CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20950

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAY 16 2000

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-950
Albuterol Sulfate (0.083%) &
Ipratropium Bromide (0.017%) Inhalation Solution

SUBMISSION DATE:
11/29/99

BRAND NAME: DuoNeb (3 ml/Vial)

SPONSOR: Dey

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Resubmission to Respond to the Agency's 05/28/99 Action Letter

BACKGROUND:

Albuterol is a β-adrenergic agonist which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic-AMP) from adenosine triphosphate (ATP). The cyclic-AMP then initiates a series of intracellular events, resulting in physiological responses such as increases in cardiac rate and force of contraction (β_1) and relaxation of bronchial and vascular smooth muscle (β_2).

Ipratropium bromide is a quarternary ammonium compound with structure and anticholinergic activity similar to that of the tertiary amine alkaloid, atropine. Ipratropium bromide metered dose inhaler (MDI) and inhalation solution are currently available on the market also as a bronchodilator for maintenance treatment of bronchospasm associated with COPD including chronic bronchitis and emphysema.

Combivent, a combination MDI product (albuterol sulfate and ipratropium bromide), is also available on the market. It is indicated for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) in patients requiring more than one bronchodilator.

On 05/28/98, under the provisions of 505(b)(2), i.e., referenced to the currently marketed products, Proventil and Ventolin Inhalation Solutions and Atrovent Inhalation Solution, Dey Laboratories submitted an original NDA 20-950 (Serial No. N-000) for DuoNeb inhalation solution, albuterol sulfate 0.083% (as albuterol base) and ipratropium bromide 0.017% per 3-ml vial. Submitted under NDA 20-950 were one pivotal clinical trial No. DL-024 and one pharmacokinetic (PK) study No. DL-031. The PK study No. DL-031 was a double-blind, randomized, 2x2 crossover, single-dose, drug-drug interaction PK study in 15 volunteers comparing Dey combination inhalation solution and albuterol sulfate inhalation. Upon the Agency's request, 56 published articles for albuterol and ipratropium PK in humans as stated were also submitted. The above NDA was reviewed by the Agency and was deemed approvable in the Action Letter dated 05/28/99. Please see previous OCPB/DPE II (Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II) reviews for this NDA and the 05/28/99 action letter for details.

SYNOPSIS:

On 12/03/99, the sponsor submitted their responses including the revised package insert (PI) to the Agency. OCPB has comments on PI revision only. Therefore, the sponsor's revised PI is reviewed here.

RECOMMENDATION:

Dey Laboratories' revised PI that was submitted on 11/29/99 to respond to the Agency's 05/28/99 action letter has been reviewed by OCPB/DPE II. OCPB is of the opinion that the revised PI is acceptable provided that the following changes are incorporated in the PI.

LABELING COMMENT: (Needs to be sent to the sponsor)

Please see the Agency's version of PI revision in Attachment 1 for details.

/S/ 05/16/2000

05/13/2000
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Ramana Uppoor, Ph.D. /S/

FT initialed by Ramana Uppoor, Ph.D. /S/ 05/16/2000

cc: NDA 20-950, HFD-570 ([redacted] Hilfiker), HFD-870 (S.M. Huang, R. Uppoor, T.M. Chen), CDR (B. Murphy). Anthracite,

Hilfiker

MAY 20 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-950
Albuterol Sulfate (0.083%) &
Ipratropium Bromide (0.017%) Inhalation Solution

SUBMISSION DATE:
05/28/98 (Serial No. N-000)

BRAND NAME: Duovent (3 ml/vial)

SPONSOR: Dey Labs

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Original NDA

Code: 3S

TITLE: "Review of Human Pharmacokinetics and Bioavailability Section"

BACKGROUND:

Albuterol is a β-adrenergic agonist and is reportedly highly selective for β_2-receptor. It causes relaxation of smooth muscles of the bronchi, uterus, and vascular supply to the skeletal muscles and inhibition of the release of immediate hypersensitivity mediators from cells (especially mast cells). Albuterol sulfate is currently available on the market in various dosage forms as a bronchodilator for treating asthma.

