

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-527

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW**NDA number:** NDA 21-527

Chemistry consult number: 005

Sequence number/date/type of submission: 000/October 5, 2005/SCS/004**Information to sponsor:** Yes () No (x)**Sponsor and/or agent:** Boehringer Ingelheim Pharmaceutical Inc**Manufacturer for drug substance:** Boehringer Ingelheim Pharma KG**Reviewer name:** Virgil Whitehurst, Ph.D.**Division name:** Division of Pulmonary and Allergy Products**Review completion date:** January 24, 2006**Drug:**

Trade name: Atrovent HFA 134 Inhalation Solution

Generic name: Ipratropium Bromide

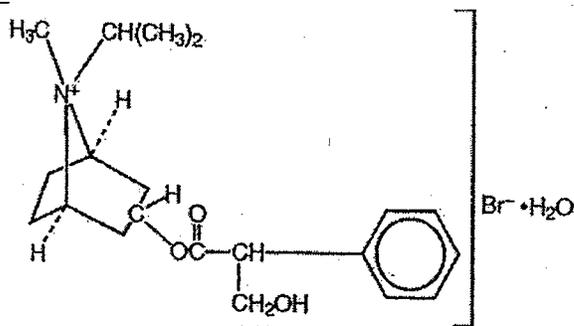
Code name: NA

Chemical name: 8-azoniabicyclo (3.2.1)-octane, 3-(3-hydroxy-1-oxo-2-phenylproxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate

CAS registry number: NA

Molecular formula/molecular weight: $C_{20}H_{30}BrNO_3 \cdot H_2O/430.4$

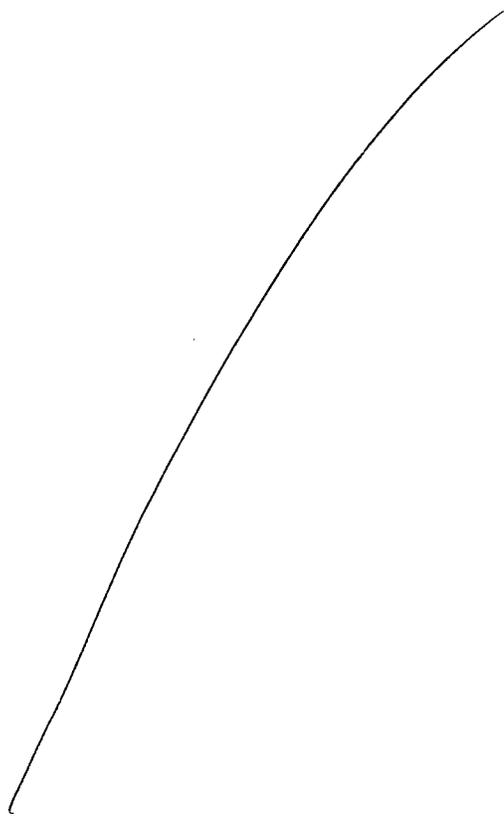
Structure:

**Drug class:** Anticholinergic bronchodilator**Route of administration:** Oral inhalation

Proposed use: The usual starting dose of ATROVENT HFA Inhalation Aerosol is 2 inhalations four times per day in subjects 12 years of age or older. Additional inhalations may be taken as required; however, the total number of inhalations should not exceed 12 in 24 hours. As each actuation contains 16.8 mcg of ipratropium bromide, the maximum daily dose is 201.6 mcg or 4.03 mcg/kg for a 50 kg person.

Introduction and History:

This review is in response to a chemistry consult from Dr. Stuart Zimmerman, CMC reviewer, to evaluate the safety of a _____
Another _____ was previously used.



Evaluation: The proposed acceptance criterion for _____ in each canister is ~ There are 200 actuations in each canister. Therefore, the maximum amount of

— is — actuation. The maximum number of actuations per day is 12 actuations. Thus, the maximum daily exposure of — is — day or — mcg/kg for a 50 kg person.

Additionally, the sponsor conducted a bacterial mutagenicity assay in support of safety for — The assay is reviewed below:

Study title: — **Mutagenicity Testing with Salmonella typhimurium TA 1535, TA 1535, TA 98, TA100 and Escherichia coli WP2 uvrA (pKM101). Plate Incorporation Reverse mutation Assay with and without Metabolic Activation**

Key findings: — was found not to be mutagenic under the conditions tested in Salmonella typhurium strains TA 1535, TA 1537, TA 98 , TA 100 and Escherchia coli WP2uvrA (pKM101) in the presence and absence of S9 mix from Arocolor induced rat liver, when tested up to 1,200 mcg/plate. — precipitated at concentrations of 600 and 1,200 mcg/plate when added to the aqueous solutions suggesting these concentrations exceeded the limits of solubility. The test article increased cytotoxicity in strain TA 100 at doses of 75 µg/plate.

Study no.: 04R132

Volume # and page #: volume 1, page 1

Conducting laboratory and location: Dept of Toxicology and Safety Assessment, Research and Development Center, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT

Date of study initiation: November 4, 2004

GLP compliance: Yes

QA reports: yes (x) no ()

Drug, lot #, and % purity: — purity was not conducted because of the complex nature of the test article.

Methods

Strains/species/cell line: Four strains of *Salmonella typhimurium*, TA 1535, TA 1537, TA 98 and TA 100 and *Escherchia coli* WP2uvrA (pKM101).

Doses used in definitive study: 38, 75, 150, 300, 600 and 1,200 mcg/plate; tests with TA100 were repeated at doses of 9, 19, 38, 75, 150 and 300 µg/plate in the absence of rat liver S9 due to observed cytotoxicity

Basis of dose selection: No independent range finding study was conducted for this study. The dose selection was based on solubility testing and toxicity.

Negative controls: DMSO

Positive controls:**With S9 mix:**

2-aminoanthracene, 1 mcg/plate for Salmonella typhurium strains TA 1535, TA 98 and TA 1000; 2 mcg/plate E. coli WP2 uvrA (pKM101) and Salmonella typhurium strain 1537

Without S9 mix:

9-Aminoacridine 50 mcg/plate for S typhurium TA 1537
2- Nitrofluorene 1 mcg for S. typhurium TA98
Sodium azide 10 mcg/plate for S. typhurium TA 100
Methyl methane sulfonate (MMS) 1.25 mcg/plate with E .coli WP2 uvrA (pKM101

Incubation and sampling times: The plate incorporation method was used. When the agar was set, the plates were inverted and incubated for 2 days at 37 degree C. The colonies were counted using an _____ automated counter. The plates were examined for precipitates of the test article and toxicity to the background lawn.

Results

Study validity: The study was valid because each test had at least two plates of each control/dose which were scorable. The selected bacterial strains were acceptable. The vehicle controls were within acceptable limits and within the historical laboratory limits. The positive controls were acceptable and were at least 2x the concurrent vehicle mean revertant numbers. There were at least 3 dose levels for each test. The test article precipitated upon addition to the aqueous solutions at the 600 and 1200 mcg /plate concentrations suggesting toxicity/exceeding the limits of solubility. Dose selection was appropriately based upon observed precipitation and cytotoxicity.

Study outcome: _____ was non-mutagenic under the conditions of the assay. There were no significant increases in colony numbers in Salmonella typhurium strains TA 1535, TA 1573, TA 98 and TA 100 and Escherichia coli WP2 uvrA (pKM101). The positive controls produced expected increased in mutation frequency. Precipitation was noted 600 µg/plate or greater. Increased cytotoxicity (~ 50-75%) was noted with strain TA 100 at doses of 75 µg/plate or greater.

Based on the results of this study, _____ tested negatively in this assay under the conditions tested.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The maximum expected exposure to _____ through the use of Atrovent HFA Inhalation Solution at the proposed acceptance criterion of _____ µg/canister is acceptable. The maximum daily exposure for _____ is expected to be _____ day _____ mcg/kg for a 50 kg person). This level of exposure is below the Division's acceptable daily maximum exposure for leachables and extractables _____

mcg/day) in the absence of any genotoxicity or respiratory irritation concerns. No concerns have been identified by the reviewing chemist and the _____ is highly similar to the previously _____

_____. Additionally, the sponsor conducted a bacterial mutagenicity assay (Ames) and the results of the assay revealed that _____ was not mutagenic under the conditions of the assay. Although this assay does not provide a complete evaluation of the individual components _____ it does provide a reasonable assurance of the mutagenic potential of the _____

Recommendations: _____ is reasonably safe at the maximum expected daily exposures associated with the acceptance criterion of _____ mg/day proposed by the sponsor.

