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:	May 31, 2018
Safety Evaluator:	Michelle Hines, PharmD Division of Pharmacovigilance I (DPV-I)
Medical Officer:	Ivone Kim, MD, FAAP DPV-I
Team Leader:	Lisa Harinstein, PharmD DPV-I
Deputy Division Director:	Monica Muñoz, PharmD, MS, BCPS DPV-I
Product Names:	Xopenex HFA inhalation (levalbuterol tartrate); Xopenex inhalation solution (levalbuterol hydrochloride)
Pediatric Labeling Approval Date:	Xopenex HFA inhalation (March 12, 2015); Xopenex inhalation solution (January 22, 2015)
Application Type/Number:	Xopenex HFA inhalation, NDA 021730; Xopenex inhalation solution, NDA 020837
Applicant/Sponsor:	Xopenex HFA inhalation, Sunovion; Xopenex inhalation solution, Oak Pharmaceuticals, Inc.
OSE RCM #:	2017-1403

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for Xopenex Inhalation Solution (IS) (levalbuterol hydrochloride) and Xopenex HFA (levalbuterol tartrate) in pediatric patients. This review was triggered by the pediatric indications for Xopenex IS and Xopenex HFA.

Xopenex IS (NDA 20837) was first approved by the U.S. Food and Drug Administration (FDA) on March 25, 1999 for treatment or prevention of bronchospasm in adults and adolescents 12 years of age and older with reversible obstructive airway disease. On January 30, 2002, the pediatric indication for Xopenex IS was expanded to children 6 years of age and older. On January 22, 2015, the product labeling for Xopenex IS was updated to state that it is not indicated for pediatric patients less than 6 years of age. Xopenex HFA (NDA 21730) was approved on March 11, 2005 for treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease. On March 12, 2015, the product labeling for Xopenex HFA was updated to state that it is not indicated for use in pediatric patients less than 4 years of age.

We evaluated all pediatric postmarketing adverse event reports with a serious outcome for levalbuterol in the FDA Adverse Event Reporting System (FAERS) database from October 1, 2013 to July 13, 2017. The pediatric postmarketing safety of Xopenex IS and Xopenex HFA was previously reviewed as part of the clinical review of supplemental NDA (sNDA) 20837/S-041 and sNDA 21730/S-036, respectively, by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP); Xopenex IS was reviewed from approval (March 25, 1999) through October 4, 2013 and Xopenex HFA was reviewed from January 2006 through September 2013. The start date of October 1, 2013 was chosen to capture all reports from the data lock date of the previous DPARP medical officer reviews. After review of all 16 serious pediatric postmarketing reports, none were included in the case series.

Of the 16 reports, six had an outcome of death; five were duplicates of a single report from a foreign literature article that describes adverse drug reactions of botulinum neurotoxin type A in children with cerebral palsy reported to the VigiBase database.[1] The single case reported that a 7-year-old female with a history of cerebral palsy experienced seizure, muscular weakness, pneumonia, and death during receipt of the following medications: acetaminophen, baclofen, botulinum neurotoxin type A, budesonide, cetirizine, clonidine, clorazepate, diazepam, gabapentin, gentamicin, ibuprofen, ipratropium, lactulose, levalbuterol, levetiracetam, metoclopramide, ranitidine, and valproic acid. The authors did not provide additional information pertaining to her hospital course or a causality assessment for levalbuterol and death; however, the fatal event was unlikely related to levalbuterol.

Of the remaining 10 reports, six contained limited information to assess causality and four described adverse events included in the product labeling for Xopenex IS and HFA; none of the four cases containing labeled adverse events resulted in hospitalization. The labeled adverse events[a] in the four reports included dizziness, trembling, rapid breathing or heart rate, and worsening asthma symptoms; no change in frequency or severity of any of the adverse events was noted during review of the reports.

No new safety signals were identified with Xopenex IS or Xopenex HFA. The Division of Pharmacovigilance I (DPV-I) will continue postmarketing surveillance of all adverse events with the use of Xopenex IS and Xopenex HFA in pediatric and adult patients.

[a] A report may contain one or more adverse events.

1 INTRODUCTION

This review evaluated postmarketing adverse event reports with a serious outcome for two levalbuterol products, Xopenex Inhalation Solution (IS) and Xopenex HFA, in pediatric patients. This review was triggered by the pediatric indications for Xopenex IS (levalbuterol hydrochloride) and Xopenex HFA (levalbuterol tartrate).

