CLINICAL PHARMACOLOGY REVIEW	
NDA Number:	20-837, Supplement 41
Submission Date:	March 28, 2014
Submission Type:	Standard
Proposed Brand Name:	Xopenex Inhalation Solution
Generic Name:	Levalbuterol hydrochloride inhalation solution
Sponsor:	Oak Pharmaceuticals, Inc. (subsidiary of Akorn, Inc.) ownership transferred from Sunovion Pharmaceuticals Inc. on 10/1/2014
Route of Administration:	Inhalation
Dosage Form:	Aqueous inhalation solution
Dosage Strength:	0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL, and 1.25 mg/0.5 mL unit dose vials
Proposed Dosing Regimen:	0.31 mg to 1.25 mg three times daily
Proposed Indication(s):	Reversible obstructive airway disease
Proposed Population(s):	≥ 6 years of age
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Satjit Brar, Pharm.D., Ph.D.
Team Leader:	Satjit Brar, Pharm.D., Ph.D.

1. EXECUTIVE SUMMARY

Xopenex (levalbuterol hydrochloride) inhalation solution (Xopenex IS), a beta2-adrenergic agonist, is approved for the treatment or prevention of bronchospasm in adults, adolescents and children 6 years of age and older with reversible obstructive airway disease. As requested by the FDA per the Pediatric Research Equity Act (PREA) post-marketing commitment, sponsor investigated the safety and efficacy of Xopenex in pediatric subjects. The purpose of this submission is to provide the reports of pediatric studies conducted to assess the safety and efficacy of Xopenex in subjects less than 6 years of age and to propose revisions to the currently approved labeling based on the outcomes of these studies.

The Sponsor is not seeking an indication for Xopenex IS in patients less than 6 years of age (b) (4) . However, the Pediatric Use section of the labeling is being updated to include safety information obtained from these studies for subjects less than 6 years of age.

Majority of the adult clinical pharmacology studies, including general clinical pharmacology and dose-ranging studies, have been previously reviewed in NDA 20837 (Clin Pharm review, Dr. Young Moon Choi, DARRTS date 1/24/2002).

In the current submission, conclusions cannot be drawn from the pharmacokinetic information obtained from the clinical trials. Measurable concentrations of (S)-albuterol were present in subjects randomized to the levalbuterol treatment groups despite the protocol-defined use of levalbuterol as rescue medication. In addition, pre-dose concentrations of (R)-albuterol and lack of measureable post-dose concentrations confounded the exposure assessment. The collective information suggests that the pharmacokinetic data obtained from these studies (b) (4)

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the NDA 20-837 Supplement 41, and recommends that no pediatric pharmacokinetic data should be included in the label.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

1.3.1 Background

Sunovion has developed (R)-albuterol (levalbuterol), the (R)-enantiomer of racemic albuterol, for the relief or prevention of bronchospasm in patients with reversible obstructive airway disease. Sunovion Inc. currently markets 3 products that have levalbuterol as the active moiety: levalbuterol inhalation solution (IS), levalbuterol IS concentrate, and levalbuterol HFA. Levalbuterol IS is supplied in 3 mL unit-dose, low-density polyethylene (LDPE) vials as a clear, colorless, sterile, preservative-free, aqueous solution, in three different strengths of levalbuterol (0.31 mg, 0.63 mg, 1.25 mg). Each strength of levalbuterol IS is available in a shelf carton containing one or more foil pouches, each containing 12 unit-dose LDPE vials.

Xopenex IS was approved for the treatment or prevention of bronchospasm in adults and adolescents (12 years of age and older) with reversible obstructive airway disease in March 1999. In January 2002, a

supplement (S-006), which provided for the use of Xopenex Inhalation Solution (Xopenex IS) in children ages 6-11 years of age was approved. FDA deferred the submission of pediatric studies for patients less than 6 years of age. [redacted] (b) (4)

[redacted] (b) (4) submit all outstanding pediatric studies to fulfill PREA requirements, Sunovion and the Division gained agreement to resubmit the studies from [redacted] (b) (4), along with additional data from recently completed pediatric studies including Xopenex IS.

The following 5 clinical studies (2 primary studies and 3 supportive studies) in pediatric subjects were conducted as part of the pediatric development program for Xopenex IS. Primary studies are defined as those sponsored by the sponsor for which Xopenex IS was the primary product for evaluation in the study. Supportive studies are those that were either sponsored by an Investigator or included a Xopenex arm as an active comparator.

