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

Pediatric Postmarketing Pharmacovigilance Review

Date:	August 11, 2017
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Product Name(s):	QNASL (beclomethasone dipropionate) nasal aerosol
Pediatric Labeling Approval Date:	December 17, 2014
Application Type/Number:	NDA 202813
Applicant/Sponsor:	Teva Branded Pharm
OSE RCM #:	2017-1404

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for beclomethasone dipropionate nasal sprays in pediatric patients. There are currently two beclomethasone dipropionate nasal sprays marketed in the United States, QNASL nasal aerosol (NDA 202813) and Beconase AQ nasal spray (NDA 019389). This review was triggered by the pediatric labeling date for QNASL nasal aerosol.

QNASL (beclomethasone dipropionate) nasal aerosol was first approved in March 23, 2012 and is indicated for the treatment of nasal symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older. The approved pediatric labeling on December 17, 2014 expanded the indication for QNASL nasal aerosol to patients 4 to 11 years of age for the treatment of nasal symptoms associated with SAR and PAR. The pediatric postmarketing safety profile of QNASL nasal aerosol was previously reviewed and presented to the Pediatric Advisory Committee (PAC) in 2015; no new safety signals were identified and standard, ongoing monitoring for all adverse events with QNASL nasal aerosol was continued.

For the purpose of this review, we searched the FDA Adverse Event Reporting System (FAERS) database for all reports with the product active ingredients, beclomethasone, beclomethasone dipropionate, and beclomethasone dipropionate monohydrate; this search strategy retrieved reports with other beclomethasone dosage forms (i.e., oral tablet, oral inhalation), in addition to the product of interest, beclomethasone nasal spray. This review focuses on adverse event reports with only beclomethasone nasal sprays, QNASL nasal aerosol and Beconase AQ nasal spray.

We evaluated all FAERS reports of serious adverse events (n=70) in the pediatric population for beclomethasone from July 1, 2014 (data lock date of previous PAC Review for QNASL nasal aerosol) to July 11, 2017. The review of the FAERS pediatric cases resulted in identification of zero serious cases containing unlabeled adverse events with beclomethasone nasal sprays. We identified two reports that contained an adverse event labeled in the QNASL product label. The labeled adverse events in the two reports are upper respiratory tract infection (n=1) and reduction in growth velocity (n=1); no change in frequency or severity of either adverse event was noted from review of the reports. No new safety signals were identified with any beclomethasone nasal spray including QNASL nasal aerosol, the product that triggered this review. There is no evidence from these data that there are pediatric safety concerns with beclomethasone nasal sprays (QNASL, Beconase AQ) at this time. DPV-I recommends returning to routine pharmacovigilance monitoring for all adverse events with beclomethasone nasal sprays (QNASL, Beconase AQ).

1 INTRODUCTION

This review evaluated pediatric postmarketing adverse event reports with a serious outcome for beclomethasone dipropionate nasal spray products (QNASL, Beconase AQ). This review was triggered by the pediatric labeling date for QNASL (beclomethasone dipropionate) nasal aerosol.

1.1 PRODUCT FORMULATIONS AND INDICATIONS

QNASL (beclomethasone dipropionate) nasal aerosol is a corticosteroid indicated for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children 4 years of age and older. QNASL is available in 2 strengths, 40 mcg and 80 mcg, for use in children 4 to 11 years of age and children and adults 12 years of age and older, respectively. Another beclomethasone dipropionate nasal spray, Beconase AQ (NDA 019389), is marketed[a] in the United States and can be differentiated from QNASL by formulation, approved indication, and population for use.

Table 1. Beclomethasone Nasal Spray Product and Approval Information

Proprietary Name	NDA	Delivery Mechanism	Original Approval Date	Approved Indications	Population for Use
QNASL	202813	Metered dose, nasal aerosol* that utilizes HFA as the propellant	3/23/2012	Treatment of SAR and PAR	Children and adults ≥ 4 years of age
Beconase AQ	019389	Aqueous suspension	7/27/1987	Relief of the symptoms of SAR, PAR, and nonallergic (vasomotor) rhinitis	Children and adults ≥ 6 years of age

* QNASL has the same drug substance and canister as QVAR (NDA 020911), inhalation beclomethasone dipropionate for the treatment of asthma, but uses a nasal actuator to allow for nasal administration.