Throughout this document, levalbuterol hydrochloride is referred to as Xopenex IS and levalbuterol tartrate is referred to as Xopenex HFA.

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Levalbuterol, the (R)-enantiomer of albuterol, is a relatively selective beta$_2$-adrenergic receptor agonist indicated for the treatment or prevention of bronchospasm in patients with reversible obstructive airway disease.[2,3] Xopenex IS and HFA can be differentiated by formulation and approved indication and usage (see Table 1.1.1).

Table 1.1.1 **Levalbuterol Product Formulations and Approval Information**

Trade name	**Generic name**	**NDA**	**Delivery mechanism**	**Original approval date**	**Approved indication**
Xopenex IS	Levalbuterol hydrochloride	020837	Unit-dose vial for nebulization	March 25, 1999	Treatment or prevention of bronchospasm in patients ≥6 years of age with reversible obstructive airway disease
Xopenex HFA	Levalbuterol tartrate	021730	Pressurized, metered-dose aerosol that utilizes the propellant HFA-134a	March 11, 2005	Treatment or prevention of bronchospasm in patients ≥4 years of age with reversible obstructive airway disease

1.2 PEDIATRIC REGULATORY HISTORY[b]

March 25, 1999: Xopenex IS (levalbuterol hydrochloride/NDA 020837) was FDA-approved for the treatment or prevention of bronchospasm in adults and adolescents 12 years of age and older with reversible obstructive airway disease.

March 16, 2000: FDA issued Pediatric Written Request (WR) #1 for Xopenex IS (IND #47363) for patients aged <6 years.

March 29, 2001: Sponsor of Xopenex IS submitted supplemental NDA (sNDA) 20837/S-006 to FDA, which provides efficacy data for use in children for the treatment or prevention of bronchospasm associated with reversible obstructive airway disease.

January 30, 2002: FDA approved Xopenex IS sNDA 20837/S-006, which extended the indication for Xopenex IS to children 6 to 11 years of age based on efficacy data from phase 3 study 051-031A. A new 0.31 mg dose formulation was approved for use in children 6 to 11 years of age.

June 30, 2002: FDA issued Pediatric WR #2 for Xopenex IS (IND #47363).

March 11, 2005: Xopenex HFA (levalbuterol tartrate/NDA 21730) was approved for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease. A pediatric postmarketing commitment (PMC) was issued under the Pediatric Research Equity Act (PREA) to study the treatment of bronchospasm in children with reversible obstructive airways in pediatric patients ages 0 to <4 years.

August 4, 2005: FDA issued Pediatric WR #3 for Xopenex IS (IND #47363).

December 14, 2005: The Sponsor of Xopenex IS notified FDA of the plan to not fulfill the WRs for Xopenex IS.

November 14, 2012: FDA issued a Deferral Extension Notice to the Sponsor of Xopenex IS regarding the outstanding PREA requirement.

June 13, 2013: FDA issued a Notification of Non-Compliance with PREA to the Sponsor of Xopenex IS for failure to submit the pediatric assessment.

March 28, 2014: The Sponsor of Xopenex IS submitted sNDA 20837/S-041 to FDA, which contained clinical data from five pediatric studies which enrolled patients under 6 years of age with asthma or reactive airway disease. Because the studies were not part of a planned pediatric

[b] The pediatric regulatory history was adapted from Dr. Stacy Chin's clinical review of pediatric efficacy supplement NDA 20837/S-041 completed on December 19, 2014.

development program, the studies varied in design and utility to the efficacy and safety evaluation.

May 27, 2014: The Sponsor of Xopenex HFA submitted sNDA 21730/S-036, which proposed to update the product labeling with data to support the safe and effective use of the product in the treatment of bronchospasm in pediatric patients 0 to 4 years of age and to fulfill the PREA requirement outlined in the March 11, 2005 approval letter.

January 22, 2015: FDA approved Xopenex IS sNDA 20837/S-041, which provided a description of pediatric studies in children less than 6 years of age. The product labeling for Xopenex IS was updated to state that it is not indicated for use in pediatric patients less than 6 years of age. S-041 fulfilled the outstanding PREA requirement. Efficacy was not established in one adequate and well controlled trial in 291 pediatric patients from 2 to 5 years of age, and another adequate and well controlled trial of 88 pediatric patients from birth to less than 2 years.[4] Adverse reactions in both studies were consistent with adverse reactions in patients 6 years of age and older; however, there was an increase in asthma-related adverse reactions following chronic Xopenex IS treatment compared to control.