The 2 primary studies of levalbuterol (Xopenex IS) in children <6 years of age were as follows:

- Study 051-032 (2 to 5 years): a multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, efficacy, safety, and tolerability study of daily dosing with levalbuterol IS, racemic albuterol, and placebo in pediatric subjects aged 2 to 5 years with asthma (Xopenex IS, NDA 20-837).

- Study 051-033 (birth to 4 years): a multicenter, randomized, double-blind, active-controlled, parallel-group, safety, tolerability, and efficacy study of levalbuterol IS and racemic albuterol in pediatric subjects from birth to 4 years of age presenting to the emergency department (ED) or physician's office with acute reactive airway disease (Xopenex IS, NDA 20-837).

The 3 additional clinical studies considered to provide supportive data regarding the use of levalbuterol in children were as follows:

- Study 091-029 (2 to 11 years): a randomized, double-blind, 2-way cross-over study of arformoterol and levalbuterol IS in pediatric subjects 2-11 years of age with asthma (Brovana, NDA 21-912).

- Study 051-359 (birth to <4 years): a double/blind open-label, randomized, placebo-controlled, multicenter, parallel-group, safety, tolerability, and efficacy study of levalbuterol HFA. Study medication (levalbuterol HFA metered-dose inhaler (MDI) [double-blind], levalbuterol IS [open-label], or placebo HFA [double-blind]) was administered in subjects birth to <4 years with asthma (Xopenex HFA, NDA 21-730).

- Study 051-SRC038 (2 to 17 years): a single-center, randomized, double-blind, efficacy and safety study of levalbuterol IS and racemic albuterol for the treatment of acute asthma in pediatric subjects aged 2 to 17 years in the ED and inpatient asthma care unit of a children's hospital (well-controlled, Investigator-sponsored study) [redacted] (b) (4) and Xopenex IS, NDA 20-837).

Pharmacokinetic assessment was performed in studies 051-032, 051-033, 091-029 and 051-359.

1.3.2 Systemic Exposure by study

1.3.2.1 Study 051-033

Few subjects (n = 8) provided blood samples for PK analyses. Given this small number of subjects, it was difficult to draw conclusions about plasma concentrations of (R)- and (S)-albuterol.

1.3.2.2 Study 091-029

Average pre-dose plasma concentration for the levalbuterol IS 0.63 mg dose group was 0.646 (SD 3.417) pg/mL. Post-dose mean concentrations were 2.402 (SD 15.125) pg/mL at 25 minutes after the first dose, and below the limit of quantitation at 120 minutes and 360 minutes after the first dose as well as at 25 minutes after the second dose. Based on the confounding factor of significant pre-dose concentrations and lack of significant post-dose concentrations for all subjects, conclusions cannot be drawn from this study.

1.3.2.3 Study 051-032 and Study 051-359

In Study 051-032, mean plasma concentrations of (R)-albuterol and (S)-albuterol increased with dose (see table 1 and table 2 below). (S)-albuterol concentrations exceeded (R)-albuterol concentrations by approximately 3- to 5-fold. Of note, measurable concentrations of (S)-albuterol were present in subjects randomized to the levalbuterol treatment groups despite the protocol-defined use of levalbuterol as rescue medication. Although measurable concentrations of (S)-albuterol were observed in these subjects, these concentrations were a small fraction of that observed in the racemic albuterol group.

Table 1 Plasma Concentrations of (R)-Albuterol (pg/mL) by Weight Group and Treatment Group (Study 051-032)