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/s/

Virgil Whitehurst
1/24/2006 02:19:01 PM
PHARMACOLOGIST

Timothy McGovern
1/24/2006 02:25:32 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: N21-527

Review number: 003

Sequence number/date/type of submission: N 000/January 6, 2002/ New Correspondence

Information to sponsor: Yes (x) No ()

Sponsor and/or agent: Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT

Manufacturer for drug substance: Boehringer Ingelheim Pharma KG

Reviewer name: V Whitehurst. Ph.D.

Division name: Division of Pulmonary and Allergy Drug Products

HFD #: HFD 570

Review completion date: February 17, 2005

Drug:

Trade name: Atrovent HFA 134 Inhalation Solution

Generic name: Ipratropium Bromide

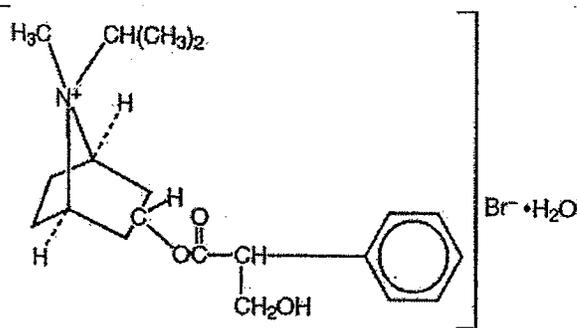
Code name: NA

Chemical name: 8-azoniabicyclo (3.2.1)-octane, 3-(3-hydroxy-1-oxo-2-phenylproxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate

CAS registry number: NA

Molecular formula/molecular weight: $C_{20}H_{30}BrNO_3 \cdot H_2O$ /430.4

Structure:



Drug class: Anticholinergic bronchodilator

Indication: Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema

Route of administration: Oral inhalation

Proposed use: The usual starting dose of ATROVENT HFA Inhalation Aerosol is 2 inhalations four times per day in subjects 12 years of age or older. Additional inhalations may be taken as required; however, the total number of inhalations should not exceed 12 in 24 hours. As each actuation contains — mcg of ipratropium bromide, the maximum daily dose is 201.6 mcg or 4.03 mcg/kg for a 50 kg person.

Introduction and History:

This review is in response to the sponsor's submission of and a request for feed back on a 90 day toxicology study proposal to qualify the newly proposed specification for the leachable — mcg/canister or — mcg/kg/day based on 200 actuations/can and a maximum of 12 actuations per day).

In teleconferences dated October 27 and 29, 2004, the Division informed BIPI that the proposed specification for the leachable — was too high (propose specification at that time was — /canister or — kg/day daily dose for a patient). This conclusion is detailed in chemistry consults by Dr. V Whitehurst dated October 6, 2003. The sponsor could address the issue through one of the following ways:

1. Lower the specification to NMT — mcg/canister (— g/day).
2. Lower the specifications to NMT — canister and provide the results of a 90 day animal qualification study for our review within nine months post approval. The Division recommended that the sponsor provide the protocol for the proposed animal qualification study for the Division's feedback within two months post-approval (approval dated 11/17/04).
3. Lower the specifications to NMT — /canister and provide published literature to support your proposed specification and/or provide information about a marketed MDI drug product similar to Atrovent HFA Inhalation solution that contains this leachable. In addition, provide the details of the proposed qualification within two months post approval. Please note that the decision on the adequacy of the data obtained from published literature or from another MDI, is a review issue.
4. Lower the specifications to NMT — mcg/canister and if available, provide the actual levels of — in the drug formulation given to the rats in the 90 day study with Atrovent HFA to allow for an adequate safety assessment within two months post-approval.

The Division explained that in order to use the completed 90-day rat study to qualify — for safety, we need the actual levels of — in the administered formulation at the time of dosing in order to determine the exposure levels in the rats.

In the current submission, the sponsor submitted a 90 day rat inhalation toxicity study proposal for comments. The sponsor has modified the proposed specification for $\mu\text{g}/\text{canister}$ in the drug product to $\mu\text{g}/\text{kg}/\text{day}$ and not the original proposed specification of $\mu\text{g}/\text{canister}$ or $\mu\text{g}/\text{kg}/\text{day}$. The sponsor also submitted the text portion of study report U96-3000, a 13-week inhalation study of Atrovent HFA in rats, that was finalized in December, 1995.

Review:

The sponsor is proposing an inhalation study in Sprague Dawley rats (15 sex/dose group). The sponsor intends to use Atrovent HFA canisters that will have been stored under stress conditions to induce formation of leachables as expected after maximum shelf life. The canisters will be analyzed in 2-4 week intervals until the principal leachable reaches a concentration of about $\mu\text{g}/\text{can}$. At that time a full leachable profile will be generated.

The sponsor proposes a study design that will allow a comparison with their original bridging study in rats (U96-3000; study reviewed by Dr. M. Chun under IND 45,938 and dated 2/28/1998). The proposed study will include 3 dose groups:

Dose Group	Targeted Ipratropium bromide Inhalation Daily Dose (mcg/kg/day)	Targeted Inhalation Daily Dose (mcg/kg/day)	Pulmonary deposited dose of ipratropium bromide (mcg/kg/d)*	Pulmonary deposited dose of (mcg/kg/d)*	Animal to human exposure margin**
Unstressed controls	1,200		120		-
Low dose	600		60		11
High dose	1,200		120		22

* Incorporation of a 0.1 pulmonary deposition factor in rats

** Pulmonary deposited dose of μg in rats divided by the maximum anticipated human exposure to $\mu\text{g}/\text{can}$ at a product specification of $\mu\text{g}/\text{kg}$.

The sponsor provided the following justification for control groups and dose level: The unstressed control allows for comparison of qualified (stressed) to unqualified material at the no effect level (NOEL) for Atrovent HFA reported in study U96-3000. The proposed low dose (target inhalation dose of 600 mcg/kg IB) is ~ 120-fold the anticipated maximum human therapeutic exposure to IB and . The high dose (target inhalation dose of 1200 mcg/kg IB) was the NOEL in study U96-3000 and, thus, any finding in the new study can be attributed to the administered leachables rather than to active substance. This dose is anticipated to be ~ 240 times the anticipated human daily intake.

The study design will be similar to that of the original bridging study (U96-3000) including in-life parameters and post-mortem examination with the following exceptions: Atrovent exposure will be measure din plasma rather than in urine; the higher strength of 42 mcg IB used in the previous study will not be used in the current one since the higher strength is no longer being pursued; the experimental design will focus on stressed versus

unstressed Atrovent HFA drug product; and due to the dose selection the maximum duration of exposure will be one hour rather than variable times up to 4 hours as described in the U96-300 report. The submission states that the earliest possible start of the study would be March 2005 provided the stress samples have reached the target levels of —. The next possible start date would be the end of June 2005. A report is expected to be available within 12 months after study initiation.

Reviewer Assessment:

A review of the proposal for the 90 day inhalation toxicity study in rats to qualify an anticipated product specification of — mcg — /canister or — mcg/kg/day reveals that the doses proposed for the study are acceptable. The previous Division review of study U96-3000 confirms the sponsor's contention that the proposed high dose of IB (1.2 mg/kg inhalation dose, 120 mcg/kg pulmonary deposited dose) in the new study is similar to the NOAEL identified for IB in the previous study (1.1 mg/kg inhalation dose; 110 mcg/kg pulmonary deposited dose). Thus, it is anticipated that no IB toxicity will be identified at the two proposed dose levels. This will, as the sponsor suggests, allow for the identification of any — or other leachable-related toxicity. The proposed doses of IB and anticipated levels of — will provide exposure margins of 11- to 22-fold based on use of pulmonary deposited doses in rats and the maximum anticipated human exposure to — through use of Atrovent HFA at a product specification of — mcg/can. The actual identification of a NOAEL dose must await review of the completed study report.

The sponsor's proposed study design is acceptable as it mirrors that of the previous study U96-3000 with the above noted exceptions. However, the sponsor should consider incorporation of an air control group which may be useful in the final assessment of the study results.

Conclusion:

The 90 day inhalation toxicity study proposal to qualify a proposed — specification of — mcg/canister or — mcg/kg/day is acceptable. Actual support of this stated specification must await review of the completed study report.

Comments to sponsor:

Your proposal for a 13-week inhalation toxicity study of Atrovent HFA in rats to qualify leachables with particular reference to — is acceptable since the study design is adequate and the proposed doses provide exposure margins that are 11-22 times the maximum expected human exposure to — (using a pulmonary deposition factor of 0.1 in rats) through use of Atrovent HFA at a product specification of — mcg/canister. A final determination as to the acceptance of the product specification will await review of the completed study report.

You are encouraged to consider incorporation of an air control group which may be useful in the final assessment of the study results.

