CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20950

PHARMACOLOGY REVIEW

Division of Pulmonary and Allergy Drug Products

Review and Evaluation of Pharmacology/ Toxicology Data

Reviewer: VE Whitehurst

HFD: HFD 570

Review Completion Date: February 14, 2001

NDA: NDA 20-950

Type of Submissions: Amendment dated September 19, 2000

Information to be conveyed to the sponsor: yes, via chemist

Sponsor: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

Drug:
NDA 20-950: Duovent ™ (Combination of Albuterol Sulfate and Ipratropium Bromide Solution for Nebulizer)

Chemistry Names:
Albuterol sulfate : α1–[(tert-butylamino)methyl]-4-hydroxy-m-xylene-α, α'-diol sulfate (2:1) (salt). Molecular weight: 576.7

Ipratropium bromide: 8-azoniabicyclo[3,2,1]-octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide. Molecular weight: 430.4

Relevent INDs/NDAs:
NDAs:
20-291 (Combivent)
20-228 (Atrovent Inhalation Solution)
19-773 (Ventolin Inhalation Solution)
19-269 (Ventolin Inhalation Solution)

17-853 (Proventil Tablets)
19-243 (Proventil Nebulizer Solution)

INDs:

(Combination Albuterol Sulfate and Ipratropium Bromide)
(Combivent)
(Ventolin)

Drug Class: Beta adrenergic agonist and anticholinergic bronchodilators

Indication: Relief of bronchospasm associated with COPD

Proposed Clinical Use:
Usual dosing for Duovent is QID, with each dose being 2.5 mg albuterol and 0.5 mg ipratropium, for a total daily dose of 10 mg albuterol (200 mcg/kg) and 2.0 mg ipratropium (40 mcg/kg). Two additional doses are allowed per day, resulting in a maximum daily dose of 15 mg albuterol (300 mcg/kg) and 3 mg (60 mcg/kg) ipratropium.

Route of Administration: Inhalation

Introduction and History:
This a chemistry consult from Dr Chong-Ho Kim requesting an evaluation of the sponsor's response to our recommendation for a 90 day inhalation toxicity study to qualify the proposed specification, less than % w/w for impurity in the drug substance, albuterol sulfate. Additionally, Dr Kim would like an evaluation of the proposed specification for an impurity in the drug product, of not more than mcg/ml. And finally, the sponsor is proposing a specification for extractables

Impurities:

The sponsor is proposing a % w/w specification for in the drug substance, albuterol sulfate. Dey agrees to conduct a 90 day inhalation

toxicity study to qualify. The study will be conducted expeditiously and the results will be submitted as a phase 4 commitment within 12 months of drug approval.

The sponsor is proposing a specification of mcg/ml for in the drug product. The maximum daily dose of 15 mg of albuterol and 3 mg ipratropium requires 6 vials which contain 3 ml each. The maximum daily exposure to is approximately mcg or mcg/kg for a 50 kg person. There are no safety data for in our database. In cases where there is no safety data, we have concluded that a daily exposure to a compound of less than 100 ng/kg does not require a toxicity assessment for qualification, provided the compound does not contain a structural alert for either irritancy or mutagenicity.

Extractables:

The sponsor is proposing a specification for extractables (one pouch contains 5 vials). If one uses the maximum daily dose of 6 vials, the maximum daily exposure is 0.12 mg, 120 mcg, 2.4 mcg/kg for a 50 kg person. The maximum daily allowable exposure for is mcg/kg.

Recommendation:

The proposed specifications for and extractables are acceptable. The sponsor has agreed to conduct a 90 day inhalation toxicity study to qualify as a phase 4 committment.

/S/

Virgil Whitehurst 2-20-01
Pharmacologist

CC: Division File
HFD-570/RHuff 2-20-01
HFD-570/VWhitehurst
HFD-570/CHKim
HFD-570/DHilfiker

Hilfiker

Division of Pulmonary Drug Products

Review of Pharmacology/ Toxicology Data

Reviewer: VE Whitehurst

HFD: HFD 570

Review Completion Date: April 17, 2000.

NDAs: NDA 20-949 and NDA 20-950

Type of Submissions:
NDA 20-949-Response to approvable letter dated March 30, 1999 (amendent # 019)
NDA 20-950- Response to approvable letter dated May 28, 1999 (amendment # 006)

Information to be Conveyed to the Sponsor: yes

Sponsor: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

Drugs:
NDA 20-949: AccuNeb ™ (Albuterol Sulfate Inhalation Solution 0.63 mg and 1.25 mg)
NDA 20-950: Duovent ™ (Combination of Albuterol Sulfate and Ipratropium Bromide Solution for Nebulizer)

Chemistry Names:
Albuterol sulfate : α1–[(tert-butylamino)methyl]-4-hydroxy-m-xylene-α, α'-diol sulfate (2:1) (salt). Molecular weight: 576.7

