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Office of Surveillance and Epidemiology**

Pediatric Postmarketing Pharmacovigilance Review

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Product Name: ProAir RespiClick (albuterol)

Pediatric Labeling Approval Date: Age 12 years and older: March 31, 2015
Age 4 years and older: April 28, 2016

Application Type/Number: NDA 205636

Applicant/Sponsor: Teva Branded Pharmaceuticals R&D, Inc.

OSE RCM #: 2017-2219

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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 ProAir RespiClick (albuterol sulfate) in pediatric patients.

ProAir RespiClick is a dry-powder, breath-actuated albuterol inhaler and was first approved on March 31, 2015. ProAir RespiClick is indicated for the treatment or prevention of bronchospasm as well as the treatment of exercise-induced bronchospasm. Pediatric labeling for these indications was approved with the original product approval for ages 12 years and older and was subsequently expanded to ages 4 years and older on April 28, 2016.

The Division of Pharmacovigilance I (DPV-I) evaluated all adverse event reports for ProAir RespiClick in the FDA Adverse Event Reporting System (FAERS) database from the U.S. approval date on March 31, 2015 to October 28, 2017. The search identified no death reports in any age group; one serious case of urinary incontinence, an unlabeled event for ProAir RespiClick, was identified. This case was confounded by the patient's participation in exertional activity. No new safety signals were identified for pediatric patients with ProAir RespiClick.

A prior pediatric review of albuterol sulfate (Ventolin HFA, NDA 020983) was presented to the pediatric advisory committee in December 2009. This prior review identified two cases of Stevens-Johnson Syndrome (SJS), however both cases were confounded and routine pharmacovigilance was recommended. It is notable that SJS is not currently labeled in inhaled albuterol product labeling, however, it is included within the product labeling for albuterol tablets and oral solution in the Warnings: Immediate Hypersensitivity Reaction section. In addition, a Medical Officer from the Office of Pediatric Therapeutics (OPT) identified a case of albuterol-associated SJS during a literature search to inform this review. As a result, Tracked Safety Issue (TSI) # 1870 was opened and DPV-I analyzed the FAERS database for an association between albuterol products and SJS. A search of the FAERS database through January 19, 2018 identified three cases of SJS with albuterol inhalation; two of three occurred in pediatric patients. One case was domestic in origin and the remaining two were foreign cases. All three cases contained an alternative cause for the events (ibuprofen, fluticasone, viral illness). Additionally, the labeling of oral albuterol products for SJS was based on one foreign case reported in 1992; this case was limited by a possible alternative etiology of concomitant erythromycin and missing clinical information regarding albuterol withdrawal, which does not allow for assessment of dechallenge. As a result of this separate review, routine pharmacovigilance was recommended for all inhaled albuterol products and SJS and TSI # 1870 was closed.

DPV-I recommends continued routine pharmacovigilance for all adverse events associated with ProAir RespiClick.

1 INTRODUCTION

This review evaluated postmarketing adverse event reports with a serious outcome for ProAir RespiClick inhalation (albuterol sulfate/ NDA 205636) in pediatric patients. This review was triggered by the pediatric labeling date for ProAir RespiClick on April 28, 2016.

1.1 PRODUCT FORMULATIONS

ProAir RespiClick is a multidose dry powder inhaler (MDPI) which contains albuterol sulfate and lactose monohydrate.¹ ProAir RespiClick obviates the need for coordination of dose dispensing and breath that is required with aerosolized inhalers. FDA-approved indications include the treatment or prevention of bronchospasm and the prevention of exercise-induced bronchospasm (EIB) in adults and children 4 years of age and older. Albuterol sulfate is widely used in the treatment of asthma and was first approved for use in the United States in 1981.² As a result of more than thirty years of experience, safety and efficacy of this product active ingredient has been well established. Currently available albuterol sulfate single ingredient products are listed in Table 1.1.1.

