

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-912**

**SUMMARY REVIEW**

**DIVISION DIRECTOR'S MEMORANDUM**

Date: October 6, 2006  
To: NDA 21-912  
From: Badrul A. Chowdhury, MD, PhD  
Director, Division of Pulmonary and Allergy products, CDER, FDA  
Product: Brovana (arformoterol tartrate) Inhalation Solution  
Applicant: Sepracor Inc

**Administrative and Introduction**

Sepracor submitted a 505(b)(1) new drug application (NDA 21-912) on December 8, 2005, (received on December 12, 2005, CDER stamp date), for use of Brovana (arformoterol tartrate) Inhalation Solution for the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The proposed dose is 15 mcg administered twice a day by nebulization. The PDUFA due date for this application is October 12, 2006. Arformoterol is the R,R-enantiomer of formoterol. The R,S racemate mixture is currently marketed in the United States by Schering and Novartis as a dry powder formulation under the tradename Foradil Aerolizer. Foradil Aerolizer is approved for use in asthma in patients 5 years of age and older and for use in COPD patients. Note that Sepracor is only seeking approval in COPD patients. [ ]

[ ] Sepracor has submitted the necessary CMC data, pre-clinical data, and clinical data that support approval of this application. [ ]

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**Chemistry, Manufacturing, and Controls, and Establishment Evaluation**

The drug substance arformoterol is not a new molecular entity; it is the R,R-enantiomer of formoterol. The formulation is an isotonic aqueous solution of arformoterol in saline with pH adjusted to 5.0 with citric acid and sodium citrate. The final drug product is 2-mL solution containing 15 mcg of arformoterol (22 mcg of the tartrate salt) contained in 2.1-mL low-density polyethylene (LDPE) unit-dose vials that are over wrapped individually in [ ] [ ] foul pouches. A carton contains 30 or 60 unit-dose individually pouched vials.

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All DMFs associated with this application are acceptable. The drug substance is manufactured in a Sepracor facility in Canada. The formulation and the final drug product are manufactured by [ ] [ ] All manufacturing and testing facilities associated with this drug product have acceptable EER status.

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There were several CMC issues identified by the CMC review team early in the review period. Those were communicated to Sepracor in a discipline review letter. Sepracor resolved these issues and the CMC team recommends an approval action. I concur with that recommendation.

### **Pharmacology and Toxicology**

Sepracor submitted results from a comprehensive preclinical program with this application. These are reviewed in detail in the PharmTox review of Dr. Robison. The PharmTox team has determined that the submitted pharmacology/toxicology program is adequate and recommends an approval action. I concur with that recommendation. Brief comments on some key preclinical issues are made in the following paragraphs.

Arformoterol is a selective long-acting beta2-adrenergic receptor agonist. In vivo and in vitro binding studies showed that arformoterol preferentially binds to beta2-receptors. It has a two-fold greater potency than R,S-formoterol and has full agonist activity at the beta-2 adrenergic receptor. The S,S enantiomer of formoterol is about 1000-fold less potent than R,R enantiomer of formoterol as a beta2-agonist.

Preclinical toxicology studies with arformoterol showed findings typical of beta agonists. There were dose dependent increases in heart rate and decrease in blood pressure in various animal species. In dogs, high doses caused cardiac ECG changes typical of this class of drug. In dogs, minipigs, and rodents, there were occurrences of arrhythmias and sudden death with histological evidence of myocardial necrosis when arformoterol was administered with methylxanthines. The chronic inhalation toxicology study in rats provided an adequate safety margin for the proposed clinical dose. NOAELs were not established in inhalation toxicology studies with dogs based upon observed cardiac effects (increased heart rate and ventricular ectopic arrhythmias); however, as noted above, these findings were attributed to the exaggerated pharmacological actions of arformoterol and considered monitorable in a clinical setting. Arformoterol was not mutagenic or clastogenic. In 2 year carcinogenicity studies, tumor findings in mice were considered typical of  $\beta_2$ -adrenergic agonists, while for tumor findings in rats, a NOAEL with an adequate safety margin was identified. Arformoterol had no effect on fertility and reproductive performance in rats. Arformoterol was teratogenic in rats and rabbits. These findings in carcinogenicity and reproductive toxicology studies were generally consistent with other beta-adrenergic agonists. The pregnancy category for arformoterol was determined to be C, which is same category for other drugs in this class.