Ipratropium bromide: 8-azoniabicyclo[3,2,1]-octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide. Molecular weight: 430.4

Relevent INDs/NDAs:

NDAs:

20-291 (Combivent)
20-228 (Atrovent Inhalation Solution)
19-773 (Ventolin Inhalation Solution
19-269 (Ventolin Inhalation Solution)

17-853 (Proventil Tablets)
19-243 (Proventil Nebulizer Solution)

INDs:

(Combination Albuterol Sulfate and Ipratropium Bromide)
(Combivent)
(Ventolin)

Drug Class: Beta adrenergic agonist and anticholinergic bronchodilators

Indication: Relief of bronchospasm associated with COPD

Drug Product:
Albuterol sulfate (active agent)
Ipratropium bromide (active agent)
Sodium chloride (tonicity agent)
Hydrochloric acid (for pH adjustment)
Edetate Disodium (chelating agent)
Purified water (vehicle)

Proposed Clinical Use:
Dosing for AccuNeb is QID, with each dose being 0.63 or 1.25 mg. The maximum daily dose is 5.0 mg or 0.1 mg/kg for a 50 kg person.

Usual dosing for Duovent is QID, with each dose being 2.5 mg albuterol and 0.5 mg ipratropium, for a total daily dose of 10 mg albuterol (200 mcg/kg) and 2.0 mg ipratropium (40 mcg/kg). Two additional doses are allowed per day, resulting in a maximum daily

dose of 15 mg albuterol (300 mcg/kg) and 3 mg (60 mcg/kg) ipratropium.

Route of Administration: Inhalation

Introduction and History:
Complete toxicology profile for ipratropium bromide alone and in combination with albuterol sulfate has been performed and submitted under NDAs 20-228 and 20-291, respectively (original Combivent pharmacology review dated November 9, 1993). Complete toxicology profile for albuterol sulfate alone has been performed and submitted under NDAs 17-559, 17-853 and 19-243.

Summary:
Approvable letters were sent to the sponsor for NDA 20-949 (March 30, 1999) and NDA 20-950 (May 28, 1999). These letters included revised final labeling for AccuNeb and Duovent and the comment that in order to accept the requested specification for two impurities in the drug substance, [redacted] the impurities must be qualified. ("In order to qualify these impurities, perform a 90 day inhalation study (refer to ICH guideline Q3A). The study should include histopathological evaluation of a complete battery of tissues. It is not necessary to perform the study with the isolated impurities, provided that a sufficient margin of safety for the impurities can be demonstrated by using a batch of drug substance in which they are present.")

Dey agreed to reduce the specification for the [redacted] impurity to less than [redacted]%, obviating the need for qualification of this impurity. Regarding the [redacted] impurity, Dey responded that they conducted analytical testing on three lots of the marketed Ventolin albuterol sulfate 0.083% product manufactured by Glaxo. The results showed that the Ventolin product contained [redacted] albuterol at levels of [redacted]% and above. Based on these results, and upon Section 505(b) (2) of the Federal Food, Drug and Cosmetic Act, Dey concluded that the toxicological information provided for the albuterol innovator product was sufficient to satisfy the applicable standards for this product. Dey did not respond to the revised final labeling for AccuNeb and Duovent.

Recommendations:

1. The revised final labeling for AccuNeb and Duovent should again be conveyed to the sponsor.

2. The request for qualification of the impurity to support the specification of % should be reiterated. A 90 day inhalation toxicity study should be performed. Genotoxicity testing is not necessary, as this impurity does not display any structural alerts for mutagenicity. The results of the 90 day study may be submitted Phase 4.

   A discussion was held with Division and ODE II officials on March 2, 2000 in which it was decided that 505 (b) (2) applications will be held to current standards regarding qualification of impurities. Because individual impurities were not as tightly controlled at the time Ventolin was approved, we have no way of knowing whether the impurity has been in the product since the time of approval or if it appeared later as a result of a manufacturing change etc. Therefore, the extent of the marketing safety database is undefined. It was, however, agreed that the marketing history of the innovator product was sufficient to allow qualification of impurities to be completed in Phase 4 (i.e., since concern is not sufficient to warrant removal of Ventolin from the market, qualification of the impurity can be performed after approval).

Comment for the Action Letter (suggested wording):

1. We reiterate our request for a 90 day inhalation toxicology study to qualify the impurity; however, the results of this study may be submitted Phase 4, within 12 months of approval. Your response that the impurity is present at similar levels in marketed Ventolin products is insufficient because drug approval criteria have evolved since the time Ventolin was approved, and current standards are being applied to your application. Because individual impurities were not as tightly controlled at the time Ventolin was approved, we do not know whether the impurity has always been present in Ventolin or if it appeared later as a result of a manufacturing or other change. Thus, the extent of the marketing safety database is undefined.