[a] Other beclomethasone dipropionate nasal sprays, Vancenase (NDA 018521/ U.S. approval date September 24, 1981) and Vancenase AQ (NDA 019589/ U.S. approval date December 23, 1987, NDA 020469/ U.S. approval date June 26, 1996), were withdrawn from the U.S. market by the Sponsor, Schering. NDA 018521 and NDA 020469 were withdrawn on June 4, 2004. NDA 019589 was withdrawn on June 16, 2006.

1.2 PEDIATRIC REGULATORY HISTORY

March 23, 2012: QNASL 80 mcg nasal aerosol was approved in the United States for the treatment of nasal symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older. The Pediatric Research Equity Act (PREA) study requirement for ages 0 to 2 years was waived because the product would be unsafe in this group for concerns of local and systemic toxicity with corticosteroids. Postmarketing requirement (PMR) studies issued at the time of approval were:

1) PMR 1882-1: Conduct a 2-week double-blind (DB), placebo-controlled (PC), dose ranging trial in children 6 to 11 years of age with SAR
2) PMR 1882-2: Conduct a 12-week DB, PC, safety, and efficacy trial in children 6 to 11 years of age with PAR
3) PMR 1882-3: Conduct a 6-week DB, PC trial to assess the effects of QNASL on the hypothalamic-pituitary-adrenal (HPA) axis in children 6 to 11 years of age with PAR
4) PMR 1882-4: Conduct a 12-week DB, PC, safety trial in children 2 to 5 years of age with PAR
5) PMR 1882-5: Conduct a 6-week DB, PC trial to assess the effects of QNASL on the HPA axis in children 2 to 5 years of age with PAR

December 5, 2012: An observational study in younger children revealed that the nasal actuator tip of the QNASL product did not fit in the nares of children less than 4 years of age. Therefore, the PREA-required studies were amended with the following:

1) Patients less than 4 years of age were excluded
2) PMR 1882-2 and 1882-4 were combined into one efficacy and safety trial in children 4 to 11 years of age
3) PMR 1882-3 and 1882-5 were not needed because of available extensive clinical data with beclomethasone

February 27, 2014: Teva Pharmaceuticals, the Sponsor of QNASL, submitted a 505(b)(2) supplemental new drug application (sNDA) to support the extension of the indication of QNASL to pediatric patients 4 to 11 years of age. Following initial submission of the sNDA, it was determine that the SAR and PAR components of allergic rhinitis are separate and distinct indications for sNDA submission and use fee purposes. The sNDA was administratively split into two supplements, S007 for SAR and S009 for PAR.

December 17, 2014: QNASL 40 mcg nasal aerosol was approved in the U.S. for the treatment of nasal symptoms associated with SAR and PAR in children aged 4 to 11 years of age. Approval was based on data from two completed PMR studies, 1) a 2-week DB, PC, dose ranging trial in children 6 to 11 years of age with SAR, and 2) a 12-week DB, PC, safety and efficacy trial in children 4 to 11 years of age with PAR.

March 24, 2015: The pediatric safety profile of QNASL was previously reviewed and presented to the Pediatric Advisory Committee (PAC).[1,2] The previous FAERS database search from March 1, 2012 through June 30, 2014 identified seven reports with QNASL, of which two resulted in a serious outcome.[b] The two serious cases described labeled events and contained insufficient information for assessment. No new safety signals were identified. This information was presented to the PAC and the recommendation was to return to standard, ongoing monitoring for all adverse events with QNASL.