### **Clinical Pharmacology and Biopharmaceutics**

Sepracor submitted results from a comprehensive clinical pharmacology program with this application. The program addressed the key pharmacokinetic issues, such as in vitro studies to assess protein binding and metabolism; pharmacokinetics after single and multiple doses; in vitro and in vivo metabolism; effects of gender, race, age, hepatic impairment, renal impairment; effect on QT and cardiac rhythm; and drug-drug interaction. These studies are reviewed in Dr. Shinja Kim's review. The OCP team has

determined that the submitted studies are adequate and recommends an approval action. I concur with that recommendation. Brief comments on some key clinical pharmacology issues are made in the following paragraphs.

Arformoterol is fairly quickly absorbed from the lung and has a relatively long half-life in the circulation. In COPD patients, the mean T<sub>max</sub> was approximately half-an-hour and the terminal plasma half-life was approximately 26 hours. Arformoterol is primarily metabolized by direct conjugation and secondarily by O-methylation. Pharmacokinetic analyses did not show any significant effects of gender, race, age, or renal impairment. Hepatic impairment increased systemic exposure by 1.3 to 2.4 fold. The magnitude of the effect is not large enough to justify dose adjustment.

Cardiovascular effects of arformoterol including QT effect were assessed in two dose ranging studies (studies 091-021, 091-026) and in pivotal efficacy and safety studies (studies 091-050, 091-051, and 091-060). These studies did not show any meaningful changes in corrected QT interval or other cardiac safety assessment parameters. In these studies, arformoterol treatment resulted in some dose related increase in heart rate and decrease in serum potassium and glucose. These findings are typical of beta-adrenergic agonist drugs.

### **Clinical and Statistical**

#### Overview of the clinical program:

The clinical program for arformoterol inhalation solution was relatively small but appropriate given that the proposed indication is limited to COPD only and that the drug is a single isomer of a racemate that is already approved for the same indication. The pivotal clinical studies included two dose-ranging studies (studies 091-021, and 091-026), two 12-week confirmatory efficacy and safety studies (studies 091-050, and 091-051), and one one-year safety study (study 091-060). Detailed review of these studies can be found in Dr. Durmowicz's medical review, and Dr. Guo's statistical review. The clinical and statistical teams have concluded that the submitted data support efficacy and safety of arformoterol in COPD patients. I concur with that recommendation.

The pivotal clinical studies mentioned above and one clinical pharmacology study comparing systemic exposure from arformoterol and racemic formoterol (study 091-019) are briefly reviewed in the following sections. The design and conduct of these studies are briefly described, followed by efficacy and safety findings and conclusions.

#### Design and conduct of the studies:

Dose ranging studies (studies 091-021 and studies 091-026):

Study 091-021 was double-blind, placebo- and active-controlled, five-way crossover in design, conducted in 8 centers in the United States, in 75 patients with COPD. Patients enrolled in the study had a high degree of reversibility. All patients were required to have 10% reversibility with albuterol; but mean reversibility of patients enrolled in the

study was 20%. Enrolled patients received five individual double-blind single day treatments in five periods with 6-13 day washout between treatment days. The double-blind treatments were arformoterol 9.6 mcg QD, 24 mcg BID, 48 mcg QD, 96 mcg QD, and placebo. In addition, all patients received an open-label single day treatment with salmeterol 42 mcg BID in a separate visit day after the double-blind treatment days. Serial spirometry was done after treatments for assessment of efficacy. Primary efficacy endpoint was time-normalized area under the curve (AUC) for the percent change from predose FEV1 over a 24-hour period. At each treatment visits ECGs, Holter monitoring, clinical laboratory measures, and PK sampling were done, along with safety assessment typical for such a study.