/S/

Virgil Whitehurst 4-19-00
Pharmacologist

CC: Division File
HFD-570/RHuff /S/ 4-19-00
HFD-570/VWhitehurst
HFD-570/VShah
HFD-570/DHilfiker

APR 15 1999

Division of Pulmonary Drug Products

Review of Pharmacology/ Toxicology Data

Reviewer: VE Whitehurst

HFD: HFD 570

Review Completion Date: April 7, 1999.

NDA: NDA 20-950

Information to be Conveyed to the Sponsor: yes

Sponsor: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

Drug: Duovent ™ (Combination of Albuterol Sulfate and Ipratropium Bromide Solution for Nebulizer)

Chemistry Name:
Albuterol sulfate : α1 –[(tert-butylamino)methyl]-4-hydroxy-m-xylene-α, α'-diol sulfate (2:1) (salt). Molecular weight: 576.7

Ipratropium bromide: 8-azoniabicyclo[3,2,1]-octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide. Molecular weight: 430.4

Relevent INDs/NDAs:
NDAs:
20-291 (Combivent)
20-228 (Atrovent Inhalation Solution)
19-773 (Ventolin Inhalation Solution
19-269 (Ventolin Inhalation Solution)
17-559 (Proventil Metered Aerosol)
17-853 (Proventil Tablets)
19-243 (Proventil Nebulizer Solution)

INDs:
(Combination Albuterol Sulfate and Ipratropium Bromide)
(Combivent)

Drug Class: Beta adrenergic agonist and anticholinergic bronchodilators

Indication: Relief of bronchospasm associated with COPD in patients requiring more than one bronchodilator.

Drug Product:
Albuterol sulfate (active agent)
Ipratropium bromide (active agent)
Sodium chloride (tonicity agent)
Hydrochloric acid (for pH adjustment)
Edetate Disodium (chelating agent)
Purified water (vehicle)

Proposed Clinical Use: Usual drug daily use is QID and each dose is 2.5 mg albuterol and 0.5 mg ipratropium or 10 mg albuterol (200 mcg/kg) and 2.0 mg ipratropium (40 mcg/kg) for a 50 kg person. Two additional doses areallowed per day. The maximum daily dose is 15 mcg albuterol (300 mcg/kg) and 3 mg(60 mcg/kg) ipratropium.

Route of Administration: Inhalation

Disclaimer: Some of the materials in this review were taken directly from the sponsor's submission.

Introduction and History:
Complete toxicology profile for ipratropium bromide alone and in combination with albuterol sulfate has been performed and submitted under NDAs 20-228 and 20-291 (Combivent-original pharmacology review dated November 9, 1993. Complete toxicological profile for albuterol sulfate alone has been performed and submitted under NDAs 17-559, 17-853 and 19-243.

This 505 (b) (2) NDA summarizes the DEY-sponsored studies and the supporting published /publicly available information from industry-sponsored and other literature-based studies. Dey Combination Solution references the individual active component NDAs 19-243, 19-773 and 19-269 (Proventil and Ventolin: Albuterol Sulfate Inhalation Solution) and 20-228 (Atrovent: Ipratropium Bromide Inhalation Solution) for individual product animal and human pharmacology and toxicology.

During a meeting with the sponsor, June 17, 1997, the FDA recommended that the sponsor carry out 30 day drug-drug interaction studies in a rodent and non-rodent species to determine whether there is potentiation when albuterol sulfate and ipratropium bromide are administered concurrently. Boehringer Ingelheim Pharmaceuticals has preclinical data (NDA 20-291-Combivent) concerning the potentiation with the concurrent use of albuterol sulfate and ipratropium bromide; however, these data are proprietary.

Studies Reviewed in this Submission:

1. An Acute and 5-Day Repeat Dose Subcutaneous Injection Toxicity Study of Albuterol Sulfate in the Albino Rat (volume 9-page 166).
2. A 30-Day Subcutaneous Study of the Effect of Ipratropium Bromide on Albuterol Sulfate in the Heavy Albino Rat (volume10-page 167).
3. An Acute Single and Repeat Dose Subcutaneous Injection Toxicity Study in the Beagle Dog (volume 11-page 168).
4. A 30–Day Subcutaneous Study of the Effect of Ipratropium Bromide on Albuterol Sulfate Cardiotoxicity in the Beagle Dog (volume 11-page 169).

Toxicology

1. **An Acute and 5-Day Repeat Dose Subcutaneous Injection Toxicity Study of Albuterol Sulfate in the Albino Rat. (volume 9-page 166)**

Study number 88458-Study carried out by [redacted]

Study Initiation: October 16, 1997
GLP Compliance: No
QA Report: Yes

Methods: This is a dose-ranging study to determine the dose to be used in the 30 day toxicity study. There were 2 phases in this study- phase 1 is the acute study and phase 2 is the repeat study.