Virgil Whitehurst
Pharmacologist

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Virgil Whitehurst
2/17/05 10:07:02 AM
PHARMACOLOGIST

Timothy McGovern
2/17/05 10:11:24 AM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: N21-527

Chemistry consult number: 004

Sequence number/date/type of submission: 000/May 18, 2004/BL

Information to sponsor: Yes (x) No ()

Sponsor and/or agent: Boehringer Ingelheim Pharmaceuticals

Manufacturer for drug substance: Boehringer Ingelheim Pharma KG

Reviewer name: V Whitehurst. Ph.D.

Division name: Division of Pulmonary and Allergy Drug Products

HFD #: HFD 570

Date of consult: November 4, 2004

Review completion date: November 4, 2004

Drug:

Trade name: Atrovent HFA 134 Inhalation Solution

Generic name: Ipratropium Bromide

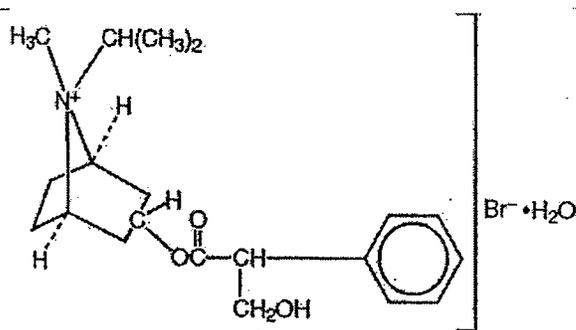
Code name: NA

Chemical name: 8-azoniabicyclo (3.2.1)-octane, 3-(3-hydroxy-1-oxo-2-phenylproxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate

CAS registry number: NA

Molecular formula/molecular weight: $C_{20}H_{30}BrNO_3 \cdot H_2O/430.4$

Structure:



Drug class: Anticholinergic bronchodilator

Indication: Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema

Route of administration: Oral inhalation

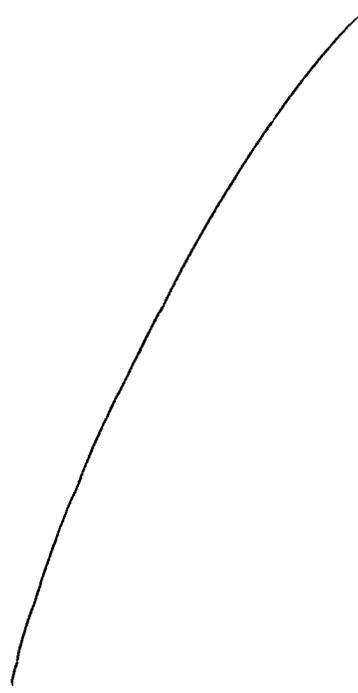
Proposed use: The usual starting dose of ATROVENT HFA Inhalation Aerosol is 2 inhalations four times per day in subjects 12 years of age or older. Additional inhalations may be taken as required; however, the total number of inhalations should not exceed 12 in 24 hours. As each actuation contains 0.05 mcg of ipratropium bromide, the maximum daily dose is 201.6 mcg or 4.03 mcg/kg for a 50 kg person.

Introduction and History:

This review is in response to a verbal request from Dr. Prasad Peri, CMC reviewer, to evaluate the safety of [redacted] namely the individual components of [redacted]. Dr. Peri was particularly interested in the safety of [redacted] and an unidentified peak in the [redacted].

Review:

The individual components of [redacted] are listed below.



Neither [redacted] or any of their components, with the exception of the unidentified peak for [redacted], have structural alerts for mutagenicity/carcinogenicity according to Dr Peri.

Since the maximum daily exposures of _____ are _____ ng/kg at the proposed acceptance criteria, both are considered to be safe since the maximum daily exposure is below the Division's qualification threshold of 100 ng/kg/day for compounds with no evidence of structural alerts for mutagenicity/carcinogenicity. The individual components are also considered safe since by definition their maximum daily human exposure would be less than 100 ng/kg/day. This conclusion assumes that the unidentified peak for _____ does not represent a compound with a structural alert.

Conclusion:

The proposed acceptance criteria for _____ are considered safe since the maximum daily exposures of _____ are below the Division's safety qualification threshold of 100 ng/kg/day for compounds without structural alerts for mutagenicity/carcinogenicity. This conclusion assumes that the unidentified peak for _____ does not represent a compound with a structural alert.

Recommendation:

The proposed acceptance criteria for the _____ and their individual components are considered to be safe. This recommendation assumes that the unidentified peak for _____ does not represent a compound with a structural alert.

Virgil Whitehurst
Pharmacologist

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/s/

Virgil Whitehurst
11/4/04 02:57:37 PM
PHARMACOLOGIST

Timothy McGovern
11/4/04 03:01:58 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY REVIEW**NDA number:** NDA 21-527**Review number:** 2**Sequence number/date/type of submission:** 000/ May18, 2008/ BL, labeling submission**Information to sponsor:** Yes (X) No ()**Sponsor and/or agent:** Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT**Manufacturer for drug substance:** Boehringer Ingelheim Pharma KG**Reviewer name:** V Whitehurst, Ph.D.**Division name:** Division of Pulmonary and Allergy Drug Products**HFD #:** HFD 570**Review completion date:** September 1, 2004**Drug:**

Trade name: Atrovent HFA Inhalation Aerosol

Generic name: Ipratropium bromide

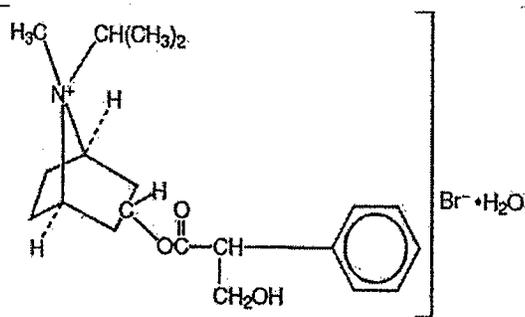
Code name: NA

Chemical name: 8-azoniabicyclo (3.2.1)-octane, 3-(3-hydroxy-1-oxo-2-phenylproxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate

CAS registry number: NA

Molecular formula/molecular weight: $C_{20}H_{30}BrNO_3 \cdot H_2O/430.4$

Structure:

**Relevant INDs/NDAs/DMFs:**

DMF —

IND 45,983, Boehringer Ingelheim, Atrovent HFA-134a Inhalation Aerosol

NDA 19-085, Boehringer Ingelheim, Atrovent Inhalation Aerosol with CFC

NDA 20-228, Boehringer Ingelheim, Atrovent Inhalation solution

NDA 20-393, Boehringer Ingelheim, Atrovent 0.03% nasal spray

NDA 20-394, Boehringer Ingelheim, Atrovent 0.06% nasal spray

Drug class: Anticholinergic bronchodilator

Indication: Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema

Clinical formulation:

TABLE 3.3.2.1:1 Composition of Ipratropium Bromide Monohydrate (HFA-134a) Inhalation Aerosol

Ingredient	Function	Weight Percent (g/100 g)	Weight per Container (g)	Weight per Actuation Ex-Valve***	Weight per Actuation Ex-Mouthpiece (label claim)
Ipratropium Bromide Monohydrate (unmiconized)	Active Ingredient	—	—	21.00 µg	—
Citric Acid, USP (anhydrous)	/	/	/	/	—
Purified Water, USP					—
Dehydrated Alcohol, USP *					—
1,1,1,2-tetrafluoroethane (HFA-134a)	Propellant	—	—	—	—
TOTAL		100.000	—	—	—

Route of administration: Oral inhalation

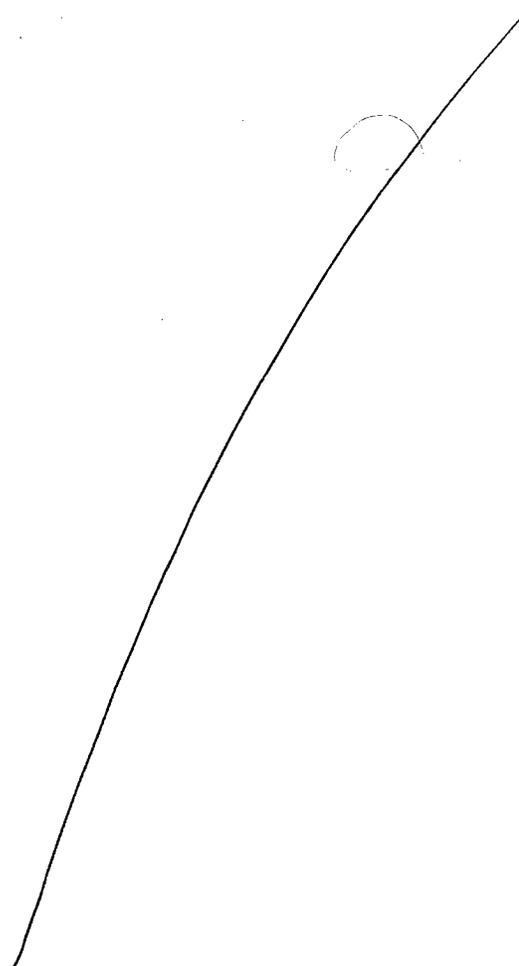
Proposed use: The usual starting dose of ATROVENT HFA Inhalation Aerosol is 2 inhalations four times per day in subjects 12 years of age or older. Additional inhalations may be taken as required; however, the total number of inhalations should not exceed 12 in 24 hours. As each actuation contains ~ .mcg of ipratropium bromide, the maximum daily dose is 201.6 mcg or 4.03 mcg/kg for a 50 kg person.