1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES

----------CONTRAINDICATIONS----------

- Patients with a history of hypersensitivity to beclomethasone dipropionate and/or any other QNASL Nasal Aerosol ingredients. (4)

----------WARNINGS AND PRECAUTIONS----------

- Nasal discomfort, epistaxis, nasal ulceration, *Candida albicans* infection, nasal septal perforation, impaired wound healing. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma. (5.1)
- Eye Disorders. Monitor patients closely with a change in vision or with a history of increased intraocular pressure, blurred vision, glaucoma, and/or cataracts. (5.2)
- Hypersensitivity, rash, and urticaria may occur after administration of QNASL Nasal Aerosol. (5.3)
- Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections. (5.4)
- Hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue QNASL Nasal Aerosol slowly. (5.5)
- Potential reduction in growth velocity in pediatric patients. Monitor growth routinely in pediatric patients receiving QNASL Nasal Aerosol. (5.6, 8.4)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (≥ 1% and greater than placebo) in patients 12 years of age and older include nasal discomfort, epistaxis, and headache. (6.1)
- The most common adverse reactions (≥ 2% and greater than placebo) in children 4 to 11 years of age include headache, pyrexia, upper respiratory tract infection, and nasopharyngitis. (6.1)

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV-I searched the FAERS database with the strategy described in Table 3.1.1. The FAERS search strategy used *Product Active Ingredient* beclomethasone, beclomethasone dipropionate, and beclomethasone dipropionate monohydrate. This search strategy retrieved reports with other beclomethasone dosage forms (i.e., oral tablet, oral inhalation),

[b] There were two searches performed for this review because the date of the presentation to the PAC was changed. The first FAERS database search from March 1, 2012 to December 31, 2013 retrieved seven adverse event reports and the second search from January 1, 2014 to June 30, 2014 retrieved zero adverse event reports.

in addition to the product of interest, beclomethasone nasal spray. The pediatric safety profile of QNASL was previously reviewed and presented to the PAC; the FAERS database search dates used in the previous review were March 1, 2012 through June 30, 2014. The data lock date of the previous review informed the start date of this review, July 1, 2014. See Appendix A for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy	
Date of Search	August 2, 2017
Time Period of Search	July 1, 2014* - July 11, 2017
Search Type	Product-Manufacturer Reporting Summary
Product Name(s)	Product Active Ingredient: beclomethasone, beclomethasone dipropionate, beclomethasone dipropionate monohydrate†
Search Parameters	All ages, all outcomes, worldwide

** This start date was chosen because the previous Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review data lock date was June 30, 2014.*
† The previous Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review search strategy used Product Name: QNASL. This current broader search strategy using Product Active Ingredient was chosen to ensure all adverse event reports with beclomethasone nasal sprays were captured.

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 3.2.1 Total Adult and Pediatric FAERS Reports* from July 1, 2014 to July 11, 2017 with Beclomethasone, Beclomethasone Dipropionate, or Beclomethasone Dipropionate Monohydrate

	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	471 (334)	250 (115)	7 (3)
Pediatrics (0 - <17 years)	160 (127)	**70‡ (37)**	8 (5)

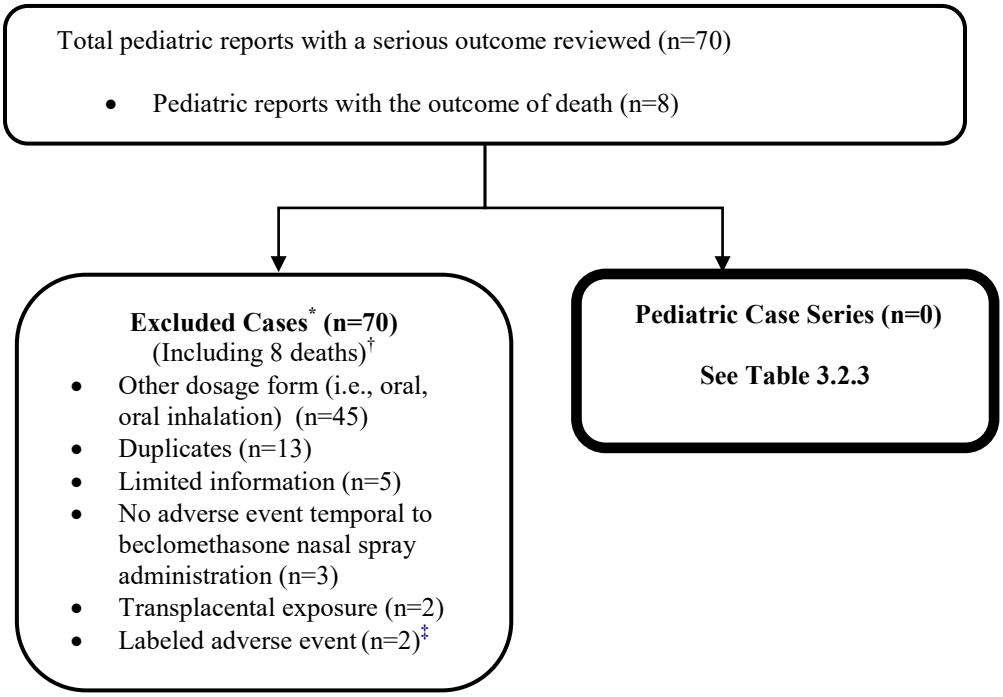
** May include duplicates and transplacental exposures, and have not been assessed for causality*
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial of prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.
‡ See Figure 2.2.2