Study 091-026 was multiple-dose, double-blind, dose-ranging, parallel group in design conducted in 31 centers in the United States, in 215 patients with stable moderately severe COPD. Study subjects were 35 years of age and older, with a clinical diagnosis of COPD, at least 15 pack-year cigarette smoking history, baseline FEV1 of 65% or lower, FEV1/FVC of 70% of less, and demonstration of 10% reversibility with albuterol. Enrolled patients were randomized approximately equally to four treatment arms and treated sequentially in two parts, part A and part B, each part lasting for 14 days and separated by 7 days. Treatment arms in part A were arformoterol inhalation solution 5 mcg, 15 mcg, 25 mcg, all dosed BID, and placebo. Treatment arms in part B were arformoterol inhalation solution 15 mcg, 25 mcg, and 50 mcg, all dosed QD, and placebo. Primary efficacy endpoint was time-normalized area under the curve (AUC) for percent change from predose FEV1 over a 12-hour period after 14 treatment days of treatment for part A and over a 24-hour period after the next 14 treatment days for part B. Safety assessment included recording of adverse events, vital signs, physical examination, clinical laboratory measures, ECG, and Holter monitoring. PK sampling was also done.

12-week efficacy and safety studies (studies 091-050, and 091-051):

Study 091-050 was double-blind, double-dummy, multiple dose level, placebo- and active-controlled, parallel group in design conducted in 60 centers in the United States. Study subjects were 35 years of age and older, with a clinical diagnosis of COPD, 15 pack-year cigarette smoking history, baseline FEV1 of 65% or lower, and FEV1/FVC of 70% of less. The study had 2-3 weeks placebo run-in period followed by 12-week double blind treatment period. The treatment arms were arformoterol inhalation solution 15 mcg BID, 25 mcg BID, 50 mcg QD, salmeterol MDI 42 mcg BID, and placebo. Primary efficacy variable was FEV1. Serial spirometry over 24 hour period was done at weeks 0, 6, and 12. Primary efficacy endpoint was percent change from study baseline FEV1 to the end of the dosing interval (i.e., trough at 12 hours post-dose for BID treatment arms and 24 hours post-dose for QD treatment arm) over the 12 weeks of treatment. Other notable efficacy variables included St. George's Respiratory Questionnaire (SGRQ), baseline and transitional dyspnea index (BDI, TDI), and 6-minute walk. The study was designed to have 115 patients per treatment arms to give 90% power to detect a 10% difference between any dose level of arformoterol and placebo in the primary efficacy endpoint at a two-sided alpha-level of 0.05. Safety assessment included recording of adverse events, vital signs, physical examination, clinical laboratory measures, and ECG.

PK sampling was also done. A total of 917 patients were randomized approximately equally to the five treatment arms and 77.6-87.9% patients completed the study. There were no preferential discontinuations in any treatment arms.

Study 091-051 was a replicate of study 091-050 and was also conducted in the United States. A total of 739 patients were randomized and 74.8-87.7% patients completed the study with no preferential discontinuations in any treatment arms.

One-year safety study (study 091-060):

Study 091-060 was open-label, multiple-dose, placebo- and active-controlled, parallel group in design conducted in 85 centers in the United States. Eligibility criteria for entry into this study were similar to studies 091-050 and 091-051. The treatment arms were arformoterol inhalation solution 50 mcg QD and salmeterol MDI 42 mcg BID. Safety assessment included recording of adverse events, vital signs, physical examination, clinical laboratory measure, ECG, and 24-hour Holter monitoring. Holter monitoring was performed on all patients on 6 treatment visits. Serial spirometry was done on all subjects on 5 treatment visits. PK sampling was also done. A total of 799 patients were randomized in 2:1 ratio between arformoterol and salmeterol treatment arms, and 58% completed the study with no preferential discontinuations in the two treatment arms. Approximately half of the discontinuations were due to adverse events.

Comparative PK study (study 091-019):

Study 091-019 was open-label, multiple-dose, three-way crossover in design conducted in 39 patients with COPD. The study was conducted to further support the proposed 15 mcg BID dose of arformoterol by demonstrating comparable pharmacokinetics to Foradil Aerolizer 12 mcg BID.

Efficacy findings and conclusion:

The submitted studies support of efficacy of arformoterol inhalation solution at a dose of 15 mcg BID in patients with COPD.

