONNA® (ciclesonide) Nasal Aerosol is a corticosteroid indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

IMPORTANT SAFETY INFORMATION: In clinical studies local nasal effects of epistaxis, ulcerations, and nasal septal perforations were observed with ZETONNA® (ciclesonide) Nasal Aerosol. In the short-term and long-term trials combined, nasal septal perforations were reported in 2 patients of 2335 treated with ZETONNA compared with none of 892 treated with placebo. Both perforations occurred in 2-week SAR trials while none occurred in the longer term trials. In clinical trials with another formulation of ciclesonide, the development of localized infections of the nose or pharynx with *Candida albicans* has occurred. Corticosteroids can interfere with wound healing.

Prior to initiating therapy, examine patients for evidence of septal perforation, erosions, ulceration, nasal surgery, and trauma. Avoid spraying ZETONNA directly onto the nasal septum. Avoid use in patients with recent septal perforation, nasal erosion, nasal ulcers, nasal surgery, or nasal trauma. Monitor patients periodically for signs of adverse reactions on the nasal mucosa. Discontinue ZETONNA if erosions, ulcerations or perforations occur.

Nasal and inhaled corticosteroids may result in the development of glaucoma and cataracts. Monitor patients closely with a change in vision or with a history of increased intraocular pressure, glaucoma, or cataracts.

ZETONNA is contraindicated in patients with a known hypersensitivity to ciclesonide or any of the ingredients of ZETONNA. Cases of hypersensitivity reactions following administration of ciclesonide with manifestations such as angioedema, with swelling of the lips, tongue and pharynx have been reported.

Patients using immunosuppressive drugs, like corticosteroids, can cause potential worsening of existing tuberculosis; fungal, bacterial, viral or parasitic infections; or ocular herpes simplex. Chicken pox and measles can have a more serious or even fatal course in susceptible individuals. Use caution in patients with the above because of the potential for worsening of these infections.

When intranasal corticosteroids are used at very high dosages or at the regular dosage in susceptible individuals, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, discontinue ZETONNA slowly.

Corticosteroids may cause a reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving ZETONNA.

In trials 2-6 weeks in duration, the most common adverse events that occurred with an incidence of at least 2% and more frequently with ZETONNA than with placebo were nasal discomfort, headache and epistaxis.

Please see Brief Summary of Prescribing Information on the following pages.

References: 1. Data on file, CSR 101. Sunovion Pharmaceuticals Inc, Marlborough, MA. **2.** Data on file, CSR 102. Sunovion Pharmaceuticals Inc, Marlborough, MA. **3.** Data on file, CSR 302. Sunovion Pharmaceuticals Inc, Marlborough, MA. **4.** ZETONNA Prescribing Information. Marlborough, MA: Sunovion Pharmaceuticals Inc; January 2012.

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BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

1.1 Treatment of Allergic Rhinitis

ZETONNA® (ciclesonide) Nasal Aerosol is indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

4 CONTRAINDICATIONS

ZETONNA Nasal Aerosol is contraindicated in patients with a known hypersensitivity to ciclesonide or any of the ingredients of ZETONNA Nasal Aerosol [*see Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Local Nasal Effects

Epistaxis and Nasal Ulceration: In clinical trials of 2 to 26 weeks in duration, epistaxis was observed more frequently in patients treated with ZETONNA Nasal Aerosol than those who received placebo. In the 26-week open-label extension of the perennial allergic rhinitis trial, nasal ulceration was identified in 4 of 824 patients administered ZETONNA Nasal Aerosol (148 mcg). [*see Adverse Reactions (6)*]

Nasal Septal Perforation: Nasal septal perforation has been reported in patients following the intranasal application of ZETONNA Nasal Aerosol. Three short-term placebo-controlled trials (2 weeks) and one long-term (26 weeks with placebo control and 26 weeks open-label extension without placebo control) trial were conducted in patients with seasonal and perennial allergic rhinitis. Nasal septal perforations were reported in 2 patients out of 2335 treated with ZETONNA Nasal Aerosol compared with none of 892 treated with placebo.