March 12, 2015: FDA approved Xopenex HFA sNDA 21730/S-036, which provided a description of pediatric study 051-359. The product labeling for Xopenex HFA was updated to state that it is not indicated for use in pediatric patients less than 4 years of age.[5] S-036 fulfilled the PREA requirement. Study 051-359, a PREA-required study in patients less than 4 years of age, was a modified-blind, placebo-controlled study that evaluated the effectiveness of Xopenex HFA 45 to 90 micrograms three times daily for 4 weeks versus placebo for reducing asthma symptoms. The study failed to meet the primary endpoint as there was no difference in Pediatric Asthma Caregiver Assessment score change from baseline at 4 weeks between groups. Regarding safety, a small increase in asthma-related treatment-emergent adverse events and discontinuations due to asthma was identified in patients who received Xopenex HFA compared to placebo. The Sponsor was released from the PREA-required study 051-361 because the study would not provide additional safety or efficacy data for Xopenex HFA beyond what was obtained and included in the product labeling.

1.3 SUMMARY OF RELEVANT PREVIOUS FDA SAFETY REVIEWS

February 14, 2003: The Division of Drug Risk Evaluation reviewed the pediatric postmarketing safety of Xopenex IS. The Adverse Event Reporting System (AERS) database was searched for all pediatric adverse events cases through January 27, 2003; 122 cases in pediatric patients less than 17 years of age were retrieved. Of the 122 cases, 75 resulted from unapproved use in patients younger than 6 years of age, including 35 cases in patients younger than 2 years of age. The most commonly reported pediatric events involved signs and symptoms of beta-adrenergic agonist overdose and hypersensitivity reactions. There were three deaths in children, including a

3-month-old infant, a 6-month-old infant, and a 15-year-old boy; however, the role of levalbuterol in the deaths was unclear, but unable to be ruled out.

December 19, 2014: The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) reviewed the pediatric postmarketing safety of Xopenex IS as part of sNDA 20837/S-041.[6] From market introduction (March 25, 1999) through October 4, 2013, a total of 809 postmarketing events were spontaneously reported for Xopenex IS. The most frequently reported events included: cough, psychomotor hyperactivity, drug ineffective, rash, tremor, increased hart rate, urticaria, and vomiting. There was one report of sudden death in a 3-month-old with reactive airway disease who received two administrations of Xopenex IS 0.63 mg. The cause of death was listed as sudden infant death syndrome associated with bronchiolitis. Asthma-related adverse events reported with off-label use of Xopenex IS in children under 6 years of age were generally similar to the adverse event profile observed in controlled clinical studies in this age group. The small number of events in the 6 years and younger age group did not support inclusion of "Do not recommend" language for this age group in the Pediatric Use section of the Xopenex IS label.

May 27, 2015: DPARP reviewed the pediatric postmarketing safety of Xopenex HFA as part of sNDA 21730/S-036.[7] From January 2006 to September 2013, a total of 8 postmarketing events were spontaneously reported in patients below 4 years of age, and 34 events were reported in patients 4 to 6 years of age. The most frequently reported events included: cough, drug ineffective, wheezing, asthma, dyspnea, and vomiting. Asthma-related adverse events reported with off-label use of Xopenex HFA in children under 4 years of age were generally similar to the adverse event profile observed in controlled clinical studies in this age group. The small number of events in the 4 years and younger age group did not support inclusion of "Do not recommend" language for this age group in the Pediatric Use section of the Xopenex HFA label.

1.4 HIGHLIGHTS OF LABELED SAFETY ISSUES[1,2]

Xopenex IS and HFA are FDA-approved for use in pediatric patients. The Xopenex IS labeling dated January 22, 2015 and the Xopenex HFA labeling dated February 27, 2017 contain similar safety highlights. Selected safety highlights from the Xopenex IS label are listed below:

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

- Hypersensitivity to levalbuterol, racemic albuterol, or any component of the product

