Pediatric Postmarketing Pharmacovigilance Memorandum

Date: December 18, 2014

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Division of Pharmacovigilance I

Product Name(s): Qnasl® (beclomethasone dipropionate) nasal aerosol

Pediatric Labeling Approval Date: March 23, 2012

Application Type/Number: NDA 202813

Applicant/Sponsor: Teva Branded Pharm.

OSE RCM #: 2014-155
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1 INTRODUCTION

This Division of Pharmacovigilance (DPV) memorandum provides an updated FDA Adverse Event Reporting System (FAERS) search as part of the Agency’s effort to prepare for the discussion of Qnasl (beclomethasone dipropionate nasal aerosol) pediatric safety at the March 24, 2015 Pediatric Advisory Committee (PAC) meeting.

Qnasl was first approved on March 23, 2012 and is indicated for treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. The current approved pediatric labeling is for seasonal and perennial allergic rhinitis in this same age group.

In accordance with the FDAAA Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing reports of adverse events and drug utilization data for Qnasl in pediatric patients. For the September 23, 2014 PAC meeting, DPV searched FAERS for all reports of adverse events from March 1, 2012 through December 31, 2013. DPV identified seven reports, none of which resulted in death. These reports do not describe unknown or unexpected events for users of an inhaled nasal corticosteroid. Two of the seven cases reported a serious adverse event that was labeled or provided insufficient information to assess an association with the drug. Accordingly, Qnasl was originally categorized under the “designated abbreviated review” process to be reviewed by one of the PAC members prior to the meeting. However, the PAC member recommended that Qnasl be moved to the March 24, 2015 meeting so all PAC members can provide input.

The prior OSE pediatric review is appended to the end of this memorandum.

2 METHODS AND MATERIALS

The FAERS database was searched with the strategy described in Table 1. See Appendix A for a description of the FAERS database.

<table>
<thead>
<tr>
<th>Table 1 FAERS Search Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of search</td>
</tr>
<tr>
<td>Time period of search</td>
</tr>
<tr>
<td>Product Name(s)</td>
</tr>
<tr>
<td>Search Parameters</td>
</tr>
</tbody>
</table>

*Date since the last Qnasl review search (March 21, 2012-December 31, 2014)

3 RESULTS

The updated FAERS search retrieved zero reports.

4 CONCLUSION AND RECOMMENDATIONS
We did not identify any new pediatric safety issues of concern in this review. DPV will continue routine pharmacovigilance monitoring for Qnasl.

5 APPENDICES

5.1 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).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

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.

1 Chamberlain, Christine, PharmD, CDE. Qnasl Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review. August 4, 2014.
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 and Drug Utilization Review

Date: August 4, 2014

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Product Name(s): Qnasl® (beclomethasone dipropionate) nasal aerosol

Pediatric Labeling Approval Date: March 23, 2012

Application Type/Number: NDA 202813

Applicant/Sponsor: Teva Branded Pharm

OSE RCM #: 2014-584

**This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.**
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EXECUTIVE SUMMARY

In accordance with the FDAAA Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing reports of adverse events and drug utilization data for Qnasl® (beclomethasone dipropionate nasal aerosol) in pediatric patients.

Qnasl® was first approved on March 23, 2012 and is indicated for treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. The current approved pediatric labeling is for seasonal and perennial allergic rhinitis in this same age group.

The FDA Adverse Event Reporting System (FAERS) was searched for all reports of adverse events from March 1, 2012 through December 31, 2013. We identified a total of seven reports, none of which resulted in death. These reports do not describe unknown or unexpected events for users of an inhaled nasal corticosteroid. Two of the seven cases reported a serious adverse event which was labeled or provided insufficient information to assess an association with the drug.