Dosage Form	Product Name	Application Number	Approval Date
Dry powder inhaler	ProAir RespiClick	NDA 205636	March 31, 2015
Metered aerosol	ProAir HFA	NDA 021457	October 29, 2004
	Ventolin HFA	NDA 020983	April 19, 2001
Inhalation solution	Albuterol inhalation solution for nebulization	Multiple ANDAs	Original approval of albuterol sulfate: 1981
Oral syrup	Albuterol oral syrup	Multiple ANDAs	
Oral tablets	Albuterol oral tablets	Multiple ANDAs	

1.2 PEDIATRIC REGULATORY HISTORY

May 5, 2014: The sponsor, Teva Branded Pharmaceuticals R&D, Inc. (“Teva”), submitted a New Drug Application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ProAir RespiClick. The 505(b)(2) application relied on the safety and efficacy findings of the reference listed drug (RLD), ProAir HFA (NDA 021457).

January 16, 2015: The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factors study results report and Phase 3 clinical trial complaint reports that were submitted with the NDA.³ The results showed errors associated with use, including not opening the cover fully prior to use and not closing the cover between inhalations. Both errors resulted in the dose not being dispensed to the patient. Additional emphasis on proper administration was recommended for the Instructions For Use (IFU).

March 31, 2015: ProAir RespiClick was approved for use in adults and adolescents 12 years of age and older for the treatment and prevention of bronchospasm and prevention of EIB. Under the Pediatric Research Equity Act (PREA), the following were required:⁴

- A study to assess the pharmacokinetics of ProAir RespiClick in pediatric asthma patients between the ages of 4 to 11 years
- A study to assess the efficacy and safety of two dose levels of ProAir RespiClick in pediatric asthma patients between the ages 4 to 11 years
- A study to assess the chronic dose efficacy and safety of ProAir RespiClick in pediatric asthma patients between the ages 4 to 11 years

Pediatric study requirements for ages birth to 3 years were waived due to the studies being impossible or highly impracticable in this age group.

June 29, 2015: Teva submitted a supplemental NDA 205636/S-004 to expand the indication of ProAir RespiClick to include pediatric patients age 4 years and older. The required PREA trials were submitted as part of this application and are summarized in Table 1.1.2. Trials for EIB were not conducted in the pediatric population ages 4 to 11 years; therefore, the sponsor extrapolated data from the clinical studies in this age group as well as prior data obtained for EIB in patients 12 years of age and older. The FDA Clinical Review of the submitted pediatric clinical trial data did not identify any new or important safety signals with the use of ProAir RespiClick.⁵

Table 1.2.1 Pediatric Clinical Trials

Study Number	Subjects	Intervention	Study Design	Purpose
NCT01844401 ⁶	15	<ul style="list-style-type: none"> • Albuterol MDPI • ProAir HFA 	<ul style="list-style-type: none"> • Open-label, crossover study • Children ages 4-11 • Persistent asthma 	Compare the pharmacokinetic profiles after administration of a single inhaled dose of 180 mcg albuterol base
NCT01899144 ⁷	61	<ul style="list-style-type: none"> • Albuterol MDPI • ProAir HFA 	<ul style="list-style-type: none"> • Randomized, double blind, double dummy, placebo controlled, single dose, 5-way crossover study • Children ages 4-11 • Persistent asthma 	Compare the efficacy and safety in pediatric asthma patients at two delivered dose levels equivalent to 90 mcg and 180 mcg of albuterol base
NCT02126839 ⁸	185	<ul style="list-style-type: none"> • Albuterol MDPI • Placebo 	<ul style="list-style-type: none"> • Randomized, double blind, placebo controlled, three week chronic-dose • Children ages 4-11 • Persistent asthma 	Evaluate the chronic-dose efficacy and safety of albuterol MDPI compared to placebo in pediatric participants with asthma

MDPI: multi-dose dry powder inhaler

April 28, 2016: The ProAir RespiClick supplemental NDA was approved to expand the use to pediatric patients 4 to 11 years of age for the treatment and prevention of bronchospasm and prevention of EIB.