Dose information: Male Sprague-Dawley rats, approximately 8 months old and weighing 400-500g, 3-6 per dose group, were included in the study.

Drug: Albuterol sulfate (batch number F453) dissolved in sterile saline with EDTA was administered subcutaneously, 1-5 days.

Group	**Dose** (mcg/kg)	**Number of males**
Phase 1:		
Albuterol sulfate	25	3
Albuterol sulfate	50	3
Albuterol sulfate	100	3
Control (untreated)		3
Phase 2:		
Albuterol sulfate	250	6
Albuterol sulfate	1000	6
Albuterol sulfate	4000	6
Control	Vehicle*	2

*vehicle = sterile water, sodium chloride and EDTA

Results:
Phase 1:
Clinical signs (daily): None, no mortality.

Body Weights (daily): Comparable in all dose groups.

EKGs (15 minutes and 2 hours post dosing): No EKG changes.

Gross Pathology (terminal): No increase in heart weight, no changes in gross pathology.

Phase 2:
Clinical signs (daily): One rat in the 1000 mg/kg group died on day 2. Microscopic analyses of myocardial tissues revealed cardiovascular related death.

Body Weight (daily): Body weight gain was comparable in all dose groups.

Heart Rates (every 15 minutes for 2 hours post dosing, days 1 and 5): On day 1, heart rates were increased in the 2 highest dose groups by approximately 15 % when compared with the controls. On day 5, heart rates were decreased when compared with the pretreatment heart rates, suggesting an effect of drug on the beta adrenergic receptors or the signal system.

EKGs: (every 15 minutes for 2 hours post dosing): No EKG changes.

Organ Weights (terminal): There were dose-related increases in absolute heart weights of the rats in the 2 highest dose groups. The increases were approximately 7 and 12 %, respectively. There were no increases in relative organ weights.

Gross Pathology (terminal): There were no gross pathology changes.

Histopathology (terminal): Treatment-related myocardial degeneration and/ or fibrosis were seen in the hearts of 1/6, 2/6 and 4/6 of the rats in the low, mid and high dose groups.

Toxicokinectics (day 5 and 50 minutes after dose): Results pending.

2. A 30-Day Subcutaneous Study of the Effect of Ipratropium Bromide on Albuterol Sulfate in the Heavy Albino Rat (volume10-page 167).

Study number: 88399-Study carried out by

Study Initiation: December 16, 1997
GLP Compliance: Yes
QA Report: Yes

Methods: To evaluate the cardiovascular toxicity and toxicokinetics in rats of albuterol sulfate/ipratropium bromide combination solution when administered subcutaneously daily for 30 days and compared with cardiotoxicity of albuterol and ipratropium, administered individually.

Drugs: Albuterol sulfate (batch F453), ipratropium bromide (batch F452), albuterol sulfate/ipratropium bromide solution (batch F451).

Dose information:

Animal	Duration	# Animals	Route	Doses (µg/kg)
Aged, heavy Sprague-Dawley, 6 months male 378-472g female 223-290g	30 days	8/sex controls 28/sex dose groups Satellite animals:2/sex /dose for toxicokinetic evaluation	s.c.	205.5 ipratropium bromide/ 1000 albuterol sulfate 205.5 ipratropium bromide alone 1000 albuterol sulfate alone vehicle

Results:

Clinical Signs (daily): No animals died during the study. There were no major clinical signs in the study.

Body Weight (weekly): Body weight gain was increased in the animals in the albuterol/ipratropium combination group (approximately 15 %) and the albuterol alone group (approximately 4 %) when compared with body weight gain in the control group. The body weight gain was significant in the females in these dose groups.

Food Consumption: Food consumption was greater in the albuterol/ ipratropium combination and albuterol alone groups. The increase in food consumption was approximately 9%.

EKGs (pretreatment, weekly, 15 to 150 minutes post dosing): There were no EKG changes in this study.

Heart Rates (pretreatment, weekly, 15 to 150 minutes post dosing): 15 minutes after dosing, heart rate increases were observed in the animals treated with albuterol alone and with the albuterol/ipratropium combination. The increases were approximately 10-15% on day 1 and approximately 20-25 % on day 28.

Hematology (end of study): There were no changes in the hematological parameters.

Clinical Chemistries (end of study): There were no changes in clinical chemistries.

Urinalysis (days 1 and 29): There were no changes in the urinalysis parameters that were treatment-related.

Organ Weights (terminal): Absolute and relative heart weights were significantly increased in the albuterol alone and albuterol/ipratropium combination groups. The increases were approximately 8 and 14 %, respectively. The relative brain weight was significantly decreased in the animals in these dose groups. The decrease was approximately 3 % .