Before starting ZETONNA Nasal Aerosol conduct a nasal examination to ensure that patients are free of nasal disease other than allergic rhinitis. Periodically monitor patients with nasal examinations during treatment for adverse effects in the nasal cavity. If an adverse reaction (e.g. erosion, ulceration, perforation) is noted, discontinue ZETONNA Nasal Aerosol. Avoid spraying ZETONNA Nasal Aerosol directly onto the nasal septum.

Candida Infection: In clinical trials with another formulation of ciclesonide, the development of localized infections of the nose or pharynx with *Candida albicans* has occurred. If such an infection develops with ZETONNA Nasal Aerosol, it may require treatment with appropriate local therapy and discontinuation of ZETONNA Nasal Aerosol.

Impaired Wound Healing: 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 ZETONNA Nasal Aerosol until healing has occurred.

5.2 Glaucoma and Cataracts

Nasal and inhaled corticosteroids may result in the development of glaucoma and cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, or cataracts.

5.3 Hypersensitivity

ZETONNA Nasal Aerosol is contraindicated in patients with a known hypersensitivity to ciclesonide or any of the ingredients of ZETONNA Nasal Aerosol. Cases of hypersensitivity reactions following administration of ciclesonide with manifestations such as angioedema, with swelling of the lips, tongue and pharynx, have been reported.

5.4 Immunosuppression

Patients who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, 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 or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; or in patients with untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex because of the potential for worsening of these infections.

5.5 Hypothalamic-Pituitary-Adrenal Axis Effect

Hypercorticism and Adrenal Suppression: When intranasal corticosteroids are used at higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of ZETONNA Nasal Aerosol should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

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 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.

5.6 Effect on Growth

Corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely (e.g., via stadiometry) in pediatric patients receiving ZETONNA Nasal Aerosol. [*see Pediatric Use (8.4)*]

6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- Epistaxis, ulcerations, nasal septal perforations, *Candida albicans* infection, impaired wound healing [*see Warnings and Precautions (5.1)*]
- Glaucoma and cataracts [*see Warnings and Precautions (5.2)*]
- Immunosuppression [*see Warnings and Precautions (5.4)*]
- Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [*see Warnings and Precautions (5.5, 5.6), Use in Specific Populations (8.4)*]

6.1 Clinical Trials Experience

The safety data described below for adults and adolescents 12 years of age and older are based on 4 clinical trials evaluating doses of ciclesonide nasal aerosol from 74 to 282 mcg. Three of the clinical trials were 2 to 6 weeks in duration and one trial was 26 weeks in duration with an additional 26-week open-label extension. Data from the first 6 weeks of the 26-week trial were pooled with data from the three 2-week trials. Short-term data (2 to 6 weeks) included 3001 patients with seasonal and perennial allergic rhinitis, of these, 884 received ZETONNA Nasal Aerosol 74 mcg once daily and 892 received placebo. The short-term data included 1098 (36.6%) males, 1903 (63.4%) females, 2587 (86.2%) Caucasians, 320 (10.7%) Blacks, 49 (1.6%) Asians, and 45 (1.5%) patients classified as Other. The 26-week trial was conducted in 1110 patients with perennial allergic rhinitis [394 (35.5%) males and 716 (64.5%) females, ages 12 to 78 years old] treated with ZETONNA Nasal Aerosol 74 mcg, 148 mcg or placebo once daily. Of these patients, 298 were treated with 74 mcg ZETONNA Nasal Aerosol, 505 with 148 mcg, and 307 with placebo. The racial distribution in this trial included 922 (83.1%) Caucasians, 146 (13.2%) Blacks, 18 (1.6%) Asians, and 24 (2.2%) patients classified as Other. The 26-week open-label extension included 824 patients [295 (35.8%) males and 529 (64.2%) females, ages 12 to 79 years old] given ZETONNA Nasal Aerosol 148 mcg once daily. The racial distribution in the open-label extension included 690 (83.7%) Caucasians, 104 (12.6%) Blacks, 15 (1.8%) Asians, and 15 (1.8%) patients classified as Other.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults and Adolescents 12 Years of Age and Older in Short-Term (2-6 weeks) Trials:

In three short-term trials and the first 6 weeks of one long-term trial, conducted in the US, 884 patients with a history of seasonal or perennial allergic rhinitis were treated with ZETONNA Nasal Aerosol 74 mcg daily. Adverse reactions did not differ appreciably based on age, gender, or race. The table below displays reactions that occurred with an incidence of at least 2.0% and more frequently with ZETONNA Nasal Aerosol 74 mcg than with placebo in seasonal or perennial allergic rhinitis clinical trials of 2 to 6 weeks duration.

Table 1: Adverse Reactions Occurring with a Frequency of at least 2.0% and Greater than Placebo 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 Reaction	ZETONNA Nasal Aerosol 74 mcg Once Daily N = 884 (%)	Placebo N = 892 (%)
Nasal discomfort[a]	28 (3.2)	16 (1.8)
Headache	27 (3.1)	11 (1.2)
Epistaxis	26 (2.9)	24 (2.7)

[a] Nasal discomfort includes both nasal discomfort and instillation site discomfort

When considering the data from higher doses evaluated in the short-term trials, epistaxis demonstrated a dose response. In addition, two patients treated with ZETONNA Nasal Aerosol 74 mcg experienced nasal septal perforations in the short-term trials compared to no patients treated with placebo.

Approximately 1.2% of patients treated with ZETONNA Nasal Aerosol 74 mcg in clinical trials discontinued because of adverse reactions; this rate was similar for patients treated with placebo.

Discontinuations due to local adverse reactions were similar in ZETONNA Nasal Aerosol 74 mcg treated patients (0.8%) compared to placebo treated patients (0.8%). Local adverse reactions leading to discontinuation that occurred only in ZETONNA Nasal Aerosol treated patients included ear infection, nasal discomfort, nasal dryness, nasal mucosal/septum disorders, pharyngitis, streptococcal pharyngitis, sinus headache, and tonsillitis.

Pediatric Patients Aged 2 to 11 Years:
Trials of ZETONNA Nasal Aerosol have not been conducted in pediatric patients aged 2 to 11 years.

Long-Term (26-Week Double-Blind and 26-Week Open-Label) Safety Trial:
In one 26-week double-blind, placebo-controlled safety trial that included 1110 adult and adolescent patients with perennial allergic rhinitis, additional adverse reactions, with an incidence of at least 2%, that occurred more frequently with ZETONNA Nasal Aerosol than with placebo were upper respiratory tract infection, urinary tract infection, oropharyngeal pain, nasal mucosal/septum disorders, viral upper respiratory tract infection, cough, influenza, bronchitis, streptococcal pharyngitis, muscle strain, and nausea. Nasal discomfort (5.7%) and epistaxis (11.4%) were also more frequent in the 26-week safety trial compared to clinical trials 2 to 6 weeks in duration. Nasal mucosal/septum disorders and cough demonstrated a dose response.

Discontinuations due to adverse reactions were higher in ZETONNA Nasal Aerosol treated patients compared to placebo treated patients and demonstrated a dose response. Local adverse reactions leading to discontinuation were also higher in ZETONNA Nasal Aerosol 74 mcg treated patients (1.7%) compared to placebo treated patients (0.7%). The only local adverse reaction leading to discontinuation that occurred in ZETONNA Nasal Aerosol treated patients and was not observed in the 2- to 6-week trials was upper respiratory tract infection.

A total of 824 patients with perennial allergic rhinitis who completed the 26-week double-blind trial enrolled into an open-label extension and received ZETONNA Nasal Aerosol 148 mcg for 26 weeks. Additional adverse reactions, observed with an incidence of at least 2% were sinusitis, nasopharyngitis, and back pain.

A total of 4 nasal septal ulcerations were also reported in the 26-week open-label extension.

There were no reports of nasal septal perforations in the long-term safety trial.