1.3 SUMMARY OF RELEVANT PREVIOUS FDA SAFETY REVIEWS

The Division of Pharmacovigilance (DPV) completed a pediatric-focused safety review of Ventolin HFA (albuterol sulfate, NDA 020983, GlaxoSmithKline) on August 27, 2008. DPV searched the Adverse Event Reporting System (AERS) database for all reports with NDA 020983 from April 19, 2001 (U.S. approval date) through April 15, 2009.⁹⁻¹⁰ The review of reports in the AERS database did not identify any new safety signals in the age group of 4 to 16 years of age or in the adult population. Two foreign cases of Stevens-Johnson syndrome (SJS) were identified (see Appendix A for a summary of the previously identified cases); however, the causal relationship of Ventolin HFA in the two cases were confounded by concurrent events (viral illness, concomitant ofloxacin use). The results of the review were presented at the December 8, 2009 Pediatric Advisory Committee (PAC) meeting as a Standard Review of Adverse Events. All Committee members (16) voted for routine, ongoing post-marketing safety monitoring for all adverse events including SJS. In addition, warnings were added to the label for pediatric patients 0 to 4 years of age due to lack of efficacy in this population (voting for warning in ages 0 to 4 years of age: 14 yes, 1 no, 1 abstained).¹¹

On June 12, 2017, DPV in the Office of Surveillance and Epidemiology (OSE) and the Office of New Drugs (OND) completed a FDAAA Section 915 Non-New Molecular Entity (non-NME) Postmarket Safety Summary Analysis for ProAir RespiClick.¹² DPV searched the FDA Adverse Event Reporting System (FAERS) database for all adverse event reports with ProAir RespiClick from March 31, 2015 to September 30, 2016. The FAERS search strategy identified 360 reports, of which the majority were associated with a non-serious outcome (335 of the 360 reports). Reports of product quality issues were identified through the FAERS search and the Sponsor's periodic reporting, therefore the Office of Product Quality (OPQ) was consulted to investigate the issue. An analysis by the Sponsor in response to an Information Request from OPQ determined that the reports appeared to be related to patients' misunderstanding of the IFU (once the dose indicator reaches "0", no medication will come out). OPQ concluded that there appears to be no drug product quality issue and no additional safety signals were identified in the non-NME Postmarket Safety Summary Analysis.

1.4 HIGHLIGHTS OF LABELED SAFETY ISSUES

The labeling for ProAir RespiClick dated 09/2016 contains the following safety highlights:¹

-----CONTRAINDICATIONS-----

- Patients with hypersensitivity to albuterol.
- Patients with severe hypersensitivity to milk proteins.

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

- Life-threatening paradoxical bronchospasm may occur. Discontinue PROAIR RESPICLICK immediately and treat with alternative therapy.
- Need for more doses of PROAIR RESPICLICK than usual may be a sign of deterioration of asthma and requires reevaluation of treatment.
- PROAIR RESPICLICK is not a substitute for corticosteroids.
- Cardiovascular effects may occur. Use with caution in patients sensitive to sympathomimetic drugs and patients with cardiovascular or convulsive disorders.
- Excessive use may be fatal. Do not exceed recommended dose.
- Immediate hypersensitivity reactions may occur. Discontinue PROAIR RESPICLICK immediately.
- Hypokalemia and changes in blood glucose may occur.

-----**ADVERSE REACTIONS**-----

- Most common adverse reactions ($\geq 1\%$ and $>$ placebo) are back pain, pain, gastroenteritis viral, sinus headache, urinary tract infection, nasopharyngitis, oropharyngeal pain and vomiting.

-----**DRUG INTERACTIONS**-----

- Other short-acting sympathomimetic aerosol bronchodilators and adrenergic drugs: May potentiate effect.
- Beta-blockers: May decrease effectiveness of PROAIR RESPICLICK and produce severe bronchospasm. Patients with asthma should not normally be treated with beta-blockers.
- Diuretics, or non-potassium sparing diuretics: May potentiate hypokalemia or ECG changes. Consider monitoring potassium levels.
- Digoxin: May decrease serum digoxin levels. Consider monitoring digoxin levels.
- Monoamine oxidase (MAO) inhibitors and tricyclic antidepressants: May potentiate effect of albuterol on the cardiovascular system. Consider alternative therapy in patients taking MAOs or tricyclic antidepressants.