Gross Pathology (terminal): There was no gross pathology that was treatment-related.

Histopathology: (terminal- standard battery of tissues was examined): Microscopic analyses of the tissues revealed no significant treatment related changes.

Toxicokinetic Parameters (1/2 – 3 hours after dosing on days 2 and 30): Toxicokinetic parameters were evaluated for albuterol alone and for the albuterol/ipratropium combination. The following table summarizes pharmacokinetics of albuterol, administered alone and concurrently with ipratropium.

Day	Group	Sex	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng.hr/ mL)	$T_{1/2}$ (hr)
2	albuterol alone	M F	271 171	0.5 0.5	349 163	0.86 0.61
2	combination	M F	222 174	0.5 0.5	306 191	0.93 0.68
30	albuterol alone	M F	180 132	0.5 0.5	204 137	0.74 0.84
30	combination	M F	204 132	0.5 0.5	220 144	0.77 0.69

C_{max} and AUC for albuterol were greater in the males than females. These parameters were similar for animals administered albuterol alone or the albuterol/ipratropium combination. The plasma elimination $t_{1/2}$ ranged from 0.61-0.93 hours.

The excretion of albuterol via the urine was not significantly affected by the concurrent dosing with ipratropium bromide. Males excreted greater amounts of intact ipratropium than females both when ipratropium bromide was given alone and when ipratropium bromide was given in combination with albuterol.

3. An Acute Single and Repeat Dose Subcutaneous Injection Toxicity Study in the Beagle Dog (volume 11-page 168).

Study number 88459- Study carried out by

Study Initiation: October 16, 1997
GLP Compliance: No
Q/A: Yes

Methods: This is a dose-ranging study to determine the dose to be used in the 30 day toxicity study. There were 2 phases in this study- phase 1 is the acute study and phase 2 is the repeat study.

Dose information: Male beagle dogs, 2/dose group, were included in the study.

Drug: Albuterol sulfate (batch number F453) dissolved in sterile saline with EDTA was administered subcutaneously, 1-5 days.

Group	**Dose (mcg/kg)**	**Number of males** .
Phase 1:		
Albuterol sulfate	1.0	2***
	3.0	2
	10	2
	20	2
Phase 2:		
Albuterol sulfate	15	2
Ipratropium bromide	3.16	2
Albuterol sulfate/	15.6**	
Ipratropium bromide	3.16	2
Control	Vehicle*	2

*vehicle = sterile water, sodium chloride and EDTA
**slightly different dose than albuterol alone because of a calculation error.
***same 2 dogs were used for each dose in the phase 1 study. The washout period was 24 hours.

Results:
Phase 1:
Clinical signs (daily): None, no mortality.

Body Weights (daily): Comparable in all dose groups.

EKGs (15 minutes - 2 hours after dosing): No EKG changes.

Heart Rates (15 minutes - 2 hours after dosing): No increase in heart rates after the administration of sc doses of 1 and 3 μg/kg. Significant increases in heart rate were observed after dose of 10 and 20 μg/kg. The increases were 52% and 70%, respectively. These changes were noted approximately 60 minutes after dosing.

Gross Pathology (terminal): No increase in heart weight, no changes in gross pathology.

Phase 2:
Clinical signs (daily): No mortality, no clinical signs were noted.

Body Weight (weekly): Body weight gain was comparable in all dose groups.

Food Consumption (weekly): Food consumption was comparable in all dose groups.

EKGs (15 minutes – 2 hours after dosing on days 1 and 5): No EKG changes were observed.

Heart Rates (15 minutes - 2 hours after dosing on days 1 and 5): Heart rates were increased on days 1 and 5, as summarized below.

Drug	**Dose** (µg/kg)	**Day**	**Percent Change**
Albuterol	15	1	28-72% ⇑
		5	36-88% ⇑
Ipratropium/ Albuterol	3.16 15.6	1 5	46-58% ⇑ 39-52% ⇑
Ipratropium	3.16	1	28-44% ⇓
		5	2-13% ⇑

Organ Weights (terminal): No increase in organ weights were found in this study.

Gross Pathology (terminal): No treatment-related gross pathology was found in this study.

Histopathology (terminal): There were no microscopic changes that were treatment-related.

4. A 30 –Day Subcutaneous Study of the Effect of Ipratropium Bromide on Albuterol Sulfate Cardiotoxicity in the Beagle Dog (volume 11-page 169).

Study Number 88400- Study carried out by[ ]

Study Initiation: December 17, 1997.
GLP Compliance: Yes
QA Report: Yes

Methods: To evaluate the cardiovascular toxicity and toxicokinetics in the beagle dog of albuterol sulfate/ipratropium bromide combination solution when administered subcutaneously daily for 30 days and compared with cardiotoxicity of albuterol and ipratropium, administered alone.