Ipratropium bromide is a quarternary ammonium compound with structure and anticholinergic activity similar to that of the tertiary amine alkaloid, atropine. Ipratropium bromide metered dose inhaler (MDI) is currently available on the market also as a bronchodilator for maintenance treatment of bronchospasm associated with COPD including chronic bronchitis and emphysema.

Combivent, a combination MDI product (albuterol sulfate and ipratropium bromide), is also available on the market. It is indicated for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) in patients requiring more than one bronchodilator.

SYNOPSIS:

On 05/28/98, under the provisions of 505(b)(2), i.e., referenced to the currently marketed products, Proventil and Ventolin Inhalation Solutions and Atrovent Inhalation Solution, Dey Laboratories submitted an original NDA 20-950 (Serial No. N-000) for Duovent inhalation solution, albuterol sulfate 0.083% (as albuterol base) and ipratropium bromide 0.017% per 3-ml vial. Each vial will provide 2.5 mg albuterol base and 0.5 mg of ipratropium bromide in an isotonic, sterile, aqueous solution. The sponsor is seeking approval of Duovent Inhalation Solution for the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator. The recommended dosing regimen is one vial QID with up to 2 additional doses allowed per day if needed. Please see the package insert (PI) in Attachment 1 for details.

Submitted under Item 6, Human pharmacokinetics (PK)/Bioavailability (Bio) section, of NDA 20-950 was one PK study No. DL-031 as agreed upon previously with the Agency in a pre-NDA meeting dated 06/17/97. The above protocol was reviewed by the Agency on 10/16/97. A summary report from 56 published literature articles (for albuterol and ipratropium PK in humans) was also submitted upon the Agency's request. For the clinical program, only one pivotal clinical trial, No. DL-024 was conducted which compared Duovent inhalation solution with albuterol and ipratropium inhalation solutions given individually.

STUDY No. DL-031:

Study No. DL-031 was a double-blind, randomized, 2x2 crossover, single-dose, drug-drug interaction PK study in 13 male and 2 female volunteers. The subjects' mean (± standard deviation; SD) age, weight, and height were 33 ± 13 years old, 171 ± 26 lbs, and 71 ± 3 inches, respectively. The test product, two inhalations of Duovent (total 5 mg as albuterol base and 1 mg ipratropium bromide) and the reference product, two inhalations of a solution containing only albuterol sulfate (total 5 mg of albuterol base) were given on separate occasions. The subjects inhaled two vials (15 min apart) on each study day. A washout period of one week was employed between treatments.

The reference (batch No. F453) was manufactured in a manner identical to Duovent inhalation solution (batch No. F451) under study. Serial blood samples were collected at various times for 24 hrs and urine samples were also collected for 24 hrs. Plasma levels of albuterol only and urinary recovery of both albuterol and ipratropium was analyzed.

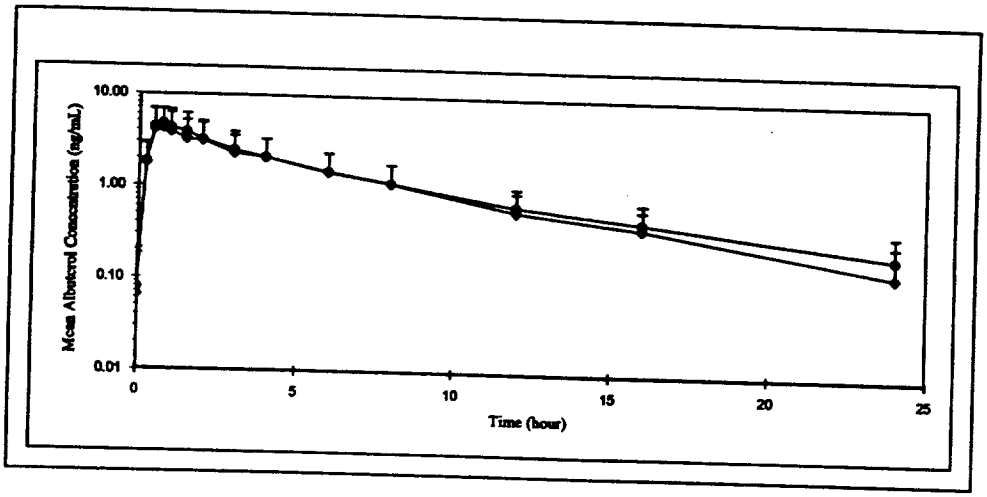
The PK study results are summarized below in **Table 1** and **Figure 1**:

Table 1. Mean (± SD) Pharmacokinetic Parameters of Albuterol Sulfate when Administered Alone or As the Dey Combination Solution for All 15 Subjects

Subjects	Dosage Form	Compound	Dose (mg)	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0\rightarrow 24hr}$ (ng-hr/mL)	Excretion (%dose in urine)
15 healthy (13M/2F)	Dey Combination Solution via Nebulizer	Albuterol Sulfate	5.0	4.7±2.9	0.78±0.38	24.2±14.5	8.4±8.9
		Ipratropium Bromide	1.0	-	-	-	3.9±5.1
Dey-Sponsored Study DL-031	Albuterol Sulfate Inhalation Solution via nebulizer	Albuterol Sulfate	5.0	4.9±2.6	0.82±0.33	26.6±15.2	8.8±7.3

M, male; F, female; C_{max}, maximum concentration; t_{max}, time of maximum observed concentration; AUC_{0-24}, area under the plasma concentration-time curve from time 0 to 24 hours after the dose.

Figure 1. **Mean (± SD) albuterol plasma concentrations after 5 mg doses of albuterol base administered as Albuterol Sulfate Inhalation Solution (-O-) or Dey Combination Solution (-◊-)**



The above results show that the mean peak levels (C_{max}) and the mean area under the curve (AUC_{0-24}) of albuterol following administration of a 5-mg dose of albuterol base administered as Duovent or albuterol sulfate inhalation solution were similar between treatments. No statistical differences in the primary PK parameters were found. The ratios of mean C_{max} and AUC_{0-24} values between treatments for all subjects were 0.96 and 0.92, respectively. Analyses of log transformed values for C_{max} and AUC_{0-24} showed that the 90% confidence intervals for C_{max} were 0.79 to 1.14 and for AUC_{0-24} were 0.66 to 1.18. The mean apparent terminal half-life ($T_{1/2}$) values for Duovent inhalation solution or albuterol sulfate inhalation given alone were also similar, 6.7 and 7.2 hr, respectively. The above data demonstrated comparable plasma PK when albuterol was given with or without co-administration of ipratropium bromide.

The mean recoveries of albuterol in the urine over a 24-hour period (as % of dose administered) obtained from Duovent and albuterol inhalation solutions were 8.4 (± 8.9)% and 8.8 (± 7.3)%, respectively. The differences were not significantly different indicating little or minor changes in the renal excretion of albuterol when albuterol was given with or without co-administration of ipratropium bromide. The above urinary data are consistent with results obtained from plasma PK. The mean recovery of ipratropium in urine over a 24-hour period following a 1.0 mg dose of ipratropium bromide as the Duovent Inhalation Solution was 3.9 (± 5.1)% of the dose. The value is also consistent with existing data reported for healthy volunteers receiving inhaled ipratropium bromide. Please see PK summary for Study No, DL-031 in Attachment 2 for details.

The formulation used in the human PK/Bio and clinical studies was the same as the to-be-marketed formulation and it was manufactured using the commercial equipment (50% of what a full-scale production batch size will be). The quantitative composition of Duovent Inhalation Solution is provided below:

Component	Amount/Vial	Amount/Batch
Albuterol Sulfate USP	3 mg	Kg
Ipratropium Bromide EP*	mg	g
Sodium Chloride USP	mg	Kg
Hydrochloric Acid 1N	mL	ml
Edetate Disodium USP	mg	Kg
Purified Water	mL	L

* Amount of ipratropium bromide is expressed as monohydrate. The amount of ipratropium bromide monohydrate added to the batch is calculated based on water content.