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 70 pediatric reports with a serious outcome for beclomethasone (See Table 3.2.1). We performed a high-level overview of the 70 reports; all reports were excluded after review (See **Figure 2.2.2** below for the specific selection of cases to be summarized in **Section 2.3** and **2.4**). Forty-five of the 82 reports were excluded because the adverse events were associated with

a dosage form containing beclomethasone other than nasal spray (i.e. oral tablet[c] (n=3), oral inhalation[d] (n=42)); review of the reports did not inform the pediatric safety profile of the product of interest, beclomethasone nasal spray. The remaining 25 reports were excluded because they were duplicates (n=13), contained limited information for assessment (n=5), did not contain an adverse event temporal to beclomethasone nasal spray administration (n=3), were associated with transplacental exposure (n=2), or contained an adverse event labeled in the QNASL product label (n=2). The labeled adverse events in the two reports are upper respiratory tract infection (n=1) and reduction in growth velocity (n=1); no change in frequency or severity of either adverse event was noted from review of the reports.

Figure 2.2.2 Selection of Serious Pediatric Cases with Beclomethasone



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

† The eight death cases were excluded for the following reasons: duplicate report (n=4), different route of administration (n=3), and no adverse event temporal to beclomethasone administration (n=1).

‡ An adverse event or Preferred Term (PT) that is included in the respective beclomethasone nasal spray product label was considered a "labeled adverse event" across all beclomethasone nasal spray products.

[c] All three reports were foreign. Two of three reports described the use of beclomethasone oral tablet with concomitant immunosuppression for treatment of graft versus host disease and one described the adverse event of esophageal candidiasis.

[d] The adverse events reported with beclomethasone oral inhalation were generally labeled events such as psychiatric and behavioral changes, reduction in growth velocity, and infection.

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

There were no pediatric cases with a fatal outcome included in the case series.

2.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=0)

There were no pediatric cases with a non-fatal serious outcome included in the case series.

3 DISCUSSION

We evaluated all FAERS pediatric reports of adverse events with a serious outcome (n=70) for beclomethasone nasal sprays (QNASL, Beconase AQ) from July 1, 2014 to July 11, 2017. A high-level review of the 70 reports was completed; no new safety signals were identified with beclomethasone nasal sprays.

4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with beclomethasone nasal sprays (QNASL, Beconase AQ) at this time.

5 RECOMMENDATIONS

DPV-I recommends returning to routine pharmacovigilance monitoring for all adverse events with beclomethasone nasal sprays (QNASL, Beconase AQ).

6 REFERENCES

[1] Kalra, D. QNASL Pediatric Postmarketing Pharmacovigilance Memorandum. December 18, 2014. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM437729.pdf

[2] Chamberlain, CE. QNASL Pediatric Postmarketing Pharmacovigilance Memorandum. August 4, 2014. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM437729.pdf

7 APPENDICES

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

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.

7.2 APPENDIX B. FAERS CASE NUMBERS*, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS RETRIEVED BY THE FAERS SEARCH (N=70)

***** All cases were excluded from the case series for the reasons in section 2.2.2. The bolded cases below correspond to the two cases containing labeled adverse events with QNASL nasal aerosol.