Drugs: Albuterol sulfate (batch F453), ipratropium bromide (batch F452), albuterol sulfate/ipratropium bromide solution (batch F451).

Dose Information:

Species	Number of Animals	Dose (µg/kg)	Route	Duration
Beagle dog	3/sex	Combination: albuterol- 15 µg/kg/ ipratropium- 3.08 µg/kg Ipratropium bromide- 3.08 µg/kg Albuterol sulfate- 15 µg/kg	sc	30 days

Results:

Clinical Signs (daily): No mortality or clinical signs in this study.

Body weight (weekly): Body weight gain was similar in all dose groups.

Food Consumption (weekly): There were no drug-related effects on food consumption in this study.

EKGs (weekly, 15-150 minutes after dosing): There were no treatment related EKG changes.

Heart Rates (weekly, 15-150 minutes after dosing): Heart rates were increased in the dogs in the albuterol alone and albuterol/ipratropium combination groups throughout the study. The increases were observed primarily 15-60 minutes after dosing. The heart rate increases in the albuterol alone group were approximately 88-93%, while heart rate increases in the combination ipratropium/albuterol group were approximately 63%.

Hematology (week 4): No significant changes in the hematological parameters were found.

Clinical Chemistries (week 4): Alanine aminotransferase values were increased by approximately 18 % in the albuterol alone and ipratropium/albuterol combination groups. BUN values were increased in these groups by approximately 38 %, and serum glucose values were in increased in these groups by approximately 16%.

Urinalyses (week 4): No treatment-related changes in this study.

Organ Weights (terminal): No major treatment-related changes in the organ. weights.

Gross Pathology (terminal): There was no treatment-related gross pathology in the dogs in this study.—

Histopathology (terminal- standard battery of tissues was examined): There were no treatment-related microscopic changes observed in the tissues of the dogs in this study.

Toxicokinetics (days 2 and 30, 0.5-4 hours after dosing):
Toxicokinetic parameters were evaluated for albuterol alone and for the albuterol/ipratropium combination. The following table summarizes pharmacokinetics of albuterol.

Day	Sex	Dose group	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-4\ hr}$ (ng.hr/mL)	$T_{½}$ (hr)
2	M and F	albuterol alone	5.8	0.5	8.8	1.8
2	M and F	combination	7.3	0.5	10.1	2.0
30	M and F	albuterol alone	6.4	0.5	10.3	2.4
30	M and F	combination	6.5	0.5	9.9	2.3

The C_{max} for albuterol in both the albuterol alone and albuterol/ipratropium combination groups occurred approximately 30 minutes after dosing. The AUC for albuterol was similar in both groups on both day 2 and 30. There were no gender differences for C_{max}, AUC or elimination. There were no significant differences in the pharmacokinetics of albuterol administered alone or albuterol administered concurrently with ipratropium bromide.

Overall Toxicology Summary:
Subchronic studies (30 day) were carried out in the rat and the dog to determine whether the cardiotoxicity of albuterol is potentiated by the concurrent administration of ipratropium bromide. In these studies, the drug was administered subcutaneously, rather than by inhalation, to increase systemic exposure. Five day subchronic studies were conducted in order to determine the doses to be used in the 30 day studies. The 30 day subchronic studies are summarized below:

Species	Duration (days)	Route	Dose levels µg/kg	AUCs (ng.hr/mL) 30 day	Results
Rat, Sprague, Dawley	30	sc	205.5 ipratropium/ 1000 albuterol 205.5 ipratropium 1000 albuterol	M 220 F 144 - M 204 F 137	No deaths. ⇑ heart rates in the albuterol alone and the ipratropium /albuterol groups by 20%. No treatment related micro-scopic changes.
Dog, Beagle	30	sc	3.08 ipratropium/ 15 albuterol 3.08 ipratropium 15 albuterol	9.9 - 10.3	No deaths ⇑ heart rates in the albuterol alone and the ipratropium /albuterol groups by 70%.+++ No treatment related micro-scopic changes.

The major findings of these studies are:
1. The concurrent subcutaneous administration of ipratropium bromide with albuterol sulfate did not potentiate the cardiotoxicity of albuterol.

2. The concurrent subcutaneous administration of ipratropium bromide and albuterol sulfate did not alter the pharmacokinetics of albuterol.

3. On a mg/kg basis, the subcutaneous doses used in the rat study were approximately 25 times the dose expected to reach the lungs of patients that inhale the maximum recommended daily dose. The subcutaneous doses given to dogs were approximately half the dose expected to reach the lungs of patients. These comparisons take into account that only 10 – 20% of an inhaled dose reaches the lung.