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

- Life-threatening paradoxical bronchospasm may occur. Discontinue XOPENEX Inhalation Solution immediately and treat with alternative therapy. (5.1)
- Need for more doses of XOPENEX Inhalation Solution than usual may be a sign of deterioration of asthma and requires reevaluation of treatment. (5.2)
- XOPENEX Inhalation Solution is not a substitute for corticosteroids. (5.3)
- Cardiovascular effects may occur. Consider discontinuation of XOPENEX Inhalation Solution if these effects occur. Use with caution in patients with underlying cardiovascular disorders. (5.4)
- Excessive use may be fatal. Do not exceed recommended dose. (5.5)
- Immediate hypersensitivity reactions may occur. Discontinue XOPENEX Inhalation Solution immediately. (5.6)

- Hypokalemia and changes in blood glucose may occur. (5.7, 5.8)

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

- XOPENEX Inhalation Solution: Most common adverse reactions are palpitations, chest pain, tachycardia, headache, dizziness, tremor, and nervousness. (6)

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

- Other short-acting sympathomimetic aerosol bronchodilators and adrenergic drugs: May potentiate effect. (7.1)
- Beta-blockers: May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. Patients with asthma should not normally be treated with beta-blockers. (7.2)
- Diuretics: May worsen electrocardiographic changes or hypokalemia associated with diuretics may worsen. Consider monitoring potassium levels. (7.3)
- Digoxin: May decrease serum digoxin levels. Consider monitoring digoxin levels. (7.4)
- Monoamine oxidase inhibotors (MAOs) or tricyclic antidepressants: May potentiate effect of albuterol on the cardiovascular system. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants. (7.5)

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The Division of Pharmacovigilance I (DPV-I) searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy

Date of Search	July 13, 2017
Time Period of Search	October 1, 2013* to July 13, 2017
Search Type	Quick Query Product-Manufacturer Reporting Summary
Product Active Ingredients	Levalbuterol, levalbuterol hydrochloride, levalbuterol tartrate
Search Parameters	All ages, all outcomes, worldwide

* The pediatric postmarketing safety of Xopenex IS and HFA was previously reviewed as part of the clinical review of sNDA 20837/S-041 and sNDA 21730/S-036, respectively, by DPARP; Xopenex IS was reviewed from approval (March 25, 1999) through October 4, 2013 and Xopenex HFA was reviewed from January 2006 through September 2013. This start date was chosen to capture all reports from the data lock date of the previous DPARP clinical reviews (see section 1.3 for results of the reviews).

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Number of Adult and Pediatric FAERS Reports* from October 1, 2013 to July 13, 2017 with Levalbuterol, Levalbuterol Hydrochloride, and Levalbuterol Tartrate

	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥17 years)	105 (105)	50 (50)	3 (3)

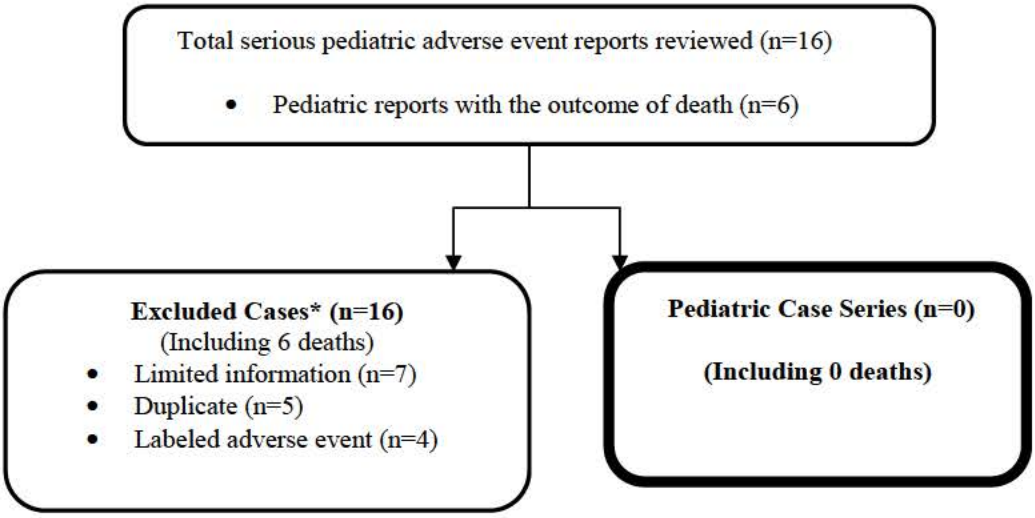
Table 2.2.1 Number of Adult and Pediatric FAERS Reports from October 1, 2013 to July 13, 2017 with Levalbuterol, Levalbuterol Hydrochloride, and Levalbuterol Tartrate*			
Pediatrics (0 to <17 years)	26 (23)	16‡ (13)	6 (3)

* May include duplicate reports and transplacental exposures; reports 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 2.2.2

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 16 serious pediatric adverse event reports out of 26 total pediatric adverse event reports (See Table 2.2.1) for levalbuterol from October 1, 2013 to July 13, 2017. See **Figure 2.2.2** below for the specific selection of cases.