Introduction:

The May 18, 2004 labeling supplement is in response to the Division's Approvable letter to the sponsor dated October 9, 2003. The sponsor was requested to submit revised labeling as shown in the marked up labeling. The originally proposed nonclinical sections of the product label were discussed in a review dated October 1, 2003. We have

reviewed the currently proposed labeling submitted by the sponsor and the sponsor has accepted most of the Division's recommended changes to these sections except for several minor omissions (omissions are in bold type) that are described below.

Review of Nonclinical Sections of Product Label:



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 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 ✓ § 552(b)(4) Draft Labeling

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/s/

Virgil Whitehurst
9/1/04 03:04:25 PM
PHARMACOLOGIST

Timothy McGovern
9/1/04 03:19:44 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 21-527

Chemistry consult number: 2

Sequence number/date/type of submission: 000/December 6, 2002/Original NDA

Information to sponsor: Yes () No (x)

Sponsor and/or agent: Boehringer Ingelheim Pharmaceuticals

Manufacturer for drug substance: Boehringer Ingelheim Pharma KG

Reviewer name: Timothy J. McGovern, Ph.D.

Division name: Pulmonary and Allergy Drug Products

HFD #: 570

Date of consult: October 7, 2003

Review completion date: October 7, 2003

Drug:

Trade name: Atrovent HFA 134 inhalation solution

Generic name: Ipratropium Bromide

Chemical name: 8-azoniabicyclo (3.2.1)-octane, 3-(3-hydroxy-1-oxo-2-phenylproxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate

CAS registry number: NA

Molecular formula/molecular weight: $C_{20}H_{30}BrNO_3 \cdot H_2O/430.4$

Drug class: Anticholinergic bronchodilator

Indication: Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema

Route of administration: Oral inhalation

Proposed use: The usual starting dose of ATROVENT HFA Inhalation Aerosol is 2 inhalations four times per day in subjects 12 years of age or older. Additional inhalations may be taken as required; however, the total number of inhalations should not exceed 12 in 24 hours. As each actuation contains --- mcg of ipratropium bromide, the maximum daily dose is 201.6 mcg or 4.03 mcg/kg for a 50 kg person.

Introduction and History:

This review is in response to a verbal chemistry consult to evaluate the safety of ---

--- Therefore, --- μg /actuation of ---
total daily exposure is --- /day.

Sponsor's assessment:

The sponsor was unable to identify any references characterizing the toxicology profile of _____ Results of single and repeated dose experiments utilizing oral, parenteral and inhalational administration of _____ to mice, rats, dogs and/or cats reveal that enormous doses are required to illicit evidence of systemic toxicity. For example, IP administration of _____ 50 mg/kg/d to mice (14 days) and dietary administration 1500 mg/kg to rats (2 years) were "no effect" doses. Based on this data, the sponsor contends that there is a 450,000 to 2,000,000 safety margin compared to a worst case daily dose of _____ µg/kg of _____

In addition, _____ was without mutagenic potential in an Ames assay and there was no evidence of carcinogenic potential in rats during a 2-year dietary study. _____ exhibited neither irritant nor sensitizing potential in human volunteers (maximization test), although it was reported to possess sensitizing potential in guinea pigs in Freunds adjuvant in a maximization test.

The following information was submitted by the sponsor:

Route	Species	Description	Results	Referenece
Acute systemic toxicity studies				
Oral	Rat	5-15 ml/kg	LD50 ~ 7 ml/kg; weakness, depression, hyperirritability, convulsions, respiratory failure	/
Oral	Cat	1.1 to 10.8 g/kg	LD50 ~ 4 g/kg; nausea, vomiting, weakness, tremor, hypothermia, shallow respiration, prostration, convulsions, respiratory failure	/
IP	Mice and rats	Dose range not specified	LD50 was 1.75 g/kg in mice; LD50 was 4.2 ml/kg in rats; hemorrhage in lung, pancreas and thymus and marked congestion in kidney and liver.	/
SC	Rats	Dose range not specified	LD50 ~ 6.6 ml/kg; pulmonary and thymic hemorrhage; necrotic lesions at injection site	/
Dermal	Guinea pigs and rabbits	Applied to skin	LD50 > 10 g/kg (guinea pigs) LD50 > 5 g/kg (rabbits)	/
IH	rats	1300 – 3500 ppm vapor for 6 hours	6 hr LC50 was ~ 1300 ppm	/
Repeated dose systemic studies				

IP	Mice	350 mg/kg for 14 days	Reduced BW gain
IH	Rats	296 ppm or more for 6 hr/d for 62 d	Weakness, pleural infusion and pulmonary edema; no effect at 296 ppm
Dietary	Rats	0.5, 1 or 2% for 8 weeks	No toxicity
Dietary	Rats	5% for 12 days	1 of 8 rats died
Dietary	Dogs	55 or 280 mg/kg/d	No toxicity observed
Oral	Cats	0.25 ml/kg for 8 weeks	Weakness, ataxia, depression after 4 th and 5 th doses
Dietary	rats	165, 500 or 1500 mg/kg/d for 2 years	No effects noted
Reproductive toxicity			
Instillation into eggs	Chicken embryos	Maximum instilled dose was 10 mg	No evidence of teratogenesis
Special toxicity			
ID	Guinea pig	— in Freund's adjuvant; guinea pig maximization test	Strong sensitizer in 9/10 animals
Dermal	Humans	Repeat insult patch test	No dermal irritation or contact sensitization in 50 subjects
Dermal	Rabbits	— applied to intact or abraded skin for 24 hours	No evidence of irritation
Mutagenicity			
In vitro	Yeast and bacteria	0.4 to 1.7%	No evidence of mutagenicity
In vitro	Mouse lymphocytes		3×10^{-3} M or greater inhibited growth of cells; transient effect

Reviewer's assessment:

Although the toxicity profiles of the _____ have not been documented, there is no reason to suspect that the profiles would differ significantly from that observed for _____. Therefore, the data available for _____ will be used for an overall safety assessment.

A review of the literature and databases identified similar information as described by the sponsor. In addition, _____ is considered GRAS when added directly to human food with no limit other than accordance with current good manufacturing practice as per _____. The most relevant toxicity study for the safety evaluation is the 2-year dietary study conducted by _____. In this study, no effects were observed at doses up to 1500 mg/kg/d. After applying a 100-fold safety factor for the use of oral toxicity data to support inhalation exposure and a 10-fold safety factor for cross species (rat to human) conversion, the no effect dose is considered to be 1.5 mg/kg/day (75 mg/day for a 50 kg subject) for human inhalation. Therefore, the estimated maximum dose of _____ through the use of ATROVENT HFA (_____ µg) is considered to be acceptable due to a resulting safety margin of ~ 5,500 compared to the safe inhalation dose. Even using the sponsor's calculated worst case setting of a maximum daily intake of _____ of _____, a safety margin of ~ 1,900 is present.

CONCLUSION:

The maximum expected daily exposure to _____ is considered to be acceptable from a safety perspective.

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/s/

Timothy McGovern
10/7/03 04:15:43 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: N21-527

Chemistry consult number: 001

Sequence number/date/type of submission: 000/December 6, 2002/Original NDA

Information to sponsor: Yes () No (x)

Sponsor and/or agent: Boehringer Ingelheim Pharmaceuticals

Manufacturer for drug substance: Boehringer Ingelheim Pharma KG

Reviewer name: V Whitehurst, Ph.D.

