Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date:	July 03, 2017
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Product Name(s):	Zetonna (ciclesonide)
Pediatric Labeling Approval Date:	01/20/2012
Application Type/Number:	NDA 202129
Applicant/Sponsor:	Takeda GMBH
OSE RCM #:	2017-686

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for ciclesonide nasal sprays in pediatric patients. This review was triggered by the pediatric postmarketing requirements studies for Zetonna (ciclesonide nasal aerosol spray).

Zetonna (ciclesonide nasal aerosol spray) was first approved in 2012 and is indicated for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older. Omnaris (ciclesonide nasal spray) was first approved in 2006 for the treatment of symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older; the indication was extended in 2007 for the treatment of symptoms associated with SAR in adults and children aged 6 years of age and older. The pediatric postmarketing safety of Omnaris was evaluated in 2009 and 2012 and presented at the Pediatric Advisory Committee (PAC); no safety signals were identified and routine pharmacovigilance for all adverse events was continued.

For the purpose of this review, we searched the FDA Adverse Event Reporting System (FAERS) database for all the reports with the product active ingredient, ciclesonide, which included reports for all ciclesonide tradename products. The review focuses on adverse event reports with only ciclesonide nasal spray products, Zetonna and Omnaris, to capture all events with the same active moiety and route of administration. The utilization of ciclesonide nasal sprays in the pediatric population was not analyzed in this review, as it would not inform the evaluation of safety.

We evaluated all FAERS pediatric cases with a serious outcome for ciclesonide nasal sprays (Zetonna and Omnaris) from January 20, 2012 (initial approval date for Zetonna) to April 15, 2017. We identified one non-fatal case of the unlabeled adverse event, shingles. The single case described a patient who received concomitant treatment with two corticosteroids (ciclesonide nasal spray, mometasone furoate). A plausible mechanism for the development of shingles in this case was immunosuppression, which is a labeled event for ciclesonide nasal sprays. No new safety signal was identified with ciclesonide nasal sprays. DPV plans to continue postmarketing surveillance of these events.

1 INTRODUCTION

This review evaluated postmarketing adverse event reports with a serious outcome for ciclesonide nasal spray products (Zetonna, Omnaris). This review was triggered by the pediatric labeling date for Zetonna (ciclesonide nasal aerosol spray).

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Zetonna (ciclesonide nasal aerosol spray) is a corticosteroid indicated for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older. Another ciclesonide nasal spray, Omnaris (NDA 022004 and 022124), is marketed in the United States (U.S.) and can be differentiated from Zetonna by formulation, approved indication, and population for use (see Table 1).

Table 1. Ciclesonide Nasal Spray Products and Approved U.S. Indications

Proprietary Name	*NDA*	*Delivery Mechanism*	*Original Approval Date*	*Approved Indications*
Zetonna	202129	Metered dose, nasal aerosol that utilizes HFA-134a as the propellant	01/20/2012	Treatment of SAR and PAR in adults and adolescents ≥12 years of age
Omnaris*	022004	Metered dose, manual pump spray	10/20/2006	Treatment of SAR and PAR in adults and adolescents ≥12 years of age
	022124		11/21/2007	Treatment of SAR in adults and children ≥ 6 years of age

*Omnaris NDA 022004 was initially approved in patients 12 years of age and older. A separate NDA 022124 was created for the portion of the application that related to subjects less than 12 years of age.

1.2 PEDIATRIC REGULATORY HISTORY

October 20, 2006: Omnaris nasal spray was approved in the U.S. for the treatment of SAR and PAR in adults and adolescents 12 years of age and older.

November 21, 2007: Omnaris nasal spray was approved in the U.S. for the treatment of SAR in adults and children 6 years of age and older.

April 14, 2009: In accordance with PREA, DPV summarized the pediatric postmarketing adverse event reports with a serious outcome for Omnaris nasal spray in the Adverse Event Reporting System (AERS) database from November 21, 2007 (U.S. approval date) through February 15, 2009. No pediatric reports were identified [1].

June 23, 2009: The results of the April 2009 Omnaris nasal spray review were presented at the Pediatric Advisory Committee (PAC) meeting. The recommendation was to continue routine pharmacovigilance for all adverse events with Omnaris nasal spray.

January 20, 2012: Zetonna nasal aerosol spray was approved in the U.S. for the treatment of SAR and PAR in adults and adolescents 12 years of age and older.

March 29, 2012: In accordance with PREA, DPV summarized the pediatric postmarketing adverse event reports with a serious outcome for Omnaris nasal spray in the AERS database from October 20, 2006 (U.S. approval date) through January 21, 2012. Only a single report of transplacental exposure associated with a non-fatal heart murmur was identified and assessed as unlikely to be related to Omnaris. DPV concluded that the current labeling for Omnaris nasal spray is adequate [2].

May 07, 2012: The results of the March 2012 Omnaris nasal spray review were presented at the PAC meeting. The recommendation was to continue routine pharmacovigilance for all adverse events with Omnaris nasal spray.