The pediatric population (age 0-16 years) accounted for 12% of total patients who received a dispensed Qnasl® prescription from outpatient retail pharmacies between March 1, 2012 to December 31, 2013. The safety and effectiveness of Qnasl® in children younger than 12 years of age have not been established. However, off-label use in children younger than 12 years of age accounted for 40% of pediatric patients. “Allergic Rhinitis NOS” (ICD-9 Code 477.9) was the most common diagnosis associated with the pediatric use of Qnasl® during the review period.

We found seven FAERS reports of adverse events that occurred in pediatric patients out of an estimated 24,593 pediatric patients dispensed Qnasl® Nasal Aerosol based on US retail outpatient data for the designated time period. We did not identify any new pediatric safety issues of concern in this review.

DPV will continue routine pharmacovigilance monitoring for Qnasl®.
1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

The Office of Surveillance and Epidemiology (OSE) evaluated post-market reports of adverse events, and drug utilization data with beclomethasone (Qnasl®) in pediatric patients (0 through 16 years of age) in accordance with the Pediatric Research Equity Act (PREA).

Product Information and Dosing

Beclomethasone dipropionate, the active component of Qnasl® Nasal Aerosol is an anti-inflammatory steroid, which has demonstrated improvement in nasal symptoms in adult and adolescent patients with seasonal and perennial allergic rhinitis. The efficacy and safety of beclomethasone dipropionate nasal aerosol have been established for adolescent patients 12 years and older, but have not been established in children younger than 12 years of age. Beclomethasone dipropionate is available in a nasal aerosol form with each actuation delivering 80 mcg of beclomethasone dipropionate, and is supplied in an 8.7 g canister containing 120 actuations. The recommended dose of Qnasl® Nasal Aerosol is 320 mcg per day administered as 2 nasal aerosol sprays in each nostril once daily (maximum total daily dose of 4 nasal aerosol sprays per day).

Clinical Trials in Pediatric Patients

These data are taken unchanged from FDA approved prescribing information for Qnasl®.

‘The safety and effectiveness for seasonal and perennial allergic rhinitis in children 12 years of age and older have been established. Controlled clinical trials with QNASL Nasal Aerosol included 188 adolescent patients 12 to 17 years of age. The safety and effectiveness of QNASL Nasal Aerosol in children younger than 12 years of age 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 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 QNASL Nasal Aerosol, should be monitored routinely (e.g., via stadiometry).

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1 Qnasl® (beclomethasone dipropionate) nasal aerosol) [package insert]. Horsham, PA: Teva Respiratory, LLC; March 2014.
A 12 month randomized controlled clinical trial evaluated the effects of QVAR®, an orally inhaled HFA beclomethasone dipropionate product, without spacer versus chlorofluorocarbonpropelled (CFC) beclomethasone dipropionate with large volume spacer on growth in children with asthma ages 5-11 years. A total of 520 patients were enrolled, of whom 394 received HFA beclomethasone dipropionate (100 – 400 mcg/day ex-valve) and 126 received CFC beclomethasone dipropionate (200 – 800 mcg/day ex-valve). When comparing results at month 12 to baseline, the mean growth velocity in children treated with HFA-beclomethasone dipropionate was approximately 0.5 cm/year less than that noted with children treated with CFC beclomethasone dipropionate via large volume spacer. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives.

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

Postmarket Requirements for Pediatric Studies

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the application for Qnasl® was required to contain an assessment of the safety and effectiveness of the product for allergic rhinitis in pediatric patients. The pediatric study requirement for ages 0 to 2 years was waived because the product would be unsafe in this pediatric group due to concerns of local and systemic toxicity with corticosteroids and because other treatments are available for allergic rhinitis. Deferred pediatric studies originally included as postmarket requirements are listed in Table 1. Pediatric studies in patients less than 4 years were waived because the nasal actuator nose tip is too large for this age group. Additionally, PMRs 1882-4 and 1882-2 were released in place of a single study to conduct efficacy and safety in children 4 to 11 years of age (PMR 1976-1). 2 HPA axis trials in this patient population were no longer necessary based on new data submitted for pediatric patients ages 6 through 11 years with seasonal allergic rhinitis and the extensive available clinical data for beclomethasone (PMRs 1882-3 and 1882-5). A supplemental application proposing an indication for the treatment of the nasal symptoms associated with seasonal and perennial allergic rhinitis in patients 4 through 11 years of age is currently under review by FDA’s Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). 3