Figure 2.2.2 Selection of Serious Pediatric Cases with Levalbuterol



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

Of the 16 reports, six had an outcome of death; five were duplicates of a single report from a foreign literature article that describes adverse drug reactions of botulinum neurotoxin type A in children with cerebral palsy reported to the VigiBase database.[1] The single case reported that a 7-year-old female with a history of cerebral palsy experienced seizure, muscular weakness, pneumonia, and death during receipt of the following medications: acetaminophen, baclofen, botulinum neurotoxin type A, budesonide, cetirizine, clonidine, clorazepate, diazepam, gabapentin, gentamicin, ibuprofen, ipratropium, lactulose, levalbuterol, levetiracetam, metoclopramide, ranitidine, and valproic acid. The authors did not provide additional information pertaining to her hospital course or a causality assessment for levalbuterol and death.

Of the remaining 10 reports, six contained limited information to assess causality and four described adverse events included in the product labeling for Xopenex IS and HFA; none of the four cases containing labeled adverse events resulted in hospitalization. The labeled adverse events[c] in the four reports included dizziness, trembling, rapid breathing or heart rate, and worsening asthma symptoms; no change in frequency or severity of any of the adverse events was noted during review of the reports.

3 DISCUSSION

DPV-I evaluated all pediatric postmarketing adverse event reports with a serious outcome for Xopenex IS and Xopenex HFA in the FAERS database from October 1, 2013 to July 13, 2017. The start date of October 1, 2013 was chosen to capture all reports from the data lock date of previous DPARP reviews for NDA 20837/S-041 and NDA 21730/S-036, which reviewed all pediatric postmarketing adverse event reports with Xopenex IS from March 25, 1999 (U.S. approval date) through October 4, 2013 and with Xopenex HFA from January 2006 through September 2013. After review of all 16 serious pediatric postmarketing reports, none were included in the case series; the reports contained limited information for assessment (n=7), were duplicates (n=5), or described a labeled adverse event (n=4). No change in frequency or severity of any of the labeled adverse events was noted during review of the reports.

4 CONCLUSION

DPV-I evaluated all pediatric postmarketing adverse event reports with a serious outcome for Xopenex IS and Xopenex HFA in the FAERS database from October 1, 2013 to July 13, 2017. There is no evidence from these data that there exist pediatric safety concerns with Xopenex IS and Xopenex HFA at this time.

5 RECOMMENDATIONS

DPV-I recommends continuing routine postmarketing surveillance of all adverse events with Xopenex IS and Xopenex HFA in pediatric patients.

6 REFERENCES

1. Montastruc J, Philippe M, Moulis F, et al. Adverse drug reactions of botulinum neurotoxin A in children with cerebral palsy: a pharmaco-epidemiological study in Vigibase. *Dev Med Child Neurol* 2017;59:329-34.

[c] A report may contain one or more adverse events.

2. Xopenex (levalbuterol hydrochloride) [package insert]. Lake Forest, IL: Oak Pharmaceuticals, Inc.; Label revised March 2015.
3. Xopenex HFA (levalbuterol tartrate) [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc.; Label revised February 2017.
4. Xopenex Inhalation Solution. New Pediatric Labeling Information Database. Accessed on January 7, 2018. Available at https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?filter=xopenex&sortColumn=1d&sd=labelingdatabase&page=1
5. Xopenex HFA Inhalation. New Pediatric Labeling Information Database. Accessed on January 7, 2018. Available at https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?filter=xopenex&sortColumn=1d&sd=labelingdatabase&page=1
6. Chin, Stacy J. Supplemental NDA 20-837/S-041 clinical review. *DARRTS* December 20, 2014.
7. Chin, Stacy J. Supplemental NDA 21-730/S-036 clinical review. *DARRTS* February 19, 2015.

7 APPENDIX

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 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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/s/

MICHELLE C HINES
05/31/2018

IVONE E KIM
05/31/2018

LISA M HARINSTEIN
06/01/2018

MONICA MUNOZ
06/01/2018