FAERS Case Number	FAERS Version Number	Manufacturer Control Number
10284840	1	NL-GLAXOSMITHKLINE-B1011533A
10285033	1	NL-TEVA-492692ISR
10310324	1	NL-MYLANLABS-2014S1016291
10311607	1	GB-GLAXOSMITHKLINE-B1014740A
10351064	1	PHHY2014CA091767
10388131	1	US-TEVA-502426USA
10397071	**1**	**Direct**
10410174	1	US-TEVA-503895USA
10441829	2	JP-MYLANLABS-2014M1003793

FAERS Case Number	FAERS Version Number	Manufacturer Control Number
10458589	1	FK201403685
10461640	1	JP-TEVA-508370ISR
10462700	2	US-TEVA-509712USA
10488055	4	IE-009507513-1409IRL015526
10744504	1	Direct
11004857	1	JP-GLAXOSMITHKLINE-JP2015GSK045388
11088641	1	SE-GLAXOSMITHKLINE-SE2015GSK059587
11105605	**1**	**Direct**
11177106	1	US-TEVA-568887USA
11216390	2	BR-GLAXOSMITHKLINE-BR2015GSK088141
11456339	1	NL-TEVA-550787ISR
11585769	1	US-TEVA-597405USA
11596490	1	US-JNJFOC-20150924527
11670064	1	BR-GLAXOSMITHKLINE-BR2015GSK152792
11685410	1	Direct
11778273	1	BR-GLAXOSMITHKLINE-BR2015GSK167114
11779033	1	US-TEVA-611175USA
11884150	2	FR-GLAXOSMITHKLINE-FR2015GSK182525
11907870	1	FR-BRISTOL-MYERS SQUIBB COMPANY-11919339
11930187	1	Direct
11990404	5	US-MEDTRONIC-1047217
12134281	1	FR-GLAXOSMITHKLINE-FR2016GSK027070
12172235	2	US-TEVA-641042USA
12237368	2	CA-AMGEN-CANSP2016039991
12247341	3	CA-PFIZER INC-2016195992
12458514	1	Direct
12520250	1	US-GLAXOSMITHKLINE-US2016GSK093226

FAERS Case Number	FAERS Version Number	Manufacturer Control Number
12546699	1	IE-GLAXOSMITHKLINE-IE2016GSK098433
12552803	1	Direct
12597321	1	Direct
12610341	1	BR-GLAXOSMITHKLINE-BR2016GSK109735
12655028	1	US-TEVA-682657USA
12704166	1	GB-TEVA-688337ACC
12710116	1	Direct
12761682	3	US-TEVA-694102USA
12812716	2	US-VERTEX PHARMACEUTICALS-2016-005642
12854427	3	US-TEVA-696383USA
12888223	2	CA-ORION CORPORATION ORION PHARMA-TREX2016-2075
12921380	3	BR-GLAXOSMITHKLINE-BR2016GSK159023
12929934	1	Direct
12995355	1	CA-APOTEX-2016AP015012
13012613	1	Direct
13074392	2	CA-ORION CORPORATION ORION PHARMA-TREX2016-2837
13075373	1	GB-GLAXOSMITHKLINE-GB2016192594
13106618	1	US-TEVA-727626USA
13114986	2	US-TEVA-724479USA
13131835	1	US-009507513-97-06-0992
13180541	1	US-TEVA-735417USA
13282231	1	US-GLAXOSMITHKLINE-US2017GSK026775
13284540	1	FR-IPCA LABORATORIES LIMITED-IPC201702-000044
13292252	1	FR-APOTEX-2017AP007333
13299775	1	US-TEVA-745077USA

FAERS Case Number	FAERS Version Number	Manufacturer Control Number
13318405	2	US-TEVA-747207USA
13368793	1	US-TEVA-751870USA
13387299	2	US-TEVA-752803USA
13404131	1	FR-NORTHSTAR HEALTHCARE HOLDINGS-FR-2017NSR000125
13404347	1	PHHY2017US049284
13406524	1	FR-LANNETT COMPANY, INC.-FR-2017LAN000664
13432560	2	NL-TEVA-596209ISR
13691515	1	US-ROCHE-674272
13698915	1	FR-TEVA-781618ROM

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