-----**USE IN SPECIFIC POPULATIONS**-----

- **Pediatric Use:** The safety and effectiveness of PROAIR RESPICLICK for the treatment or prevention of bronchospasm in children 12 to 17 years of age and older with reversible obstructive airway disease is based on two 12-week clinical trials in 318 patients 12 years of age and older with asthma comparing doses of 180 mcg four times daily with placebo, one long-term safety study in children 12 years of age and older and one single-dose crossover study comparing doses of 90 and 180 mcg with albuterol sulfate inhalation aerosol (ProAir® HFA) in 71 patients. The safety and effectiveness of PROAIR RESPICLICK for treatment of exercise-induced bronchospasm in children 12 years of age and older is based on one single-dose crossover study in 38 patients age 16 and older with exercise-induced bronchospasm comparing doses of 180 mcg with placebo. The safety profile for patients ages 12 to 17 was consistent with the overall safety profile seen in these studies.
The safety of PROAIR RESPICLICK in children 4 to 11 years of age is based on two single-dose, controlled, crossover studies: one with 61 patients comparing doses of 90 and 180 mcg with matched placebo and albuterol HFA MDI and one with 15 patients comparing a dose of 180 mcg with matched albuterol HFA MDI; and one 3-week clinical trial in 185 patients 4 to 11 years of age with asthma comparing a dose of 180 mcg four times daily with matched albuterol HFA MDI. The effectiveness of PROAIR RESPICLICK in children 4 to 11 years with exercise-induced bronchospasm is extrapolated from clinical trials in patients 12 years of age and older with asthma and exercise-induced bronchospasm, based on data from a single-dose study comparing the bronchodilatory effect of PROAIR RESPICLICK 90 mcg and 180 mcg with placebo in 61 patients with asthma, and data from a 3-week clinical trial in 185 asthmatic children 4 to 11 years of age comparing a dose of 180 mcg albuterol 4 times daily with placebo.
The safety and effectiveness of PROAIR RESPICLICK in pediatric patients below the age of 4 years have not been established.

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 2.1.1 to identify pediatric adverse event reports with ProAir RespiClick. See Appendix B for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy

Date of Search	December 1, 2017
Time Period of Search	March 31, 2015* - October 28, 2017
Search Type	Product-Manufacturer Reporting Summary (Profile report)
Product Name(s)	Product Name: ProAir RespiClick NDA: 205636
Search Parameters	All ages, all outcomes, worldwide

* Start date selected is U.S. approval date for ProAir RespiClick

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS Reports* from March 31, 2015 through October 28, 2017 with ProAir RespiClick

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	118 (118)	24 (24)	0 (0)
Pediatrics (0 - <17 years)	27 (27)	4 [‡] (4)	0 (0)

* May include duplicates and transplacental exposures, and have not been assessed for causality

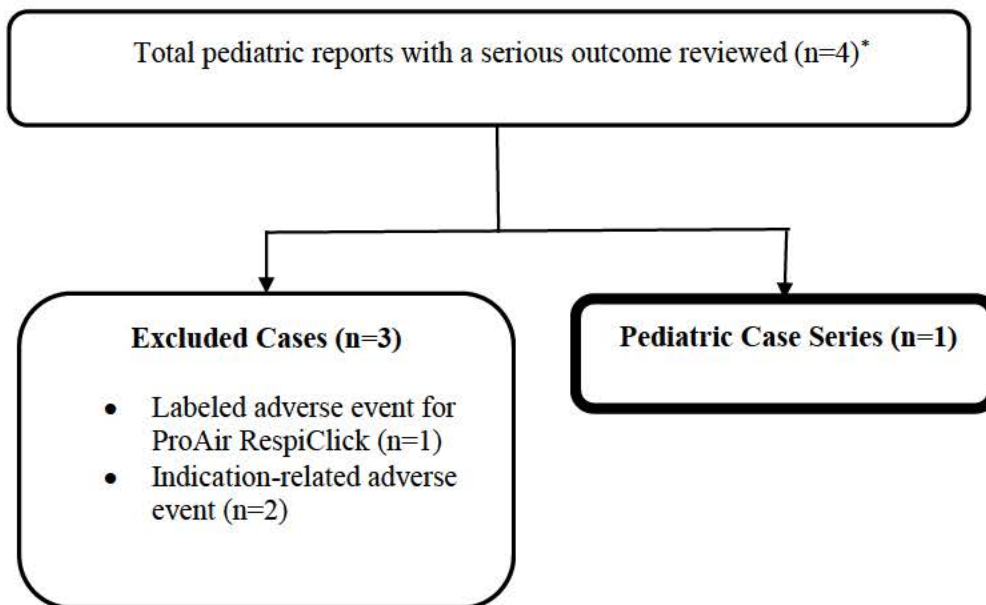
[†] For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