The above 3 assay methods were reviewed and found acceptable.

Finally, upon the Agency's request in the pre-NDA meeting, the sponsor did literature search for both albuterol and ipratropium PK in humans. The summary review of the literature studies was also submitted. They were briefly reviewed by the Agency as well.

Conclusion:

There is no significant PK drug-drug interaction between ipratropium bromide and albuterol sulfate that would lead to greater systemic exposure of patients to the β-agonist, albuterol sulfate.

RECOMMENDATION:

Dey's original NDA 20-950 (serial No. 000) for Duovent inhalation solution (a combination product of albuterol sulfate 0.083% as albuterol base and ipratropium bromide 0.017%) that was submitted on 05/28/98 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB is of the opinion that the Human PK/Bio section of this NDA is acceptable. The following Labeling Comments as appropriate need to be conveyed to the sponsor.

GENERAL COMMENT: (Need not be sent to the sponsor)

As previously agreed with the Agency, Study No. DL-031 was conducted comparing the Duovent inhalation solution with albuterol inhalation solution alone. The ipratropium inhalation solution should have been given as well and compared with Duovent inhalation solution in a 3x3 crossover PK study to see whether albuterol has some effects on ipratropium. Although complete plasma profiles of ipratropium after inhalation administration could not be obtained, the information on the % of ipratropium dose excreted unchanged in urine may be sufficient to provide additional evidence to address the above concerns. Ideally, for a combination product, its PK should be studied comparing with the individual active ingredient given concurrently.

LABELING COMMENTS: (Need to be sent to the sponsor)

05/20/99

/S/

05/14/99

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by R. Uppoor, Ph.D. 05/18/99

FT initialed by R. Uppoor, Ph.D. /S/ 05/20/99

cc: NDA 20-950, HFD-570 (Anthracite, Hilfiker), HFD-870 (M.L. Chen, R. Uppoor, T.M. Chen), CDR (B. Murphy).

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Proposed Package Insert

NDA 20-950 (Serial No. N-000) for Duovent Inhalation Solution (Albuterol Sulfate / Ipratropium Bromide)

ATTACHMENT 2

Study No. DL-031 Individual Study Report

STUDY SYNOPSIS

Name of Sponsor: Dey Laboratories

Name of Drug Product: Dey Combination Solution (Combination Albuterol Sulfate/Ipratropium Bromide Inhalation Solution)

Name of Active Ingredients: albuterol sulfate and ipratropium bromide

Title of Study: A Randomized, Double-blind, Single-dose, Two-period Crossover Study of the Effects of Ipratropium Bromide on the Pharmacokinetics of Albuterol Sulfate when the Two Compounds Are Used in a Fixed Combination as an Inhalation Solution.

Investigators and Study Sites:

Publication: None

Study Period: October 1997 through November 1997
First Subject Treated: 28 October 1997
Last Subject Completed: 04 November 1997

Clinical Phase: Phase 1

Study Objective: The primary objective of this study was to determine if the pharmacokinetics of albuterol sulfate were altered by the simultaneous administration of ipratropium bromide.
The secondary objective of the trial was to evaluate the safety of the Dey Combination Solution compared with Albuterol Sulfate Inhalation Solution.
Product, Mode of Administration and Dosing Regimen: The test product, Dey Combination Solution (Lot Number F451) contained 2.5 mg albuterol and 0.5 mg ipratropium bromide in 3-mL volume. The study medications were supplied in low density polyethylene (LDPE) vials containing a solution for inhalation from a standard nebulizer. The subjects inhaled two vials 15 minutes apart on both study days.