Table 1. Post Market Requirements (PMRs) For Studies in Pediatric Patients

<table>
<thead>
<tr>
<th>FDA PMR No.</th>
<th>Description of Study</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1882-1</td>
<td>Conduct a 2-week double-blind, placebo-controlled dose-ranging trial in children 6-11 years of age with seasonal allergic rhinitis. At least 2 doses of Qnasl® will be evaluated.</td>
<td>On-going</td>
</tr>
</tbody>
</table>


1.2 **SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS**

During a postmarket safety evaluation (FDAAA Section 915 Non-NME Review) of all reports for Qnasl®, a majority of cases did not report a serious outcome; labeled events did not appear to occur at an increased frequency or severity; and the reported unlabeled events were non serious and included burning sensation and dysphonia.  

1.3 **HIGHLIGHTS OF LABELED SAFETY ISSUES**

Known safety concerns described in the Warnings and Precautions section of labeling for adults include nasal ulceration, nasal septal perforation, impaired wound healing, development of glaucoma or cataracts, hypercorticism and adrenal suppression. Additional concerns include potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A known safety concern in pediatric patients is potential reduction in growth velocity.

Additionally, contraindications to Qnasl® include patients with a history of hypersensitivity to beclomethasone dipropionate and/or any other Qnasl® nasal aerosol ingredients. Hypersensitivity reactions including anaphylaxis, angioedema, urticaria and rash have been reported with beclomethasone dipropionate products and are described in the Warnings and Precautions section of labeling.

The most common adverse reactions (≥ 1% incidence and greater than placebo) include nasal discomfort, epistaxis, and headache.

2 **DRUG UTILIZATION DATA**

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5 Kalra D. Qnasl (beclomethasone dipropionate) Nasal Aerosol, 80 mcg, NDA 202813. FDAAA Section 915 Non-New Molecular Entity (non-NME) Postmarket Safety Summary. Panorama # 1820. 23 March 2012.

6 Qnasl® (beclomethasone dipropionate) nasal aerosol) [package insert]. Horsham, PA: Teva Respiratory, LLC; March 2014.
2.1 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct this analysis.

2.1.1 Determining Settings of Care

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for Qnasl® (beclomethasone dipropionate) from March 1, 2012 through December 31, 2013. Approximately 87% of Qnasl® canisters were distributed to outpatient retail pharmacy settings, 10% to mail-order/specialty pharmacies, and 3% to non-retail pharmacies. As a result, outpatient retail pharmacy utilization patterns were examined. Inpatient hospital, mail-order/specialty pharmacy, and clinic data were not included in this analysis.

2.1.2 Data Sources Used

Details and limitations of these databases are located in Appendix A section 7.1 of this document.

IMS Health, Vector One®: Total Patient Tracker database was used to provide the nationally estimated number of unique patients, stratified by patient age (0-11 years, 12-16 years, 17+ years), that received a dispensed prescription for Qnasl® from U.S. outpatient retail pharmacies from March 1, 2012 through December 31, 2013.

IMS Health, National Prescription Audit (NPA™) database was used to obtain the number of dispensed prescriptions by prescribing specialty for Qnasl® from U.S. outpatient retail pharmacies from March 1, 2012 through December 31, 2013.

Encuity Research, LLC, TreatmentAnswers™ database was used to obtain diagnoses associated with the use of Qnasl®, stratified by patient age (0-11 years, 12-16 years, 17+ years), for the cumulative time period of March 1, 2012 through December 31 2013.