In the dose ranging study 091-021 all active treatment arms were statistically significantly superior to placebo for the primary efficacy endpoint. Arformoterol 9.6 mcg QD had a numerically comparable response to salmeterol 42 mcg BID (13.6% compared to 16.3% for change in FEV1 AUC 0-24 hrs). Higher doses of arformoterol tended to give numerically higher responses compared to the 9.6 mcg QD dose. In the multiple dose dose-ranging study 091-026 arformoterol at BID dosing schedule gave a numerically superior response compared to at QD dosing schedule for the primary endpoint (Table 1) and for some secondary endpoints (data not shown in this document). The three BID dosing levels gave comparable numerical response (Table 1). In the two 12-week studies all three arformoterol doses were statistically superior to placebo showing comparable numerical responses amongst the doses and with salmeterol 42 mcg BID for the primary endpoint (Table 2) and some secondary endpoints (data not shown). Timed serial FEV1 curve at the first day of dosing and at week 12 showed convincing

efficacy of the 15 mcg BID dose, and with the higher two doses there was a numerical trend of a small increase in effect size. The small numerical trends of increased effect sizes do not justify the higher dose because of clear dose related increase in adrenergic adverse effects. Therefore, 15 mcg BID is the appropriate dose for this product. The timed FEV1 curve showed a quicker onset of action with arformoterol compared to salmeterol. This finding is consistent with the known more rapid onset of action of racemic formoterol compared to salmeterol.

Throughout the clinical program arformoterol inhalation solution was delivered via a Pari LC Plus nebulizer and a PARI Dura-neb 300 compressor. The product label will state that arformoterol be used with a standard jet nebulizer and air compressor and not with nebulizers that can substantially change the delivery characteristics and the ultimate delivered dose.

**Table 1. Study 091-026, Percent change in FEV1 12 hr AUC from baseline**

	Placebo	ARF 5 mcg BID	ARF 15 mcg BID	ARF 25 mcg BID
<b>Part A</b>	n=45	n=44	n=49	n=47
LS mean (SE)	-1.3 (2.0)	18.0 (2.8)	20.5 (2.5)	20.8 (2.9)
p-value vs placebo		<0.001	<0.001	<0.001
	Placebo	ARF 15 mcg QD	ARF 25 mcg QD	ARF 50 mcg QD
<b>Part B</b>	n=47	n=44	n=44	n=44
LS mean (SE)	-2.9 (1.9)	8.8 (1.7)	6.5 (2.2)	7.9 (1.8)
p-value vs placebo		<0.001	0.001	<0.001

**Table 2. Studies 050 and 051, Percent change in trough FEV1 from baseline over the 12 weeks**

	Placebo	ARF 15 mcg BID	ARF 25 mcg BID	ARF 50 mcg QD	Sal 42 mcg BID
<b>Study 091-050</b>	N=134	N=138	N=142	N=143	N=138
LS mean (SE)	6.0 (1.7)	16.9 (1.6)	18.9 (1.6)	14.9 (1.6)	17.4 (1.6)
		<0.001	<0.001	<0.001	<0.001
<b>Study 091-051</b>	N=141	N=140	N=142	N=138	N=138
	5.3 (1.6)	15.7 (1.6)	21.0 (1.6)	17.8 (1.6)	17.3 (1.6)
		<0.001	<0.001	<0.001	<0.001

From a regulatory standpoint such a choice is acceptable. Availability of arformoterol inhalation solution with the established efficacy of racemic formoterol in asthma raises the possibility that this product will likely be used in patients with asthma, particularly in pediatric patients with asthma in emergency and urgent care settings. This issue was discussed with Sepracor during the review of the NDA and Sepracor acknowledges this potential use. On the Division's recommendation, Sepracor has agreed to initially study the safety of arformoterol inhalation solution in pediatric patients 12 years of age and younger with asthma, and study efficacy in the setting of acute use. This issue was also discussed at a CDER regulatory briefing and by unanimous consensus it was agreed that Sepracor should conduct such a program. Pediatric asthma studies will be phase 4 commitment studies.

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Safety findings and conclusion:

The submitted studies support safety of arformoterol inhalation solution at a dose of 15 mcg BID in patients with COPD.

The overall safety database for arformoterol includes 1968 patients of which 1456 patients were in the 12-week studies. In the 12-week studies 293 patients received arformoterol at the proposed dose of 15 mcg BID. In the one-year study a 50 mcg QD dose of arformoterol was used. Use of a different dose in the one-year safety study was acceptable because the nominal daily dose was higher than the proposed dose.