Division name: Division of Pulmonary and Allergy Drug Products

HFD #: HFD 570

Date of consult: August 1, 2003

Review completion date: October 6, 2003

Drug:

Trade name: Atrovent HFA 134 inhalation solution

Generic name: Ipratropium Bromide

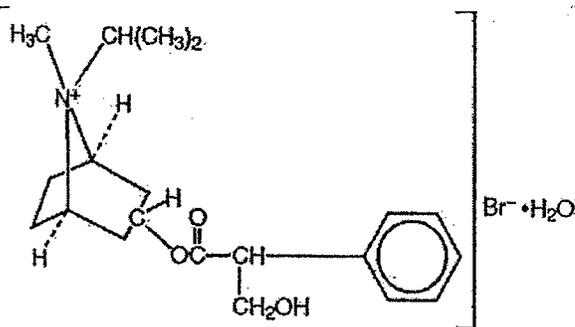
Code name: NA

Chemical name: 8-azoniabicyclo (3.2.1)-octane, 3-(3-hydroxy-1-oxo-2-phenylproxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate

CAS registry number: NA

Molecular formula/molecular weight: $C_{20}H_{30}BrNO_3 \cdot H_2O/430.4$

Structure:



Drug class: Anticholinergic bronchodilator

Indication: Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema

Route of administration: Oral inhalation

Proposed use: The usual starting dose of ATROVENT HFA Inhalation Aerosol is 2 inhalations four times per day in subjects 12 years of age or older. Additional inhalations may be taken as required; however, the total number of inhalations should not exceed 12 in 24 hours. As each actuation contains — mcg of ipratropium bromide, the maximum daily dose is 201.6 mcg or 4.03 mcg/kg for a 50 kg person.

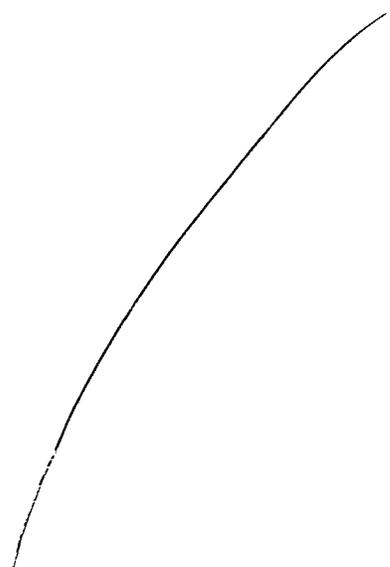
Introduction and History:

This review is in response to a chemistry consult from Dr. Prasad Peri, CMC reviewer to evaluate the safety of the maximum potential number and mass per dose of —, leachables believed to be derived from the —.

The maximum daily projected exposure for — is — mcg/day, respectively. According to Dr. Peri, the identity of the particulate matter has not been completely accomplished.

Talc: Information provided by the sponsor indicates that the maximum potential mass of — is — µg/dose (one dose is equal to two actuations). In terms of particle size, the exposure is —. The maximum daily — exposure based upon 12 actuations per day is expected to be —.

The sponsor's rationale for qualification is as follows:



46 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

A safety assessment of total _____ leachables is not possible without a complete identification of all particulate matter. However, based upon the identified types of particles by the sponsor, the potential exposure to the _____ particles is considered to be acceptable. Further, the maximum expected exposure to the _____ extractables, with the exception of _____ are acceptable. Since the maximum expected daily exposure to the _____ exceeds _____ /day, the sponsor should provide adequate toxicological qualification to support chronic administration. Possible routes would be for the sponsor to provide either leachable data to demonstrate that the actual levels of _____ in the formulation would be less than _____ day or to provide actual levels of _____ in the drug formulation given to rats in the 3 month inhalation study with ATROVENT HFA. The maximum expected daily exposures to the _____ extractables, _____ are considered to be acceptable based upon their GRAS status for foods with incorporated safety margins for inhalation as well as other supporting data.

Recommendations:

The maximum expected exposure to _____ through the use of ATROVENT HFA Inhalation Solution is considered to be acceptable.

The maximum expected daily exposure to _____ extractables through the use of ATROVENT HFA Inhalation Solution is considered to be acceptable.

The maximum expected daily exposure to _____ extractables through the use of ATROVENT HFA Inhalation Solution, with the exception of _____ is considered to be acceptable. The sponsor should provide adequate toxicological qualification to support chronic administration of _____. Possible avenues for qualification include the sponsor providing either leachable data to demonstrate that the actual levels of _____ in the formulation or to provide actual levels of _____ in the drug formulation given to rats in the 3 month inhalation study with ATROVENT HFA to allow for an adequate safety assessment.

The maximum expected daily human exposures of the _____ extractables (_____) through use of ATROVENT HFA are considered to be acceptable.

Identification should be provided for any particulate matter that has not yet been identified to allow for an adequate safety assessment.

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/s/

Virgil Whitehurst
10/6/03 05:42:19 PM
PHARMACOLOGIST

Timothy McGovern
10/6/03 05:48:03 PM
PHARMACOLOGIST

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA #: 21-527

Drug Name: Atrovent HFA Inhalation Aerosol

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Indication: Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema

Division: Pulmonary and Allergy Drug Products

Reviewer: Virgil E. Whitehurst, Ph.D.

Regulatory Recommendation: AP

Date: October 1, 2003

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability

This NDA is approvable from a nonclinical perspective pending inclusion of the recommended changes to the product label.

1.2 Recommendation for nonclinical studies

None

1.3 Recommendations on labeling

The "Carcinogenesis, mutagenesis, impairment of fertility", "Pregnancy" and the "OVERDOSAGE" sections should be revised in terms of the estimated animal to human dose comparisons and other edits to conform with the most recently approved ATROVENT labels and the CFR (see suggested labeling in Section 3.5 of this review). In addition, the deletion of information from the _____ should be evaluated by the Medical Officer.

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings

No significant nonclinical findings were revealed. Ipratropium bromide, the active ingredient of the application, has been approved for the treatment of COPD in a metered dose inhaler (MDI) and inhalation solutions. Atrovent Inhalation Aerosol containing CFCs is being phased out because of its harmful effects on the environment. As a result, a new Atrovent formulation with HFA 134a as the propellant has been developed. The sponsor met with the FDA several times to discuss non-clinical development issues. In 1992, the FDA and the sponsor agreed that 14 day toxicology studies in 2 species and a 90 day study in the most sensitive would be sufficient to compare non-clinical toxicities between the Atrovent CFC and Atrovent HFA 134a formulations. The 14 day studies were submitted to IND 9,814 and reviewed in August, 1994 and the 90 day study in rats was submitted to IND 45,983 and reviewed (review dated February 6, 1998). The 14 day inhalation study in the Sprague Dawley rat included an air control, a vehicle control and 0.043, 0.13 and 0.2 mg/kg of Atrovent HFA 134a and a positive control, Atrovent CFC. The high dose of Atrovent HFA134a was increased to 4.6 mg/kg on day 8 and 9.2 mg/kg on day 12. The NOAEL was determined to be 9.2 mg/kg. Both formulations caused thickening of the nasal turbinates and salivation. In the dog (Beagle) study, air and vehicles controls, 170, 350 and 620 mcg/kg of Atrovent HFA 134a and positive dose of 180 mcg/kg Atrovent CFC were included. These studies revealed that the toxicity profile and toxicokinetics of the CFC and HFA 134a formulations were comparable. In the 90 day in the Sprague-Dawley rat, air control, HFA 134a vehicle, 1.1, 4.6, and 9.2 mg/kg of Atrovent HFA 134a and a positive control, 1.1 mg/kg Atrovent CFC were included. The NOAEL was determined to be 1.1 mg/kg. The results of this study support the results obtained in the 14 day studies and show that the toxicological profile and toxicokinetics

of the two formulations are comparable. The target organs for Atrovent in toxicity studies (dog and rat) are liver and the GI tract.

2.2 Pharmacologic activity

Atrovent is an anticholinergic (parasympatholytic) agent that acts to block transmission of vagally-mediated impulses by competitive inhibition of acetylcholine. Atrovent is a quaternary ammonium of atropine. Atrovent has bronchodilator and anti-secretory activities. Atrovent is a selective muscarinic receptor antagonist with potent in vitro and in vivo activities. The broncho-spasmolytic activities of Atrovent occurred at doses well below those where CNS, cardiovascular and gastrointestinal effects were seen with atropine or other atropine derivatives.

2.3 Nonclinical safety issues relevant to clinical use

None

**APPEARS THIS WAY
ON ORIGINAL**

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 21-527

Review number: 001

Sequence number/date/type of submission: 000/December 9, 2002/Original NDA submission

Information to sponsor: Yes (X) No ()

Sponsor and/or agent: Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT

Manufacturer for drug substance: Boehringer Ingelheim Pharma KG

Reviewer name: V Whitehurst, Ph.D.