2.2 RESULTS

2.2.1 Patient Demographics

Table 2.2.1 shows the nationally estimated number of patients, stratified by patient age, with a dispensed prescription for Qnasl® from U.S. outpatient retail pharmacies, March 2012 through December 2013. Pediatric patients aged 0-16 years accounted for approximately 12% (25,000 patients) of total patients for Qnasl® during the review period. The largest proportion of pediatric patients who received a dispensed prescription for Qnasl® were aged 12-16 years, accounting for approximately 61% (15,000 patients) of pediatric patients. Off-label use in children younger than 12 years of age accounted for 40% (9,900 patients) of pediatric patients. Adults 17 years and older accounted for 88% of total patients (184,000 patients).

Table 2.2.1

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Nationally estimated number of unique patients, stratified by patient age*, who received prescriptions for Qnasl dispensed from U.S. outpatient retail pharmacies March 2012 - December 2013

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Patients (N)</th>
<th>Share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grand Total</td>
<td>208,662</td>
<td>100.0%</td>
</tr>
<tr>
<td>Age 0-16 years</td>
<td>24,593</td>
<td>11.8%</td>
</tr>
<tr>
<td>Age 0-11 years</td>
<td>9,915</td>
<td>40.3%</td>
</tr>
<tr>
<td>Age 12-16 years</td>
<td>14,979</td>
<td>60.9%</td>
</tr>
<tr>
<td>Age 17+ years</td>
<td>184,157</td>
<td>88.2%</td>
</tr>
<tr>
<td>UNKNOWN AGE</td>
<td>23</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>


*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months).

*Patient age subtotals may not sum exactly due to patients aging during the study ("the cohort effect"), and may be counted more than once in the individual age categories. Summing across patient age bands is not advisable and will result in overestimates of patient counts.

2.2.2 Prescriber Specialty

Table 2.2.2 shows the top 10 prescribing specialties for Qnasl® by number of prescriptions dispensed from U.S. outpatient retail pharmacies, March 2012 through December 2013. During the cumulative time period examined, approximately 471,000 prescriptions were dispensed for Qnasl®. Approximately 30% (142,000 prescriptions) of dispensed prescriptions for Qnasl® were prescribed by Allergy specialists, followed by Otolaryngology specialists at 24% (112,000 prescriptions) of dispensed prescriptions. Pediatricians accounted for approximately 4% (17,000 prescriptions) of dispensed prescriptions.

<table>
<thead>
<tr>
<th>Prescriber Specialty</th>
<th>TRx</th>
<th>Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRAND TOTAL</td>
<td>470,952</td>
<td>100.0%</td>
</tr>
<tr>
<td>ALLERGY</td>
<td>141,719</td>
<td>30.1%</td>
</tr>
<tr>
<td>OTOLARYNGOLOGY</td>
<td>111,672</td>
<td>23.7%</td>
</tr>
<tr>
<td>FAMILY PRACTICE</td>
<td>37,385</td>
<td>7.9%</td>
</tr>
<tr>
<td>OSTEOPATHIC MEDICINE</td>
<td>36,349</td>
<td>7.7%</td>
</tr>
<tr>
<td>INTERNAL MEDICINE</td>
<td>33,775</td>
<td>7.2%</td>
</tr>
<tr>
<td>NURSE PRACTITION</td>
<td>23,364</td>
<td>5.0%</td>
</tr>
<tr>
<td>PHYSICIAN ASSISTANT</td>
<td>23,090</td>
<td>4.9%</td>
</tr>
<tr>
<td>PEDIATRICS</td>
<td>17,333</td>
<td>3.7%</td>
</tr>
<tr>
<td>PULMONARY DISEASES</td>
<td>16,387</td>
<td>3.5%</td>
</tr>
<tr>
<td>SPECIALTY UNSPECIFIED</td>
<td>5,004</td>
<td>1.1%</td>
</tr>
<tr>
<td>ALL OTHERS</td>
<td>24,874</td>
<td>5.3%</td>
</tr>
</tbody>
</table>


2.2.3 Diagnoses Associated with Use
Table 2.2.3 shows diagnoses associated with the use of Qnasl® by number of drug use mentions as reported by office-based physician survey from March 2012 through December 2013. Diagnoses associated with the use of Qnasl®, stratified by patient age, were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were applied to the estimates. For the pediatric population (age 0-16 years), diagnoses associated with allergic rhinitis (ICD-9 Code 477.x) were the most common diagnoses associated with the use of Qnasl® during the review period. However, the number of mentions of Qnasl® among the pediatric population was below the acceptable count allowable to provide a reliable estimate of national use, and should therefore be interpreted with caution.