October 23, 2014: Supplement 004 (S-004) for Zetonna nasal aerosol spray was approved; S-004 fulfilled the four postmarketing requirements (PMRs) issued at the time of initial U.S. approval. S-004 contained the four PMR studies described below:

> SEP060-305 and SEP060-306: Two randomized, double blind, parallel placebo-controlled, two dose studies evaluated the efficacy and safety of Zetonna nasal aerosol spray for the treatment of SAR and PAR in children 6 to 11 years of age, respectively; the studies did not provide consistent evidence of efficacy. Because of the findings, the Sponsor did not pursue extension of the indication to pediatric patients less than 12 years of age and they received a waiver of PREA requirements studies in patients 2 to 5 years.
>
> SEP060-308: Evaluated the effect of 6 weeks of Zetonna nasal aerosol spray on the hypothalamic-pituitary-adrenal (HPA) axis in children 6 to 11 years of age with PAR; the study found no significant difference between Zetonna nasal aerosol spray and placebo on HPA axis suppression. The findings observed were consistent to those in adolescents.
>
> SEP060-401: Evaluated the long-term nasal and ocular safety of Omnaris nasal spray and Zetonna nasal aerosol spray in a 26-week, postmarketing, randomized, open-label trial in patients 12 to 74 years of age; local treatment-emergent adverse events were consistent with those observed with other intranasal corticosteroids and no nasal septal perforations were reported with Omnaris or Zetonna.

1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES

----------4 CONTRAINDICATIONS----------

ZETONNA is contraindicated in patients with a known hypersensitivity to ciclesonide or any of the ingredients of ZETONNA [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 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 (148 mcg). [see *Adverse Reactions* (6)]

The occurrence of local nasal adverse events was further evaluated in a separate, postmarketing 26-week randomized, open-label, active-controlled nasal and ocular safety trial conducted in patients with perennial

allergic rhinitis. In this study epistaxis was observed in 6% of patients treated with ZETONNA and nasal ulceration was identified in 3 of 367 patients administered ZETONNA. [see *Adverse Reactions* (6)]

Nasal Septal Perforation: Nasal septal perforation has been reported in patients following the intranasal application of ZETONNA. 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 compared with none of 892 treated with placebo. No nasal septal perforations were reported in 367 patients treated with ZETONNA in a postmarketing 26-week, open-label, active-controlled trial in patients with perennial allergic rhinitis. [see *Adverse Reactions* (6)]

Before starting ZETONNA 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. Avoid spraying ZETONNA 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, it may require treatment with appropriate local therapy and discontinuation of ZETONNA.

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 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 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.

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 Suppression
Hypercorticism and adrenal suppression may occur when intranasal corticosteroids, such as ZETONNA, are used at higher than recommended dosages or in susceptible individuals at recommended dosages. If such changes occur, the dosage of ZETONNA 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. [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)]

6.2 Post-marketing Experience
The following adverse reactions have been identified during post-approval use of 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.

2 DRUG UTILIZATION DATA

On June 6, 2017, the safety team for the Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review determined that a drug utilization analysis would not inform the evaluation of postmarketing safety (see Section 3); therefore, drug utilization data was not included in this review.

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. The FAERS search strategy use *Product Active Ingredient* ciclesonide, which retrieved reports with ciclesonide inhalation (Alvesco) and another nasal spray (Omnaris), in addition to the nasal spray of interest (Zetonna). The review will focus on adverse event reports with all ciclesonide nasal spray products, Zetonna and Omnaris, to ensure all events with the same active moiety and route of administration are captured. See Appendix A for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy	
Date of Search	April 21, 2017
Time Period of Search	January 20, 2012* – April 15, 2017

Table 3.1.1 FAERS Search Strategy	
Search Type	Quick Query Product Manufacturer Reporting Summary
Product Active Ingredient	Ciclesonide
Search Parameters	All ages, all outcomes, worldwide

* *U.S. approval date of Zetonna; the initial approval included patients 12 years of age and older.*

3.2 RESULTS

3.2.1 Total Number of FAERS Reports by Age

Table 3.2.1 Total Adult and Pediatric FAERS reports* January 20, 2012 to April 15, 2017 with ciclesonide