6.2 Post-marketing Experience
Additional adverse reactions have been identified during worldwide post-marketing use with other formulations of ciclesonide, ALVESCO® Inhalation Aerosol and OMNARIS® Nasal Spray. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

ALVESCO® Inhalation Aerosol: immediate or delayed hypersensitivity reactions such as angioedema with swelling of the lips, tongue, and pharynx.

OMNARIS® Nasal Spray: nasal congestion, nasal ulcer, and dizziness. Localized infections of the nose or mouth with *Candida albicans* have also occurred with OMNARIS® Nasal Spray.

7 DRUG INTERACTIONS
In vitro studies and clinical pharmacology studies suggested that des-ciclesonide has no potential for metabolic drug interactions or protein binding-based drug interactions [*see Clinical Pharmacology (12.3) in the full prescribing information*]. In a drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of des-ciclesonide by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged. Erythromycin, a moderate inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of either des-ciclesonide or erythromycin following oral inhalation of ciclesonide [*see Clinical Pharmacology (12.3) in the full prescribing information*].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled trials in pregnant women. ZETONNA Nasal Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Oral administration of ciclesonide in rats at approximately 120 times the maximum recommended human daily intranasal dose (MRHDID) in adults (on a mcg/m^2 basis at a maternal dose of 900 mcg/kg/day) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at similar to MRHDID (on a mcg/m^2 basis at a maternal dose of 5 mcg/kg/day) produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at ¼ of the MRHDID in adults (on a mcg/m^2 basis at a maternal dose of 1 mcg/kg/day).

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

8.3 Nursing Mothers
It is not known if ciclesonide is excreted in human milk. However, other corticosteroids are excreted in human milk. In a study with lactating rats, minimal but detectable levels of radiolabeled ciclesonide were recovered in milk. Caution should be used when ZETONNA Nasal Aerosol is administered to nursing women.

8.4 Pediatric Use
The safety and effectiveness for seasonal and perennial allergic rhinitis in children 12 years of age and older have been established. The safety and efficacy of ZETONNA Nasal Aerosol for treatment of the symptoms of seasonal and perennial allergic rhinitis in patients 11 years of age and younger have not been established.

Controlled clinical trials have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including ZETONNA Nasal Aerosol, should be monitored routinely (e.g., via stadiometry). A 52-week, multi-center, double-blind, randomized, placebo-controlled parallel-group trial was conducted to assess the effect of orally inhaled ciclesonide (ALVESCO® Inhalation Aerosol) on growth rate in 609 pediatric patients with mild persistent asthma, aged 5 to 8.5 years. Treatment groups included orally inhaled ciclesonide 40 mcg or 160 mcg or placebo given once daily. Growth was measured by stadiometer height during the baseline, treatment and follow-up periods. The primary comparison was the difference in growth rates between ciclesonide 40 and 160 mcg and placebo groups. Conclusions cannot be drawn from this trial because compliance could not be assured. Ciclesonide blood levels were also not measured during the one-year treatment period. There was no difference in efficacy measures between the placebo and the orally inhaled ciclesonide (ALVESCO® Inhalation Aerosol) groups.

The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

The potential for ZETONNA Nasal Aerosol to cause growth suppression in susceptible patients or when given at higher than recommended dosages cannot be ruled out.

8.5 Geriatric Use

Clinical trials of ZETONNA Nasal Aerosol did not include sufficient numbers of patients age 65 and over to determine whether they responded differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Chronic overdosage may result in signs or symptoms of hypercorticism [*see Warnings and Precautions (5.5)*]. There are no data on the effects of acute or chronic overdosage with ZETONNA Nasal Aerosol.

16 STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temp]. For optimal results, canister should be at room temperature when used.

CONTENTS UNDER PRESSURE

Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw canister into fire or incinerator.

Keep out of reach of children. Avoid spraying in eyes or directly onto the nasal septum.

ZETONNA Nasal Aerosol 37 mcg, 60 metered actuations; net fill weight 6.1 g.

NDC Number 63402-737-60

SUNOVION

Manufactured for:
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752 USA
Made in the United Kingdom

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To report adverse events, call 1-877-737-7226
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