Table 2.2.3

<table>
<thead>
<tr>
<th>Diagnoses associated with the use* of Qnasl, stratified by patient age (0-11, 12-16, 17+ years) as reported by U.S. office-based physicians, March 1, 2012 through December 31, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2012 - December 2013</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Grand Total</td>
</tr>
<tr>
<td>Age 0-11 years</td>
</tr>
<tr>
<td>4779 ALLERGIC RHINITIS NOS</td>
</tr>
<tr>
<td>4778 ALLERGIC RHINITIS NEC</td>
</tr>
<tr>
<td>4739 CHRONIC SINUSITIS NOS</td>
</tr>
<tr>
<td>9953 ALLERGY, UNSPECIFIED</td>
</tr>
<tr>
<td>4720 CHRONIC RHINITIS</td>
</tr>
<tr>
<td>Age 12-16 years</td>
</tr>
<tr>
<td>4779 ALLERGIC RHINITIS NOS</td>
</tr>
<tr>
<td>Age 17+</td>
</tr>
<tr>
<td>UNSPEC</td>
</tr>
</tbody>
</table>

Source: Encuity Research, LLC, TreatmentAnswers™ with Pain Panel, Mar 2012- Dec 2013 Extracted June 2014  File: PDDA 2014-584 Qnasl by AgeDx4 6-6-14

*Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease.

NOS - Not Otherwise Specified  NEC - Not Elsewhere Classifiable

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The FAERS database was searched with the strategy described in Table 3.1.1. See Appendix B Section 2 for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

8 "Drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.
3.2 RESULTS

3.2.1 Total number of FAERS cases by Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>All reports (US)</th>
<th>Serious* (US)</th>
<th>Death (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17 years)</td>
<td>113 (110)</td>
<td>14 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pediatrics (0 - &lt;17 years)</td>
<td>7 (7)</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* May include duplicates and transplacental exposures, and have not been assessed for causality
† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
‡ No additional cases of pediatric deaths were identified among cases not reporting an age.

3.2.2 Selection of Serious Pediatric Cases in FAERS
The FAERS search identified two serious pediatric cases in this search period. Pediatric cases less than 12 years of age are considered off label use of Qnasl®.

3.2.3 Pediatric Case Series Summary (n=7)
We reviewed all cases regardless of seriousness. Appendix C section 3 lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the pediatric case series. Each case is summarized below.

Case Id: 8636957 (USA)
A 16-year-old female received Qnasl® 80mcg for seasonal allergies after switching from Qvar. Concomitant meds include omeprazole for gastroesophageal reflux disease and montelukast. Immediately after the first dose of Qnasl® the patient experienced painful burning sensation, neck swelling, urticaria on neck and face, and throat tightness that lasted over an hour. The patient went to the emergency room and was treated with diphenhydramine, ranitidine and intravenous fluids. Her symptoms resolved. A second dose was not administered. The physician was contacted for follow-up and reported that the patient was not seen in their office for any adverse event to Qnasl®.

Case #8636952 (USA)
A 16-year-old male received Qnasl® 80 mcg, one inhalation in each nostril, for allergic rhinitis.
Almost immediately after starting therapy the patient experienced burning in each nostril. The patient stopped the medication temporarily and it was unknown at the time of reporting if the medication would be restarted. No further information was provided.