In the clinical program there were a total of 10 deaths. Review of the deaths did not raise any specific concerns for arformoterol. Serious adverse events were not common and not of types that raise specific concerns for formoterol. Cardiac safety assessment did not raise any specific concerns. ECGs were obtained in all the multi-dose studies and 24-hour Holter monitoring was done in all patients at multiple time points in the one-year safety study. Cardiac safety database was adequate. In the comparative study 091-019 the steady state R,R-formoterol pharmacokinetic parameters between arformoterol 15 mcg BID and Foradil 12 mcg BID were comparable. The ratio (95% CI) between the two for AUC was 1.16 (1.00, 1.35) and for Cmax was 0.91 (0.76, 1.09). Comparative systemic exposure between the two lends further assurance from a systemic safety perspective.

One of the known safety concerns with LABA is asthma related deaths. For this specific serious safety concern, labeling changes were done recently for salmeterol and formoterol, two other members of this class. Labeling changes included addition of boxed warning and medication guide for products containing these drugs. It is unknown whether increased death risk with LABA applies to COPD patients because no large safety studies have been done with LABA in COPD patients. Because of the potential use of arformoterol in asthma, it is reasonable that boxed warning related to asthma related death be added to this product. This was discussed at a CDER regulatory briefing and there was a unanimous consensus that the arformoterol product label should have a boxed warning relating asthma related death. At the CDER regulatory briefing there was a general consensus that this product label should also include a medication guide for the same reason. The Division was initially of the opinion that a medication guide is not necessary, but based on the opinion at the regulatory briefing, the Division has changed its opinion and will ask Sepracor to include a medication guide for this product.

Sepracor is cognizant about the possibility of use of arformoterol in asthma patients. Within the review period Sepracor ☐

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☐ On Division's recommendation, Sepracor has agreed to conduct a large simple safety trial with arformoterol in COPD patients. At the CDER regulatory briefing there was a general consensus that Sepracor should conduct such a study. A large simple COPD safety study will be a phase 4 commitment study.

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### **Data Quality, Integrity, and Financial Disclosure**

No DSI audit for the clinical studies sites were conducted because: arformoterol is not a new molecular entity; racemic formoterol is already approved for the treatment of asthma and COPD; the clinical studies conducted to support this application were routine and straight forward; and during review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements. There were four investigators who either received significant payment from Sepracor or had significant financial interest in Sepracor. These investigators did not enter disproportionately large number of patients in the trials, and review of the data of these particular investigators' site did not show any suspicious trends.

### **Pediatric Considerations**

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD. Sepracor will conduct studies in pediatric asthma patients as phase 4 commitments as mentioned above.

### **Labeling**

Sepracor submitted a label that generally conforms with labeling of other products of this class, specifically with the labeling of Foradil Aerolizer. The notable differences were that the warning, including boxed warning, and medication guide related to the risk of asthma death with the use of LABA were not present. When this NDA was submitted, boxed warning was not present on the Foradil Aerolizer label, but it was included within the review period of this NDA. Review of the label was done by various disciplines of the Division, and on consult by OSE and DDMAC. Various changes to different sections of the label were done to better reflect the data and better communicate the finding to health care providers. There were some discussion with Sepracor on the display of efficacy data figures in the Clinical Trials section of this label given the precedence with other drugs of this class and the nature of the clinical study findings with arformoterol. It was decided to show the FEV1 time response curve from one trial on the first day of dosing and at week 12 using mean change from baseline FEV1 as the vertical axis. This display is consistent with the efficacy endpoint used in the arformoterol clinical studies and with the Serevent product label. Warning statements, including boxed warning and medication guide were added. The language of the warning was consistent with that of the Foradil Aerolizer label with some changes reflective of the fact that the indication is specific to COPD. The Division and Sepracor have agreed to the final version of the label.

### **Product Name**

Sepracor originally submitted two tradenames for this product, these were  and  and Brovana. Sepracor indicated that their preference is  OSE found the

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name unacceptable ☹

☹ ☞ The name Brovana was found to be acceptable by OSE and DDMAC. On hearing Agency concerns Sepracor decided to go with the trade name Brovana for this product. ☞

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**Action**

Sepracor has submitted adequate data to support approval of arformoterol inhalation solution for maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. The action on this application will be APPROVAL.

As discussed above Sepracor has agreed to conduct phase 4 studies to evaluate the safety and efficacy of arformoterol inhalation solution in pediatric patients with asthma, and conduct a large simple safety study in patients with COPD.

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MEDICAL OFFICER