	Treatment Group							
	Levalbuterol 0.31 mg		Levalbuterol 0.63 mg		Racemic Albuterol		Placebo	
	<33 pounds (n=15)	≥33 pounds (n=43)	<33 pounds (n=15)	≥33 pounds (n=36)	<33 pounds (1.25 mg) (n=17)	≥33 pounds (2.5 mg) (n=35)	<33 pounds (n=14)	≥33 pounds (n=36)
(R)-Albuterol (pg/mL)								
Samples drawn prior to randomization (Day -7)								
Predose								
n	4	14	4	9	6	11	4	13
Mean (SD)	69.5 (111.6)	76.3 (163.3)	BLQ	30.0 (50.7)	9.5 (20.6)	40.9 (52.1)	8.0 (10.9)	20.7 (50.1)
Median	22.0	BLQ	BLQ	BLQ	BLQ	26.5	4.5	BLQ
Range	BLQ, 234.0	BLQ, 482.0	BLQ, BLQ	BLQ, 153.0	BLQ, 51.2	BLQ, 175	BLQ, 23.1	BLQ, 181.0
Samples drawn at steady-state (Day 21 or at Early Termination)								
Predose								
n	4	13	7	8	6	8	5	12
Mean (SD)	7.6 (8.9)	44.7 (61.2)	85.3 (96.0)	389.7 (903.5)	38.7 (35.7)	244.4 (151.3)	12.1 (27.1)	15.9 (30.8)
Median	6.8	21.2	41.9	55.4	39.0	233.0	BLQ	BLQ
Range	BLQ, 16.9	BLQ, 198.0	BLQ, 283.0	BLQ, 2620.0	BLQ, 86.8	25.5, 465.0	BLQ, 60.6	BLQ-104.0
30-60 Minutes Postdose								
n	3	10	6	7	6	9	5	10
Mean (SD)	218.3 (86.6)	242.0 (139.3)	438.7 (101.2)	299.2 (157.0)	263.8 (138.6)	1082.9 (612.6)	BLQ	37.1 (47.7)
Median	234.0	184.5	450.0	255.0	321.5	857.0	BLQ	17.0
Range	125.0, 296.0	81.0, 496.0	326.0, 593.0	79.5, 538.0	35.9, 390.0	369.0, 2370.0	BLQ-BLQ	BLQ-123.0
180-360 Minutes Postdose								
n	2	10	6	6	6	9	4	10
Mean (SD)	74.9 (23.3)	94.3 (31.6)	189.6 (106.1)	155.4 (95.8)	317.8 (322.9)	540.8 (145.5)	16.7 (33.4)	21.4 (27.2)
Median	74.9	86.6	149.0	133.5	204.0	524.0	BLQ	11.4
Range	58.4, 91.4	40.0, 150.0	75.9, 362.0	66.3, 317.0	99.7, 955.0	363.0, 818.0	BLQ, 66.9	BLQ, 72.4

Note: For the racemic albuterol treatment group, subjects weighing ≥33 pounds were randomized to 2.5 mg and subjects weighing <33 pounds were randomized to 1.25 mg.
BLQ=below the limit of quantification.

Table 2 Plasma Concentrations of (S)-Albuterol (pg/mL) by Weight Group and Treatment Group (Study 051-032)

	Treatment Group							
	Levalbuterol 0.31 mg		Levalbuterol 0.63 mg		Racemic Albuterol		Placebo	
	<33 pounds (n=15)	≥33 pounds (n=43)	<33 pounds (n=15)	≥33 pounds (n=36)	<33 pounds (1.25 mg) (n=17)	≥33 pounds (2.5 mg) (n=35)	<33 pounds (n=14)	≥33 pounds (n=36)
(S)-Albuterol (pg/mL)								
Samples drawn prior to randomization (Day -7)								
Predose								
n	4	14	4	9	6	11	6	13
Mean (SD)	15.8 (18.6)	564.2 (1512.7)	BLQ	214.7 (478.8)	2.8 (4.6)	225.6 (329.1)	15.9 (19.3)	125.6 (390.1)
Median	13.8	2.8	BLQ	BLQ	BLQ	107.0	12.2	BLQ
Range	BLQ, 35.8	BLQ, 5510.0	BLQ, BLQ	BLQ, 1460.0	BLQ, 11.1	BLQ, 1110.0	BLQ, 39.2	BLQ, 1420.0
Samples drawn at steady-state (Day 21 or at Early Termination)								
Predose								
n	4	13	7	8	6	8	5	12
Mean (SD)	3.0 (5.9)	6.5 (19.6)	11.2 (15.5)	203.7 (360.4)	226.3 (128.9)	1372.1 (833.2)	12.0 (26.8)	31.2 (66.7)
Median	BLQ	BLQ	BLQ	BLQ	237.5	1410.0	BLQ	BLQ
Range	BLQ, 11.8	BLQ, 70.3	BLQ, 35.2	BLQ, 830.0	BLQ, 369.0	143.0, 2390.0	BLQ, 60.0	BLQ, 218.0
30-60 Minutes Postdose								
n	3	10	6	7	6	9	5	10
Mean (SD)	32.4 (44.0)	15.3 (17.4)	19.3 (30.7)	44.1 (95.8)	788.3 (373.8)	3883.3 (2075.5)	BLQ	47.3 (61.9)
Median	9.0	11.0	8.8	11.3	880.0	3720.0	BLQ	13.4
Range	5.0, 83.1	BLQ, 57.5	BLQ, 79.3	BLQ, 261.0	237.0, 1170.0	1840.0, 8340.0	BLQ, BLQ	BLQ, 183.0
180-360 Minutes Postdose								
n	2	10	6	6	6	9	4	10
Mean (SD)	BLQ	3.4 (7.1)	13.4 (6.6)	14.3 (26.2)	1099.0 (596.6)	2970.0 (1319.7)	14.8 (29.6)	22.4 (33.9)
Median	BLQ	BLQ	13.4	4.3	977.0	2540.0	BLQ	BLQ
Range	BLQ, BLQ	BLQ, 22.5	4.0, 21.3	BLQ, 67.0	482.0, 2200.0	1380.0, 4840.0	BLQ, 59.2	BLQ, 95.3