**Case # 8636960 (USA)**
An 11-year-old male received Qnasl® for an unknown indication. A physician reported the patient experienced epistaxis while using Qnasl® inhaler with an unspecified time to onset. No further information was provided.

**Case # 9648847 (USA)**
A 12-year-old male received Qnasl® for an unknown indication. Concomitant medications and medical history were unspecified. The patient (son of the reporting physician) experienced nasal congestion after an unknown period of time from the initiation of therapy. No further information was provided.

**Case # 8779694 (USA)**
A 16-year-old male received Qnasl® 2 puffs in each nostril daily for relief of problems associated with chronic sinusitis. Concomitant medication include acetaminophen/oxycodeone, carisoprodol, and clonazepam. After recently starting Qnasl® therapy, the patient experienced a burning sensation in his nose immediately after administration that quickly subsides. The dosage of medication was maintained. No further information was provided.

**Case Id: 9167991 (USA)**
A 14-year-old male received Qnasl® for allergies. Concomitant medications include pseudoephedrine and cetirizine. Within three days of starting therapy the patient experienced pain during administration and noticed a lack of effect. The outcome at the time of the report was unresolved and action taken with the medication was unknown. No further information was provided.

**Case # 9444635 (USA, direct report)**
This case describes a 2.5-year-old male with a medical history of asthma and allergies who was prescribed Qnasl® twice a day (1 puff in each nostril) for one week and then once a day thereafter. Concomitant medications included pediatric multivitamin, beclomethasone dipropionate HFA oral inhaler (Qvar®) and mometasone furoate monohydrate nasal spray (Nasonex®). He developed aggressive, defiant and combative behavior the evening of the first dose, and vomited milk and food and experienced increased hyperactivity and combativeness the following day. The mother was instructed by the pediatrician to stop Qnasl®. The mother noted improvement of nasal drainage with Qnasl® but did not report outcome of behavioral changes when Qnasl® was discontinued. No further information was provided.

### 4 DISCUSSION

This review focuses on all pediatric adverse events and death cases spontaneously reported with Qnasl®. We did not identify any pediatric death cases. We identified a single serious hypersensitivity case requiring emergency room treatment with histamine blockers. This adverse event is described in the Warnings and Precautions section of labeling. A second serious pediatric adverse event case involved off-label use of Qnasl® in a 2.5-year-old patient in which...
hyperactivity and combative behavior occurred with the first dose. No follow-up information was provided to adequately assess a causal relationship. Other adverse events reported as non-serious in this case series included burning sensation in nostrils, epistaxis and nasal congestion.

The drug utilization data in this review indicate the pediatric population (age 0-16 years) accounted for 12% of the total 208,662 patients that received a dispensed prescription for Qnasl® in outpatient retail pharmacies nationwide from March 2012 through December 2013. Of these pediatric patients, the largest proportion of use was among pediatric patients 12-16 years. Off-label use in children younger than 12 years of age accounted for 40% of pediatric patients for the examined time. Among the pediatric adverse event reports we received via FAERS, none represent rare or unexpected adverse events for an inhaled nasal corticosteroid. The most common diagnosis associated with the use of Qnasl® during the review period was allergic rhinitis.

5  CONCLUSION

Our review of FAERS case reports and drug utilization data has not identified new pediatric safety concerns with Qnasl® at this time.

6  RECOMMENDATIONS

DPV will continue routine pharmacovigilance monitoring for Qnasl®.

7  APPENDICES

7.1  APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

**IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**
The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that 87% of Qnasl® was distributed to outpatient retail settings, based on the IMS Health, IMS National Sales Perspectives™. The data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

**IMS Vector One®: Total Patient Tracker (TPT)**
The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software
systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

**IMS, National Prescription Audit**
The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 80% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data are available on-line for 72-rolling months with a lag of 1 month.

**Encuity Research, LLC., TreatmentAnswers™**
Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

**7.2 APPENDIX B. 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

Reference ID: 36052828
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).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

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.

7.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS

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/s/

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