[‡] See Figure 3.2.2

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified four pediatric reports with a serious outcome (See Table 2.2.1). See **Figure 2.2.2** below for the specific selection of cases to be summarized in **Sections 2.3 and 2.4**.

Figure 2.2.2 Selection of Serious Pediatric Cases with ProAir RespiClick



* There were no pediatric reports with the outcome of death

Of the four pediatric reports with serious outcomes, one was included in our case series and the remaining three were excluded. Two excluded reports described indication-related labeled adverse events; one reported an asthma exacerbation requiring an emergency department visit and treatment despite intervention with ProAir RespiClick (labeled in section 5.2, Deterioration of Asthma) and the second report contained minimal information about assessment of a patient’s pulmonary function which did not show test improvement after treatment with ProAir RespiClick (lack of efficacy is labeled in section 6.2, Postmarketing Experience). These two reports were associated with the serious outcome of other serious important medical event. One excluded report with the serious outcome of life-threatening described a patient with a dairy allergy who developed anaphylaxis after receiving ProAir RespiClick. The formulation of the dry-powder inhalant used in ProAir RespiClick contains alpha-lactose monohydrate.¹ The use of ProAir RespiClick is labeled to avoid use with severe hypersensitivity to milk proteins (section 4, Contraindications) and it also states in the label that ProAir RespiClick contains small amounts of lactose, which may contain trace levels of milk proteins (section 5.6, Immediate Hypersensitivity Reactions).

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

No pediatric deaths were reported with ProAir RespiClick in the FAERS database from March 31, 2015 through October 28, 2017.

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

2.4.1 Renal and Urinary Disorders (N=1)

Urinary Incontinence

Case #12750772, serious outcome—other serious important medical event, United States, 2016: A patient's mother reported that her 12-year-old daughter used ProAir RespiClick for asthma prior to a two-mile, fast-paced cross country race. Upon completion of the race, she lost control of her bladder twice. It was reported that the patient's urinalysis did not show signs of infection. No past medical history or concomitant medications were reported. Prior to the initiation of ProAir RespiClick, the patient had participated in a race without incontinence a week earlier than the reported event; however, she experienced an asthma attack.

Reviewer Comment: This case reports a temporal relationship between the use of ProAir RespiClick and the adverse event of urinary incontinence. However, this case is confounded by the patient's participation in exertional activity. Urinary incontinence is associated with physical activity, particularly in females.¹³ This single report does not represent a new safety signal.

2.5 STEVENS-JOHNSON SYNDROME

SJS was identified previously as a potential safety signal during the review of pediatric safety for Ventolin HFA (albuterol sulfate, NDA 020983).¹⁰ SJS is not contained in the product labeling for albuterol inhalation products, but is included within the product labeling for albuterol tablets and oral solution in the Warnings: Immediate Hypersensitivity Reaction section.^{14,15} As noted above, we did not identify any pediatric reports of SJS with ProAir RespiClick. However, on November 14, 2017, a Medical Officer in the Office of Pediatric Therapeutics (OPT) performed a literature search to identify any safety issues in the pediatric population with albuterol to inform DPV-I during completion of this safety review. The literature search was conducted in PubMed and Embase for the date range of March 31, 2015 to October 28, 2017. OPT identified a single literature article of SJS associated with albuterol use published in 2017. Tracked Safety Issue (TSI) # 1870 was opened to address the safety issue of albuterol sulfate and SJS.