Division name: Division of Pulmonary and Allergy Drug Products

HFD #: HFD 570

Review completion date: October 1, 2003

Drug:

Trade name: Atrovent HFA Inhalation Aerosol

Generic name: Ipratropium bromide

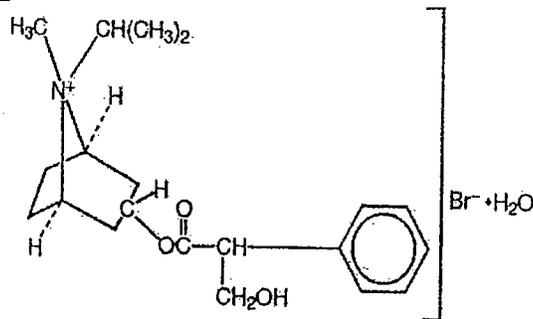
Code name: NA

Chemical name: 8-azoniabicyclo (3.2.1)-octane, 3-(3-hydroxy-1-oxo-2-phenylproxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate

CAS registry number: NA

Molecular formula/molecular weight: $C_{20}H_{30}BrNO_3 \cdot H_2O/430.4$

Structure:



Relevant INDs/NDAs/DMFs:

DMF

- IND 45,983, Boehringer Ingelheim, Atrovent HFA-134a Inhalation Aerosol
- NDA 19-085, Boehringer Ingelheim, Atrovent Inhalation Aerosol with CFC
- NDA 20-228, Boehringer Ingelheim, Atrovent Inhalation solution
- NDA 20-393, Boehringer Ingelheim, Atrovent 0.03% nasal spray
- NDA 20-394, Boehringer Ingelheim, Atrovent 0.06% nasal spray

Drug class: Anticholinergic bronchodilator

Indication: Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema

Clinical formulation:

TABLE 3.3.2.1:1 Composition of Ipratropium Bromide Monohydrate (HFA-134a) Inhalation Aerosol

Ingredient	Function	Weight Percent (g/100 g)	Weight per Container (g)	Weight per Actuation Ex-Valve***	Weight per Actuation Ex-Mouthpiece (label claim)
Ipratropium Bromide Monohydrate (unmiconized)	Active Ingredient			21.00 µg	
Citric Acid, USP (anhydrous)	Propellant				---
Purified Water, USP					---
Dehydrated Alcohol, USP *					---
1,1,1,2-tetrafluoroethane (HFA-134a)					---

TOTAL		100.000			---

Route of administration: Oral inhalation

Proposed use: The usual starting dose of ATROVENT HFA Inhalation Aerosol is 2 inhalations four times per day in subjects 12 years of age or older. Additional inhalations may be taken as required; however, the total number of inhalations should not exceed 12 in 24 hours. As each actuation contains 1 mcg of ipratropium bromide, the maximum daily dose is 201.6 mcg or 4.03 mcg/kg for a 50 kg person.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: None

Studies not reviewed within this submission: The studies described in the table below were previously submitted and reviewed under INDs 9,814 or 45,938.

Study title	Report #	Volume #
Pharmacokinetics/Toxicokinetics		
Report on the pharmacokinetic portion of toxicology trial 93-153: Fourteen-day nose only inhalation toxicity study with ATROVENT HFA-134a formulation in rats	U93-0846	22
Report on the pharmacokinetic portion of toxicology trial 93-155: Fourteen-day inhalation range-finding toxicity study in the dog on ipratropium bromide formulation as a solution MDI using alternate propellant 134a.	U93-0956	22
Report on the pharmacokinetic portion of toxicology trial 40006-01: A thirteen-week inhalation (nose-only) toxicology study in rats with ATROVENT HFA-134a formulation conducted at IITRI.	U95-3316	28
General Toxicology		
Acute IV toxicity study (LD50) with beagles	U75-0148	21
Acute oral and intravenous toxicity of the in the mouse and rat	U75-0155	21
Acute intravenous toxicity study (LD50) with the in beagles (NS)	U77-0050	21
Fourteen day nose-only inhalation toxicity study with ATROVENT HFC-134a formulation in rats.	U94-3031	23
Fourteen-day inhalation range-finding toxicity study in the dog on ipratropium bromide formulated as a solution MDI using alternate propellant 134a.	U94-3032	25
Thirteen-week inhalation (nose-only) toxicity study in rats with ATROVENT HFA 134a formulation.	U96-3000	29

In addition to the studies listed above, the sponsor submitted numerous studies that were performed for qualification of various leachables/extractables. The CMC staff is evaluating the relevant information and will submit a consult for a safety assessment if warranted. Two pharmacokinetic studies with an ipratropium dry powder were also submitted.

3.2 PHARMACOLOGY

3.2.1 Brief summary

Atrovent has bronchodilator and anti-secretory activities. Atrovent is a selective muscarinic receptor antagonist with potent in vitro and in vivo activities. The broncho-spasmodic activities of Atrovent occurred at doses well below those where CNS, cardiovascular and gastrointestinal effects were seen with atropine or other atropine derivatives. Inhaled Atrovent does not alter ciliary activity or mucous clearance from the lungs. Ipratropium bromide did not produce CNS effects, resulted in elevated heart rate under certain conditions, and antagonized acetylcholine-induced smooth muscle contraction. No drug interaction effects have been observed with β -adrenergic agonists.

3.2.2 Primary pharmacodynamics

No studies were conducted for this NDA submission. Most studies were submitted and reviewed under NDA 19-805 and INDs 9,814, 14,026, 30,690 and 32,529. Ipratropium bromide, a quaternary ammonium derivative of atropine, is an anticholinergic agent that acts to block transmission of vagally-mediated impulses by competitive inhibition of acetylcholine. Ipratropium bromide has bronchodilator and anti-secretory activities and was 15-times more potent than atropine in inhibiting acetylcholine-induced smooth muscle contraction in vitro, and was more effective than atropine in longer duration in vivo studies. Inhaled ipratropium did not alter ciliary activity or mucous clearance from the lungs

3.2.3 Secondary pharmacodynamics

No studies were conducted for this NDA submission.

3.2.4 Safety pharmacology

No studies were conducted for this NDA submission. Most studies were submitted and reviewed under NDA 19-805 and INDs 9,814, 14,026, 30,690 and 32,529. In anesthetized guinea pigs, oral administration of ipratropium (5-500 μ g/kg) produced a marked increase in lung clearance volume, whereas at high doses (mg/kg range), a slight decrease was noted.

Ipratropium demonstrated no effects in the central nervous system. Ipratropium had almost no effect on the oxotremorine-induced tremor ($ED_{50} = 0.35$ mg/kg for atropine vs 11 mg/kg for ipratropium). No changes in EEG were observed in rabbits (< 10 mg/kg, IV), although heart rate was increased slightly, and there was no effect on the carbachol-induced tremor in rabbits (0.3-10 mg/kg, IV).

Ipratropium was equally or one-fifth as active as atropine in elevating heart rate following SC dosing. Intravenous doses abolished carotid sinus reflex but did not affect the blood pressure. When administered as a metered aerosol to anesthetized dogs, Atrovent at total doses up to 8 mg/animal did not affect heart rate or ECG pattern. A

similar lack of effect was noted in normally ventilated or hypoventilated dogs at doses up to 4 mg/animal.

Ipratropium was ~ 1.3 times more effective than atropine in blocking ACh-induced smooth muscle contraction and almost twice as active in antagonizing pilocarpine-induced contraction.

3.2.5 Pharmacodynamic drug interactions

Studies were conducted under the development program for NDA 19-085 to assess drug interactions with β -adrenergic agonists. Ipratropium did not increase either the incidence or severity of β -adrenergic agonist effects (tachycardia, ECG changes, increased heart weights and myocardial necrosis).

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief summary

No studies were conducted for this NDA submission. Most studies were submitted and reviewed under NDA 19-805 and INDs 9,814, 14,026, 30,690 and 32,529. Ipratropium bromide is not highly bioavailable in animals. The half-life is short, approximately 3-3.5 hours, and the drug is eliminated rapidly. The major route of elimination is fecal following oral administration and urinary following iv administration. Minimal protein binding (0-9%) was observed in the mouse, rat, dog and monkey. Kinetic parameters were comparable in studies assessing the HFA 134a and CFC formulations although systemic exposure to ipratropium was slightly increased in rats with the HFA 134a formulation.

3.3.2 Absorption

Ipratropium bioavailability was low following oral administration (10%) in rats and humans. Nasal bioavailability in rats was < 9% in rats. Less than 1% of an inhaled dose is absorbed systemically.

3.3.3 Distribution

Major organs of distribution were the small intestine, stomach and colon following oral administration. Following IV dosing, distribution was primarily to the small intestine, liver, colon, kidney and heart. Minimal protein binding (0-9%) was observed in various species.

3.3.4 Metabolism

Ipratropium was metabolized to an acrylic acid or a phenylacetic acid after both oral and intravenous dosing. Eventually these are hydrolyzed to an isopropyl nortropanium metabolite.

3.3.5 Excretion

Excretion was primarily via feces following oral administration while renal excretion was predominant following intravenous dosing in rats and dogs.

3.3.6 Pharmacokinetic drug interactions

No data is available.