Note: For the racemic albuterol treatment group, subjects weighing ≥33 pounds were randomized to 2.5 mg and subjects weighing <33 pounds were randomized to 1.25 mg.
BLQ=below the limit of quantification.

In Study 051-359, a six-fold increase in median (R)-albuterol concentration was observed in the levalbuterol HFA group and a seven-fold increase was observed in the levalbuterol IS group (Table 3). At 4 hours post-dose, median (R)-albuterol concentration was 81 pg/mL in the levalbuterol HFA group and 59 pg/mL in the levalbuterol IS group. Median (R)-albuterol concentration in the placebo HFA group was around 4.5 to 5.0 pg/mL at post-dose time points. Notably, most subjects in the levalbuterol HFA and levalbuterol IS groups had measureable concentrations of (R)-albuterol prior to dosing at Visit 4, whereas a substantial fraction of pre-dose (R)-albuterol samples were below the limit of quantification in subjects receiving placebo.

For the levalbuterol HFA group, the median (R)-albuterol concentrations at 1 hour post-dose were 123.5 pg/mL and 131.0 pg/mL in subjects 0 to < 24 months and subjects 24 to < 48 months, respectively. For the levalbuterol IS group, median (R)-albuterol concentrations at 1 hour post-dose were 154 pg/mL and 125 pg/mL in subjects 0 to < 24 months and subjects 24 to < 48 months, respectively.

Table 3 Plasma Concentrations (pg/mL) of (R)-Albuterol at Visit 4 (Study 051-359)

Time point		Placebo MDI N = 59	Levalbuterol MDI N = 54	Levalbuterol UDV N = 49
Pre-Dose	N	51	47	45
	Mean (SD)	29.27 (70.154)	67.80 (131.396)	26.49 (26.125)
	Min	1.0	1.0	1.0
	Median	2.50	21.10	17.50
	Max	407.0	825.0	91.6
1 Hour Post Dose	N	53	49	40
	Mean (SD)	118.16 (558.018)	220.87 (326.561)	144.17 (85.106)
	Min	1.0	9.5	5.5
	Median	4.49	130.00	128.50
	Max	4050.0	2170.0	397.0
4 Hours Post Dose	N	48	41	36
	Mean (SD)	38.95 (86.397)	104.66 (88.721)	93.43 (126.771)
	Min	1.0	3.3	19.0
	Median	5.12	81.10	59.55
	Max	512.0	410.0	789.0

Abbreviations: MDI = metered dose inhaler; PK = pharmacokinetic SD = standard deviation; UDV = unit dose vial; LOQ = limit of quantification
The LOQ was 2.0 pg/mL. Plasma concentrations below the LOQ were assigned a value of ½ LOQ or 1 pg/mL.

Reviewer's comments:
Conclusions cannot be drawn from the pharmacokinetic information obtained from the clinical trials. Measurable concentrations of (S)-albuterol were present in subjects randomized to the levalbuterol treatment groups despite the protocol-defined use of levalbuterol as rescue medication. The reasons of the presence of S-albuterol are not clear. While the sponsor claimed that no detectable S-albuterol were observed the earlier study in healthy adults (original NDA 20837 Clin Pharm review, DARRTS date 1/24/2002), the assay was not as sensitive as the present study. The detection limit of S-albuterol was 250 pg/ml in the adult study compared to 2 pg/ml in the present study. Furthermore, in vitro inter-conversion of R-and S-albuterol has been observed at the increased temperature (original NDA 20837 Clin Pharm review, DARRTS date 1/24/2002). Therefore, the possibility of in vivo inter-conversion cannot be ruled out. In addition, pre-dose concentrations of (R)-albuterol and lack of measureable post-dose concentrations confounded the exposure assessment. (b) (4)

3 DETAILED LABELING RECOMMENDATIONS

The sponsor has not suggested any Clinical Pharmacology edits to the current label and the reviewer concurs.

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/s/

SATJIT S BRAR
12/29/2014