CLINICAL PHARMACOLOGY REVIEW	
NDA Number:	21-730, Supplement 36
Submission Date:	May 27, 2014
Submission Type:	Standard
Proposed Brand Name:	Xopenex HFA
Generic Name:	Levalbuterol [redacted] (b) (4) inhalation aerosol
Sponsor:	Sunovion Pharmaceuticals Inc.
Route of Administration:	Inhalation
Dosage Form:	Aqueous inhalation solution
Dosage Strength:	59 mcg of levalbuterol tartrate (equivalent to 45 mcg of levalbuterol free base) from the actuator mouthpiece . Supplied in 15 gram pressurized canister containing 200 actuations and 8.4 gram pressurized canister containing 80 actuations.
Proposed Dosing Regimen:	Two inhalations (90 mcg of levalbuterol) repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient
Proposed Indication(s):	Reversible obstructive airway disease
Proposed Population(s):	patients ages 0 to < 4 years
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 [redacted] (b) (4) inhalation solution, 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 patients 0 to <4 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 4 years of age reportedly due to the fact that efficacy was not consistently demonstrated across studies. 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 should not be incorporated into the label because of these confounding factors.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the NDA 21-730, Supplement 36, 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 HFA is supplied as a pressurized aluminum canister in a box (the canister is labeled with a net weight of 15 g or 8.4 g and contains 200 metered actuations or 80 metered actuations (or

inhalations), respectively. The formulation utilizes the L-tartrate salt of levalbuterol and HFA-134a (hydrofluoroalkane; non-ozone-depleting) as the propellant.

Xopenex HFA 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 on March 11, 2005. At the time of NDA approval, FDA deferred the submission of pediatric studies for ages 0 to < 4 years. Following receipt of the approval letter, Sunovion and the FDA conducted three meetings (10 January 2006, 15 May 2006 and 12 September 2007) to discuss the pediatric development plan to fulfill the PREA post-marketing commitment.

Two sequential studies were agreed upon to fulfill the PREA commitment: Study 1 (051-359) entitled: "A Safety, Efficacy, and Tolerability Study of Daily Dosing with Levalbuterol Tartrate HFA MDI and Placebo in Subjects Aged Birth to <48 Months with Asthma" and Study 2 (051-361) entitled: "A Safety and Tolerability Study of Levalbuterol Tartrate HFA Inhalation Aerosol Metered Dose Inhaler (MDI) In Pediatric Subjects Birth to ≤ 48 Months of Age with Reactive Airways Disease in an Acute Setting". The second study (051-361) will be initiated in the coming year (2014).

Study 051-359 (birth to < 4 Years) is a double-blind (levalbuterol HFA, Placebo)/open-label (levalbuterol IS), randomized, placebo-controlled, multicenter, parallel-group, study of the safety and efficacy of levalbuterol HFA. Study medication (levalbuterol HFA metered-dose inhaler (HFA) [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). The primary objective of this study was to examine the safety and tolerability of levalbuterol HFA. A total of 197 children were randomized and received treatment. Of these subjects a total of 65 subjects were administered levalbuterol HFA: 23 subjects < 2 years of age and 42 subjects ≥ 2 to < 4 years of age. Pharmacokinetic assessment was performed in study 051-359.

1.3.2 Systemic Exposure in Study 051-359

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 1). 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 1 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. The collective information suggests that the pharmacokinetic data obtained from these studies should not be incorporated into the label because of these confounding factors.

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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
02/23/2015