Duration of Treatment: Treatment was on 2 days, which were 6 days apart, and consisted of single doses administered over a 30-minute period.

Reference Product and Dosing Regimen: The reference product, Albuterol Sulfate Inhalation Solution, contained albuterol (Lot Number F453) at 2.5 mg in 3-mL volume in LDPE vials and was administered in a manner identical to the Dey Combination Solution under study.

Good Clinical Practice Compliance: This study was performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki, and 21 CFR Parts 50, 56, and 312.

Number of Subjects:
Planned enrollment: 15 (to achieve 12 evaluable)
Actual enrollment: 15
Randomized: 15
Included in pharmacokinetic evaluation: 15
Evaluated for safety: 15

Results:

Subject Disposition and Demographics: A total of 15 subjects were enrolled in this study. All patients were randomized and completed the study. The majority of the subjects were black (11) and male (13). The subjects in the study ranged in age from 18 to 58 years, with a mean and median age of 33 years.

Pharmacokinetics:

- Peak albuterol plasma concentrations occurred at approximately 0.8 hours after dosing for both treatments.
- Mean albuterol C_{max} values were 4.86 ng/mL, and 4.65 ng/mL for the Albuterol Sulfate Inhalation Solution and the Dey Combination Solution, respectively.
- Mean $AUC_{0\text{-}24hr}$ values for the two treatments were 26.6 ng/hr/mL (Albuterol Sulfate Inhalation Solution) versus 24.2 ng/hr/mL (Dey Combination Solution).
- Mean $t_{1/2}$ values for the two treatments were 7.2 hours (Albuterol Sulfate Inhalation Solution) and 6.7 hours (Dey Combination Solution).
- The mean ratios C_{max} and $AUC_{0\text{-}24hr}$ between treatments for all subjects were 0.95 and 0.88, respectively. Similar quantities of albuterol were excreted in the urine, 8.8% (±7.3) and 8.4% (±8.9) of the dose for Albuterol Sulfate Inhalation Solution and the Dey Combination Solution, respectively.
- Overall there was no significant effect of ipratropium bromide on the pharmacokinetics of albuterol sulfate.
- There were no statistically significant differences in the parameters (C_{max}, $AUC_{0\text{-}24hr}$, t_{max}) between the 2 treatments. Additionally, no significant sequence or period effects were observed for these parameters.

Safety:

- Cardiovascular adverse event (AE) rates (summarized by total number of patients with AEs or AEs related to study drug) were not higher for Dey Combination Solution, implying that ipratropium bromide does not alter the pharmacokinetics or potentiate the systemic effects of albuterol sulfate.
- The number of patients with AEs were lower in the Dey Combination Solution treatment group compared to the Albuterol Sulfate Inhalation Solution treatment group.
- There were no clinically significant changes in vital signs observed from baseline to the completion of the study.
- There were no clinically significant changes or trends in laboratory values from baseline to the completion of the study.

Conclusions: Study DL-031 demonstrated that the pharmacokinetic profiles of albuterol when inhaled using nebulized solutions of Albuterol Sulfate Inhalation Solution or the Dey Combination Solution were very similar and there were no statistically significant differences in the primary pharmacokinetic parameters between the two treatments. The urinary excretion of albuterol was not affected by administration with ipratropium bromide. Safety assessments demonstrated that there were fewer AEs associated with Dey Combination Solution compared with that of Albuterol Sulfate Inhalation Solution. Thus, the current study indicates that there is no significant pharmacokinetic drug interaction between ipratropium bromide and albuterol sulfate that would lead to an increase in the systemic exposure of patients to the β-agonist albuterol sulfate and, thereby, raise concerns about potential drug toxicity.

Transfer of Obligations: was responsible for the protocol, Investigator's Brochure, informed consent forms, IND filing and for the conduct and monitoring of the trial. was responsible for the analysis and Final Study Report of the trial.

Reviewer's Comments:

The study was reviewed and found acceptable. For study results, please see the PK summary review section (pages 1-6) for details.