3.3.7 Tables and figures to include comparative TK summary

TK data from 13-week HFA study in rats. Data from the 90-day rat study with ipratropium bromide in an HFA formulation indicate that less than 3% of the estimated inhaled dose for all treated animals was excreted in the urine. Steady state was reached by Week 7, and a comparable amount was excreted at Week 13 demonstrating that chronic accumulation does not occur. The systemic absorption of ipratropium was slightly higher from the HFA 134a formulation in comparison to the CFC formulation. Similarly, kinetics of the HFA 134a and CFC formulations were comparable in 14-day studies in rats and dogs.

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology: Acute toxicity studies were conducted in rats, mice, rabbits and dogs via various routes of administration (oral, SC, IP, or IV). Acute oral median lethal doses were 1429-4000 mg/kg in the rat, 1120-2050 mg/kg in the mouse, 1557-2282 mg/kg in the rabbit and 400-1300 mg/kg in the dog. Clinical signs were observed in all species and were characteristic of anticholinergic effects. Median lethal doses following SC dosing were 635-1960 mg/kg in the rat, 322-650 mg/kg in the mouse, and 71 mg/kg in dogs. Median lethal doses following IV dosing were 15-20 mg/kg in the rat, 12-18 mg/kg in the mouse, and 17-20 mg/kg in dogs. Median lethal doses following IP dosing were 113-240 mg/kg in the rat and 72-94 mg/kg in the mouse. The median lethal dose in rats following intraduodenal dosing was 310 mg/kg.

Inhalation studies of up to 26 weeks duration in rats, dogs and monkeys were conducted in support of the Atrovent CFC formulation. In rats, no toxicity other than retardation of body weight gain (18-40%) in males was noted at nose-only doses up to 384 µg/day. Similarly, no drug-related effects were observed in monkeys following 6-month dosing up to 426 µg/kg via nasal catheter. Thirteen week intratracheal dosing of an aerosolized powder in dogs produced no effects at doses up to 36 µg/kg; increased heart rate was noted at the high dose of 179 µg/kg. Atrovent administered to rats and dogs for 26 weeks at oral doses of 30 mg/kg did not induce toxic effects. Oral chronic toxicity studies were conducted in rats and dogs. Atrovent administered to rats, doses 6-200 mg/kg for 55 and 78 weeks, induced manifestations of the drug's anticholinergic activity. Doses of ≥ 30 mg/kg produced a decrease in body weight and food consumption, xeromycteria and coprostasis (with dilation of the large bowel, dyschylia, sialadenosis and enteritis). In the dog, the doses were 3, 15 and 75 mg/kg. In the dogs in the high dose group, microscopic examinations revealed localized necrosis of the pylorus region. These dogs also exhibited tachycardia.

To support the change in the ATROVENT formulation from CFC to HFA 134a propellant, the sponsor conducted two 14-day nose-only inhalation toxicity and toxicokinetic studies in rats and dogs. These studies were originally submitted to IND 9,814 in 1994 and reviewed by Dr. C. Joseph Sun. The two formulations were similar in toxicity and bioavailability. Based upon this review, the rat was considered to be the most appropriate species to be utilized in a 90-day inhalation study to bridge the CFC development program to the HFA program. The sponsor submitted 13-week toxicity and toxicokinetic studies in rats to IND 45,938 in February 1996 and these studies were reviewed by Dr. Misoon Chun (dated February 1998). The toxicity study utilized an air control, an HFA 134a placebo, three dose groups for ipratropium in HFA and an ATROVENT/CFC control group. A NOAEL of 1.1 mg/kg/d (deposited dose of 0.22 mg/kg/d) was identified based upon decreased body weight and histopathological findings. The animals tolerated dosing up to the maximum feasible targeted inhaled dose of 9.2 mg/kg/d (deposited dose of 1.84 mg/kg/d). Other than chronic suppurative rhinitis in the nasal turbinates and diffuse submucosal mixed inflammatory cell infiltration in the larynx, the ipratropium HFA formulation produced no significant target organ toxicity. Observations of squamous metaplasia in the nasal turbinate was determined to be an adaptive response and not of significant toxicologic consequence. Findings in response to the HFA formulation were comparable or less significant than those in response to the CFC formulation.

Genetic toxicology: Results of various mutagenicity studies (Ames test, mouse dominant lethal test, in vivo mouse micronucleus test, and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Carcinogenicity: In two-year carcinogenicity studies in rats and mice, ipratropium bromide at oral (dietary) doses up to 6 mg/kg showed no carcinogenic activity.

Reproductive toxicology: Fertility of male or female rats was unaffected by ipratropium bromide at oral doses up to 50 mg/kg. At an oral dose of 500 mg/kg, ipratropium bromide produced a decrease in the conception rate. Oral reproduction studies were performed at doses of 10 mg/kg in mice, 1,000 mg/kg in rats and 125 mg/kg in rabbits. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg, respectively. These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses above 90 mg/kg in rats embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration. ATROVENT is listed as a Pregnancy Category B. Two segment III studies were conducted in the rat. No effects were seen in the first at oral doses of up to 90 mg/kg. In the second study vaginal bleeding and deaths were found in the high dose group (500 mg/kg). Body weight gain was reduced in the dams in the 50 and 500 mg/kg dose groups. The number of viable pups (day 21) was decreased and the stillbirths was increased in the high dose. Additionally, the mortality was significantly increased in the 500 mg/kg dose group. The measurement of reproductive capability in the F₁ offspring did not reveal differences in copulation rate, conception rate or mean litter data; however, there

appeared to be lower number of corpora lutea, implantation sites and viable fetuses at 500 mg/kg.

Special toxicology: Studies were conducted under the development program for NDA 19-085 to assess local irritant and antigenic activity of ipratropium as well as local tolerance to repeated SC injections. No evidence of antigenicity or topical irritancy was reported. Repeated SC injections of 100 mg/ml in dogs caused site of injection edema, purulent infection, fibrin exudates and cicatricial increase in connective tissue.

3.4.2 Single-dose toxicity

Acute toxicology studies were conducted and reviewed in support of the previously approved ATROVENT products. Acute toxicity studies were conducted in rats, mice, rabbits and dogs via various routes of administration (oral, SC, IP, or IV). Acute oral median lethal doses were 1429-4000 mg/kg in the rat, 1120-2050 mg/kg in the mouse, 1557-2282 mg/kg in the rabbit and 400-1300 mg/kg in the dog. Clinical signs were observed in all species and were characteristic of anticholinergic effects. Median lethal doses following SC dosing were 635-1960 mg/kg in the rat, 322-650 mg/kg in the mouse, and 71 mg/kg in dogs. Median lethal doses following IV dosing were 15-20 mg/kg in the rat, 12-18 mg/kg in the mouse, and 17-20 mg/kg in dogs. Median lethal doses following IP dosing were 113-240 mg/kg in the rat and 72-94 mg/kg in the mouse. The median lethal dose in rats following intraduodenal dosing was 310 mg/kg. Acute nose-only inhalation studies in rats demonstrated no intolerance following 8 hours dosing to a nebulized 0.025% ATROVENT solution or to a metered dose aerosol (3.2 mg).

3.4.3 Repeat-dose toxicity

Repeat-dose toxicology studies were conducted and reviewed in support of the previously approved ATROVENT products. These studies included inhalation studies of up to 26 weeks duration in rats, dogs and monkeys. In rats, no toxicity other than retardation of body weight gain (18-40%) in males was noted at nose-only doses up to 384 µg/day. Similarly, no drug-related effects were observed in monkeys following 6-month dosing up to 426 µg/kg via nasal catheter. Thirteen week intratracheal dosing of an aerosolized powder in dogs produced no effects at doses up to 36 µg/kg; increased heart rate was noted at the high dose of 179 µg/kg.

Studies utilizing other routes of administration demonstrated no adverse effects in rats following 26-week dosing up to 30 mg/kg, po; higher doses produced typical anticholinergic manifestations (dryness of nose, eyes and mucosa), lethargy, aphagia and death in some cases. Oral dosing for 55-78 weeks in rats induced clinical manifestations of anticholinergic activity at doses of 6-200 mg/kg. Oral dosing in dogs for 52 weeks (3-75 mg/kg) produced a dose-dependent reduction of conjunctival, nasal, and oral mucosa secretions. Localized necrosis of the pyloric region was observed at a dose of 75 mg/kg.