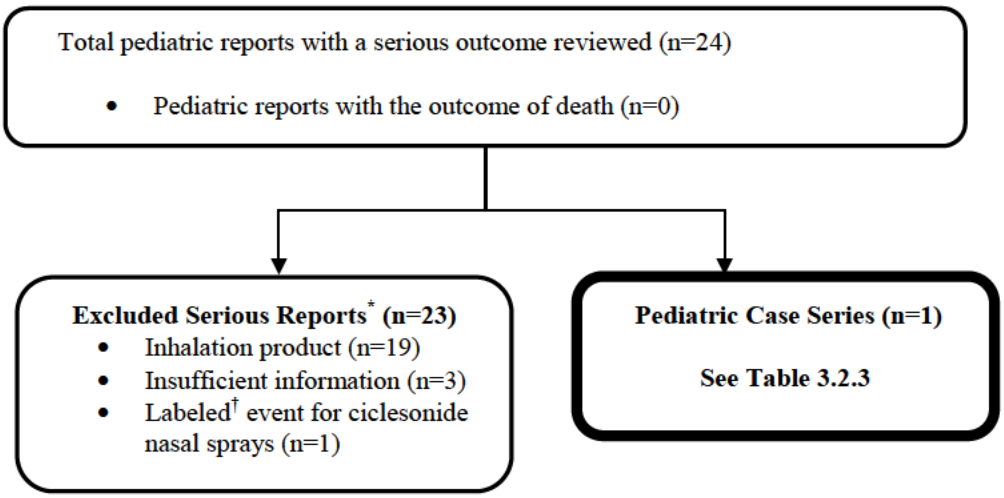
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	164 (55)	143 (38)	7 (1)
Pediatrics (0 - <17 years)	26(8)	24‡ (6)	0 (0)

* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.
‡ The FAERS search strategy used Product Active Ingredient ciclesonide, which retrieved adverse event reports with ciclesonide inhalation (Alvesco, n=19) and another ciclesonide nasal spray (Omnaris, n=3), in addition to the product of interest (Zetonna, n=2) to ensure all events with the same active moiety were captured. The remainder of the review will focus on the five pediatric adverse event reports with a serious outcome for ciclesonide nasal sprays, Zetonna and Omnaris (see Figure 3.2.2).

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 24 serious pediatric adverse event reports with ciclesonide from January 20, 2012 to April 15, 2017 (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Ciclesonide



* DPV reviewed these cases, but they were excluded from the case series for the reasons below.
†An adverse event or Preferred Term (PT) that is included in the respective ciclesonide product label was considered a "labeled event" across all ciclesonide nasal spray products.

Of the 24 serious pediatric reports, 23 were not included in the pediatric case series. Nineteen reports were excluded because they were associated with the ciclesonide inhalation product, Alvesco. Three reports did not provide sufficient information to infer causality between ciclesonide use and the adverse event. Lastly, one report was excluded because it contained an adverse event, glaucoma, which is labeled for ciclesonide nasal spray products; no change in severity was noted regarding this labeled event.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no reported deaths in pediatric patients using ciclesonide nasal spray from January 20, 2012 through April 15, 2017.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=1)

Unlabeled Event: Shingles

Case 8438059v2, MCN: 2012SP000607, outcome – other serious important medical events, U.S., 2012: An investigator reported that an 11-year-old Caucasian female who participated in Sunovion sponsored study 060-306 developed shingles 26 days after initiating ciclesonide nasal aerosol spray. The patient developed a rash on her upper right shoulder and was examined by the investigator the next day. The investigator diagnosed the patient with shingles and referred her to a dermatologist, who confirmed the diagnosis with the completion of a biopsy. The patient was placed on valacyclovir 500 mg twice daily for two weeks and ciclesonide nasal aerosol was discontinued. The patient recovered from the event approximately 11 days after the onset of the adverse event. The patient's past medical history includes cardiac murmur, perennial rhinitis, asthma, chicken pox at age 2 or 3, and eczema. The patient's concomitant medications included levalbuterol, mometasone furoate, ibuprofen, diphenhydramine hydrochloride, and unspecified allergy immunotherapy.

Reviewer Comment: Immunosuppression is labeled in Warnings and Precautions Section 5.4, Adverse Reactions Section 6.1, and Patient Counseling Information Section 17 of the Zetonna product label. This provides a plausible mechanism for the adverse event of shingles. Chicken pox infection is labeled within Warnings and Precautions Section 5.4 Immunosuppression; however, shingles is not specifically mentioned. The patient was also receiving mometasone furoate, an inhaled corticosteroid that can also contribute to immunosuppression. This singular case does not represent a new safety signal at this time. Additionally, this case occurred during PMR study 060-306, which was reviewed as part of S-004, and no safety signals were identified. DPV will continue routine postmarketing surveillance of this adverse event.

4 DISCUSSION

We evaluated all FAERS pediatric cases with a serious outcome for ciclesonide nasal sprays (Zetonna and Omnaris) and identified one case of the unlabeled adverse event, shingles. The single case described a patient who received concomitant treatment with two corticosteroids (ciclesonide nasal spray, mometasone furoate). A plausible mechanism for the development of shingles in this case was immunosuppression, which is a labeled event for ciclesonide nasal sprays. No new safety signal was identified with ciclesonide nasal sprays.

5 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with ciclesonide nasal sprays (Zetonna and Omnaris) at this time.

6 RECOMMENDATIONS

DPV recommends returning to routine pharmacovigilance monitoring for all adverse events with ciclesonide nasal spray.

7 REFERENCES

1. Ryan D. Pediatric Postmarketing Adverse Event Review. April 14, 2009. See http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af801360fa

2. Kalra D. Pediatric Postmarket Adverse Event Review. March 29, 2012. See http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80271241

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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