DPV-I reviewed the FAERS database for all reports in the pediatric and adult population of SJS associated with albuterol use through January 19, 2018 and identified three cases, of which two occurred in pediatric patients. All cases were associated with the serious outcome of hospitalization. One identified case was domestic in origin and two were foreign. Each case was limited by an alternative cause or confounding factor including concomitant ibuprofen use, concomitant fluticasone use, and viral illness. Additionally, the labeling of oral albuterol products for SJS was based on one foreign case reported in 1992; this case was limited by a possible alternative etiology of concomitant erythromycin and missing clinical information regarding albuterol withdrawal, which does not allow for assessment of dechallenge. As a result

of the review, it was recommended to continue routine pharmacovigilance and TSI # 1870 was closed.

3 DISCUSSION

Numerous albuterol products are currently available on the U.S. market with over three decades of experience of use. ProAir RespiClick's approval provided a novel administration mechanism—a dry-powder, inhalation-activated inhaler—for this active ingredient. For this Pediatric Postmarketing Pharmacovigilance review, we reviewed all pediatric reports of serious adverse events with ProAir RespiClick from the initial U.S. approval on March 31, 2015 through October 28, 2017. We identified one serious unlabeled case of urinary incontinence; however, this case is confounded by the patient's participation in exertional activity and does not represent a new safety signal. We will continue postmarket surveillance for all adverse events with ProAir RespiClick.

In a prior pediatric safety review of inhaled albuterol (Ventolin HFA, NDA 020983), SJS was identified in one pediatric patient and in one adult patient. These cases were confounded by viral illness and concomitant administration of a fluoroquinolone antibiotic respectively. Additionally, enteral formulations of albuterol are currently labeled for SJS. For completeness, we searched FAERS for cases of SJS with albuterol administered via inhalation and identified three additional cases. Each case was limited by an alternative cause or confounding factor. After a considering the totality of available data, DPV-I recommended routine pharmacovigilance.

4 CONCLUSION

We did not identify any new safety signals specific to ProAir RespiClick in pediatric patients.

5 RECOMMENDATIONS

DPV will continue routine pharmacovigilance monitoring for all adverse events with ProAir RespiClick in pediatric patients.

6 APPENDICES

6.1 APPENDIX A: SJS CASE SUMMARIES FROM THE PEDIATRIC POSTMARKETING ADVERSE EVENT REVIEW, AUGUST 6, 2009¹⁰

ISR#4893729 (Foreign)

A report of Stevens-Johnson syndrome in a 10-year-old male who received Ventolin HFA over a period of 4 days for reversible airway obstruction. Prior medical history included a viral infection of unknown nature, duration, or treatment. The patient was receiving no concomitant medications. Approximately 1 day after initiation of therapy with Ventolin HFA the patient stopped eating and experienced mouth ulcer, facial pallor, skin blisters and genital blisters. The child was hospitalized and was determined by the doctor to have Stevens-Johnson syndrome. Treatment with Ventolin HFA was discontinued and at the time of reporting, the events were resolving.

ISR#5177054 (Foreign)

A report of Stevens-Johnson syndrome in a 35-year-old female patient who received Ventolin HFA over a period of five days for pneumopathy. Prior medical history included urinary infection. Co-suspect medication included ofloxacin. On the evening following administration of Ventolin HFA and ofloxacin, blisters appeared in the patient's mouth. Treatment with Ventolin HFA and ofloxacin was continued. The following days the patient experienced bilateral conjunctivitis, stomatitis, cheilitis, urethral and vaginal mucous disorder, anorexia and dehydration. The patient was hospitalized and Stevens-Johnson syndrome was diagnosed. Treatment with Ventolin HFA and ofloxacin was discontinued. The events were resolved without sequelae within 15 days after onset. *The contribution from Ventolin HFA to the occurrence of Stevens-Johnson syndrome in the two cases described above cannot be excluded based on the temporal relationship of the event and the initiation of therapy with Ventolin HFA.*

6.2 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 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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