4. The lack of microscopic changes in the cardiac tissues of these animals was unexpected, particularly following significant increases in the heart rate. Myocardial necrosis was observed in dogs administered concurrent inhalation doses of albuterol and ipratropium bromide (NDA 20-291).

5. The results of this study confirm the findings of preclinical data submitted in the Combivent NDA (NDA 20-291), except for point 4 above.

Impurities:
During the development of Duovent, Dey chose an overwrap for their product. Dey carried out stability studies and during the course of the testing realized that there was an ingress of [redacted] Dey performed a literature search and concluded that levels in their product were reasonably safe. After reviewing the literature, it was our conclusion that addition data were needed concerning the safety of [redacted] Informed of our decision, Dey decided to develop another overwrap for their product. Dey has not submitted stability data for their new overwrap to their NDA for review.

Labeling:
The labeling for the preclinical sections for Duovent should be revised as follows:

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

Labeling Revisions

Conclusion:
The NDA is approvable pending resolution of the impurities, i.e.,

Recommendations:
Our labeling revisions should be conveyed to the sponsor.

/S/ 4-15-99
Virgil Whitehurst
Pharmacologist

CC: Division file
HFD-570/RHuff
HFD-570/VWhitehurst /S/ 4-15-99
HFD-570/DHilfiker
HFD-570/Kim
HFD-570/Anthracite

OCT 15 1997

Division of Pulmonary Drug Products

Review of Pharmacology and Toxicology Data

IND [redacted] Amendment # 017 dated August 4, 1997

Reviewer : Virgil Whitehurst

Sponsor : Dey Laboratories

Drug : Combination of Albuterol Sulfate and Ipratropium Bromide

Category : Bronchodilators

Indication : Treatment of Asthma

Administration : Inhalation

Reason for the Submission : Response by the sponsor to questions/comments from the FDA.

Comments :
The FDA informed the sponsor that additional preclinical data were needed concerning the safety of their combination drug, albuterol and ipratropium. The FDA also requested additional safety data concerning EDTA, i.e., the potential for EDTA to induce bronchospasms.

The sponsor decided to carry out preclinical studies in the dog and the rat. The objective of these studies is to determine whether the concurrent use of the albuterol and ipratropium is more toxic than either of the drugs given alone. The sponsor submitted the protocols for these studies and the FDA made comments concerning the protocols (comments attached). The sponsor also submitted data/ information about the safety of EDTA. This information included the names of several approved drug solutions

which contained EDTA. However, most of these drug solutions were for intra nasal and not for inhalation into the lungs.

As part of reviewing the literature, Dr John Jenkins reported an article by Fishwick et al (attached) that reveals that EDTA can cause bronchospasm in humans at concentrations of approximately 1.2 mg/ml. Data in this study also reveal that EDTA did not induce bronchospasms in humans at concentrations of approximately 0.1 mg/ml when administered as a single dose. There are no data to determine whether EDTA at this concentration induces bronchospasms in humans when given chronically. Additionally, the number of subjects in the EDTA clinical trial were small. Preclinical data (attached) show that EDTA caused bronchospasms in normal dogs as well as dogs with hyperreactive airways

Drs Mary Purucker, the reviewing medical officer, Robert Meyer, medical team leader and I discussed the safety data for EDTA and decided :

1. We would recommend that the sponsor remove the EDTA as a preservative.
2. If the sponsor does not want to remove the EDTA, the proposed clinical trial can be initiated. This conclusion is based on the fact that the concentration of EDTA in this drug solution is 0.1 % (EDTA did not induce bronchospasms in humans when admnistered as single doses using concentrations of 0.1 %). Secondly, the combination of albuterol and ipratropium is not recommended for chronic use (however, the drug is used chronically) and finally, if the results of the clinical trial reveal a larger number of bronchospasms in the subjects treated with the combination drug with EDTA than are observed in the subjects treated with either albuterol or ipratropium alone, the current policy will be re-evaluated. Nevertheless, we will have additional clinical data concerning the potential of an 0.1 % concentration of EDTA to induce bronchospasms in human subjects. Additionally, Jim Vick and I will carry out a dose response study in rats in an attempt to determine the concentrations of EDTA that are potentially bronchospasmogenic.

Recommendation :

Qur decision should be communicated to the sponsor.