In order to support the currently proposed HFA propellant formulation, the sponsor conducted two 14-day nose-only inhalation toxicity and toxicokinetic studies in rats and dogs with ipratropium bromide HFA to compare the safety and pharmacokinetics with

ipratropium bromide CFC. These studies were originally submitted to IND 9,814 in 1994 and reviewed by Dr. C. Joseph Sun. The two formulations were similar in toxicity and bioavailability. Based upon this review, the rat was considered to be the most appropriate species to be utilized in a 90-day inhalation study to bridge the CFC development program to the HFA program. With the original IND submission of IND 45,938, the sponsor was requested to submit 90-day inhalation toxicity data with the HFA formulation to support the safety of long-term clinical trials. The sponsor submitted 13-week toxicity and toxicokinetic studies in rats to IND 45,938 in February 1996 and these studies were reviewed by Dr. Misoon Chun (dated February 1998). The toxicity study utilized an air control, an HFA 134a placebo, three dose groups for ipratropium in HFA and an ATROVENT/CFC control group. A NOAEL of 1.1 mg/kg/d (deposited dose of 0.22 mg/kg/d) was identified based upon decreased body weight and histopathological findings. The animals tolerated dosing up to the maximum feasible targeted inhaled dose of 9.2 mg/kg/d (deposited dose of 1.84 mg/kg/d). Other than chronic suppurative rhinitis in the nasal turbinates and diffuse submucosal mixed inflammatory cell infiltration in the larynx, the ipratropium HFA formulation produced no significant target organ toxicity. Observations of squamous metaplasia in the nasal turbinate was determined to be an adaptive response and not of significant toxicologic consequence. Findings in response to the HFA formulation were comparable or less significant than those in response to the CFC formulation.

3.4.4 Genetic toxicology

Genetic toxicology studies were conducted and reviewed in support of the previously approved ATROVENT products. Ipratropium bromide did not produce mutagenicity in the mouse dominant lethal study at oral doses up to 421 mg/kg given daily for 5 days, produced no chromosomal breaks at 5 daily oral doses up to 361 mg/kg in the Chinese hamster, and was negative in two separate Ames tests. In the micronucleus test in mice, although there was an increase in micronucleated erythrocytes at one of the doses tested between 401.8 -803 mg/kg, the finding was not reproducible and/or dose-related and ipratropium bromide was considered to be non-clastogenic in mice.

3.4.5 Carcinogenicity

Carcinogenicity studies were conducted and reviewed in support of the previously approved ATROVENT products. The carcinogenicity studies were carried out in the Chbb:THOM rat and the Chbb:NMRI mouse. The dietary admixture doses of 0.5, 2 and 6 mg/kg were the same in both 2-year studies. The highest dose used in the mouse study did not produce any effects indicating that the maximum tolerated dose (MTD) was not employed in the study. Similarly, dose selection in the rats was not considered to have achieved the MTD. There was no dose-dependent or increased frequency of tumors in the test groups versus the concurrent controls. Thus, ipratropium bromide was not carcinogenic in the rat or the mouse at dietary doses that were significantly greater than the proposed inhalation doses.

3.4.6 Reproductive and developmental toxicology

Reproductive toxicology studies were conducted and reviewed in support of the previously approved ATROVENT products. The effects of ipratropium bromide on male and female fertility were evaluated in 2 studies. In the first study, oral gavage doses were 0, 5, 50 and 500 mg/kg; males were dosed for 60 days prior to mating and through copulation and females were dosed for 14 days prior to mating and through Day 7 of mating. Ipratropium bromide, at the high dose, produced signs of chromodacryorrhea, smaller testes and reduced body weight gain, delayed insemination, spurious pregnancies, lower conception rates, decreased corpora lutea, lower number of implantations and reduced number of live fetuses. Doses up to 50 mg/kg did not affect fertility or reproductive capacity. In the second study, oral (dietary) doses of 0, 10, 30, and 90 mg/kg were used; males were dosed for 60-75 days prior to mating and females were dosed for 14 days prior to mating. Treated males and females were mated with untreated members of the opposite gender. There were no effects on male fertility and gonads were normal. Females in the 10 and 90 mg/kg groups showed increases in the number of resorted implantation sites compared to control values. Resorption rates returned to normal when the drug was withdrawn and they were mated again. No effects were noted on female fertility and there were no fetal malformations observed, nor effects on duration of pregnancy, littering or rearing, or maternal behavior. A lack of maternal toxicity indicated that the MTD was not achieved in this study.

In the segment II studies, aerosolized ipratropium bromide was administered nose-only at nominal doses of 0.512, 1.024 and 1.536 mg/kg during days 6-15 of gestation. There were no effects on dams or litter parameters. In the segment II study in the rabbit, aerosolized ipratropium bromide was administered by inhalation (modified tracheal tube) using estimated doses of 0.3, 0.9 and 1.8 mg/kg, days 6-18 of gestation. Tachypnea and transient anorexia were noted at 1.8 mg/kg and a retardation of body weight gain was observed in the first few days of the study. Fetal loss was observed at the mid- and high-dose levels. There were, however, no dose-related major malformations. Additional oral dosing studies were conducted at doses of 10 mg/kg in mice, 1000 mg/kg in rats and 125 mg/kg in rabbits. At oral doses above 90 mg/kg in rats embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration. Based upon these results, ipratropium bromide demonstrated no teratogenic potential in rats, mice or rabbits.

Two segment III studies were carried out in the rat. The first study included oral doses of 0, 10, 30 and 90 mg/kg, day 14 of gestation through the first 21 days after parturition. There were no peri- or postnatal developmental effects. In the second study, oral doses of 0, 5, 50 and 500 mg/kg were used. Vaginal bleeding and deaths were found in the high dose group. Body weight gain was reduced in the dams in the 50 and 500 mg/kg dose groups. The number of viable pups (day 21) was decreased and the stillbirths was increased in the high dose. Additionally, the mortality was significantly increased in the 500 mg/kg dose group. The measurement of reproductive capability in the F₁ offspring did not reveal differences in copulation rate, conception rate or mean litter data; however,

there appeared to be lower number of corpora lutea, implantation sites and viable fetuses at 500 mg/kg.

ATROVENT is listed as Category B for Pregnancy.

3.4.7 Local tolerance

See section 3.4.8 (Special toxicology studies).

3.4.8 Special toxicology studies

Studies were conducted under the development program for NDA 19-085 to assess local irritant and antigenic activity of ipratropium as well as local tolerance to repeated SC injections. No evidence of antigenicity or topical irritancy was reported. Repeated SC injections of 100 mg/ml in dogs caused site of injection edema, purulent infection, fibrin exudates and cicatricial increase in connective tissue.

3.5 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: ATROVENT inhalation aerosol (NDA 19-085) was originally approved and marketed in 1986. Subsequent formulations (inhalation solution, NDA 20-228; metered nasal spray, NDAs 20-393 and 20-394) were approved in 1993-1995. The current NDA is intended to support the approval of an HFA propellant formulation of a metered dose inhaler to replace the currently marketed CFC propellant formulation. Thus, the only toxicology studies conducted for this program were bridging inhalation toxicology studies up to 13 weeks to compare the toxicity profile of the CFC and HFA formulations. These studies were reviewed under INDs 9,814 and 45,938 and demonstrated that the toxicity and kinetic profiles were comparable. Therefore, this NDA is approvable from a non-clinical perspective.

Unresolved toxicology issues (if any): None

Recommendations:

1. This NDA is approvable from a nonclinical perspective pending inclusion of the recommended changes to the product label.
2. Recommended changes to the product label (see below) should be forwarded to the sponsor.

2 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

3.6 APPENDIX/ATTACHMENTS

Animal:human exposure comparison table

Drug:		Atrovent HFA						
	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m ²
Pediatric				0	3	0.00	25	0.00
Adult	>12	0.017	12	0.204	50	0.00	37	0.15

	route	mg/kg/d	conv. factor	mg/m ²	Dose Ratio		Rounded Dose Ratio	
					Adults	Children	Adults	Children
Carcinogenicity:								
rat	dietary	6	6	36	238.5	---	240	---
mouse	dietary	6	3	18	119.2	---	120	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
Reproduction and Fertility:								
rat	po	50	6	300	1987.3	N/A	2000	N/A
rat	po	90	6	540	3577.1	N/A	3600	N/A
rat	po	500	6	3000	19872.8	N/A	20000	N/A
rabbit			12	0	---	N/A	---	N/A
Teratogenicity:								
rat	po	1000	6	6000	39745.6	N/A	40000	N/A
mouse	po	10	3	30	198.7	N/A	200	N/A
rabbit	po	125	12	1500	9936.4	N/A	9900	N/A
rat	IH	1.5	6	9	59.6	N/A	60	N/A
rabbit	IH	1.8	12	21.6	143.1	N/A	140	N/A
Overdosage:								
mouse	po	1000	3	3000	19872.8	---	20000	---
rat	po	1700	6	10200	67567.6	---	68000	---
dog	po	400	20	8000	52994.2	---	53000	---
rabbit			12	0	---	---	---	---
Other: (Describe studies here)								
rat	po	90	6	540	3577.1	---	3600	---

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this page is the manifestation of the electronic signature.**

/s/

Virgil Whitehurst
10/2/03 12:43:53 PM
PHARMACOLOGIST

Timothy McGovern
10/2/03 01:01:13 PM
PHARMACOLOGIST
I concur.