[S]

Virgil Whitehurst 10-15-97
Pharmacologist

CC :
Division File
HFD-570/HSheevers
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JAN 2 1996

Division of Pulmonary Drug Products

Review and Evaluation of Pharmacology and Toxicology Drug Products

IND :

Original Review

Serial Number : 000

Information to be Conveyed to the Sponsor : No

Reviewer : VE Whitehurst

Date Review Completion : December 28, 1995

Sponsor : Dey Labs
2751 Napa Valley Corporate Drive
Napa, California

Drug Name :
Albuterol sulfate
Ipratropium bromide

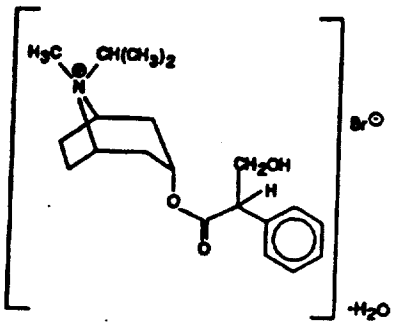
Class : Beta agonist and anti-cholinergic

Indication : Treatment of COPD (Chronic Obstructive Pulmonary Disease)

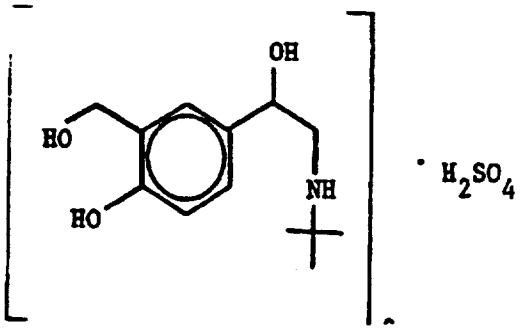
Chemical Names :
Albuterol : (1,3-benzenedimethanol, alpha-[('1,1-dimethylethyl)amino]-4-hydro, sulfate
Ipratropium : 8-Azoniabicyclo[3.2.1]octane,3-(3hydro-1-oxo-2 phenylpropoxy)-8-methyl-8-(1-methyl-ethyl)-,bromide,monohydrate (endo,syn)-,(±)-

Structure and Final Formulation :

Ipratropium bromide:



[redacted]



Albuterol Sulfate (3 mg) and Ipratropium Bromide (0.5 mg) Inhalation Solution

Ingredient	Function	Per mL Vial	Per Lot L)
Albuterol Sulfate, USP	Active Ingredient	3.0 mg [1]	g
Ipratropium Bromide Monohydrate	Active Ingredient		g [3]
Sodium Chloride, USP	To set tonicity at 280 - 320 mOsm/kg	mg	g
Edetate Disodium, USP	Chelating Agent	mg	g
Hydrochloric Acid 1N	To adjust pH to 3.4 (3 to 4)	As required	As required
Purified Water, USP	Diluent	mL	q.s L

1 - Amount needed to give 0.083% w/v Albuterol
2 - Expressed as Ipratropium Bromide, dried basis
3 - Actual quantity of Ipratropium Bromide to be used per batch (g) = 167 / (1 - (% water/100))

Route of Administration : Inhalation

Related NDAs : NDAs 20,291, 19,805, 17559, 17,853 and 19,243

Related INDs : INDs

Proposed Clinical Trial :
The sponsor is proposing a phase 3, multi-center, 12 week crossover study in COPD patients that are at least 40 years old. Both drugs, albuterol and Ipratropium will be mixed and administered as a solution. Drugs will be administered by inhalation qid. Doses proposed are 2.5 mg for albuterol and 0.5 mg for ipratropium or 200 mcg/kg, albuterol and 40 mcg/kg, ipratropium for a 50 kg person. The doses for albuterol and ipratropium given individually will be the same doses that are to be given in the combination.

Preclinical Studies :
No preclinical studies were submitted in this IND, however complete toxicology profiles have been developed for albuterol and ipratropium alone and in combination delivered via a valve have been performed and submitted in NDA 20,291. These data have been reviewed by Dr J Sun(see pharmacology review dated November 9, 1993). The conclusion of this review is that NDA is approvable.

Based on this review, the target organs are :
Albuterol Sulfate :
Tachycardia and cardiac necrosis/fibrosis and decreased liver glycogen (dogs)
Harderian gland hypertrophy, increase in growth of salivary gland, increase colloid in the pituitary gland (rats).

Ipratropium Bromide
Liver, GI tract, adrenal and male reproductive organs (rats)
Liver, GI tract and eyes (dogs)
Liver, GI tract, male reproductive organ, kidney and thymus (rabbits)

It has been shown via preclinical studies in the dog and the rat that the toxicity observed when albuterol and ipratropium are administered concurrently are no greater than when either of these drugs are administered alone.

Additionally, albuterol and ipratropium has been used in combination in the treatment of COPD since 1975. It is widely accepted that the use of the combination is superior to the use of either of the drug administered alone. The mechanism of action of these drugs are as follows :
Albuterol increases airway bronchodilation and reduces inflammation while ipratropium prevents airway constriction by inhibiting the release of acetylcholine from pulmonary nerve endings and inhibits the hypertrophy of submucous and goblet glands, thereby reducing mucous formation.

Conclusion :
Clinical trial maybe initiated as proposed.

/S/ 12-29-95

Virgil Whitehurst
Pharmacologist

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HFD-571/CSO

Approved /S/ 1/2/96