

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-457

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW
CHEMISTRY CONSULT #3

NDA number: NDA 21-457

Information to sponsor: Yes (x) No () via chemist

Sponsor and/or agent: Ivax Research, Inc.

Manufacturer for drug substance:

Reviewer name: VWhitehurst, Ph.D.

Division name: Division of Pulmonary and Allergy Drug Products

HFD #: HFD 570

Review completion date: September 27, 2004

Drug:

Trade name: Volare (albuterol sulfate) HFA Inhalation Aerosol

Generic name: Albuterol sulfate

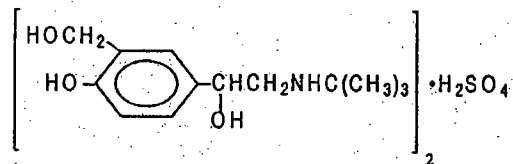
Code name: NA

Chemical name: Albuterol sulfate: á¹-[(tert-butylamino)methyl]-4-hydroxy-m-xylene-á, á-diol sulfate (2:1) (salt)

CAS registry number: NA

Molecular formula/molecular weight: $(\text{C}_{13}\text{H}_{21}\text{NO}_3)_2 \cdot \text{H}_2\text{SO}_4/576.7$

Structure:



Drug class: Beta 2 adrenergic agonist

Indication: Treatment or prevention of bronchospasm with reversible obstructive airway disease and in adults and children 12 years and older

Clinical formulation:

Formulation Details for Albuterol Metered Dose Inhaler

MATERIAL	Function	SUPPLIER	QTY Per Actuation (nominal values)	Qty per Can	Qty per batch
Albuterol Sulfate (USP) (micronized)	Active	/	/	/	/
Alcohol	Excipient	/	/	/	/
Total Suspension Weight				/	/
Propellant HFA 134a	Propellant	/	/	/	/
Total Theoretical Weight				8.5 g	/
Actuator	Actuator	/	N/A	1	/
Valve	Valve	/	N/A	1	/
Aerosol Can	Canister	/	N/A	1	/
		/	N/A	N/A	N/A

Route of administration: Oral inhalation

Proposed use: The recommended inhalation dose is 2 actuations (90 mcg albuterol base/actuation) repeated every 4-6 hours for a maximum of 12 actuations per day. Maximum daily dose is 1080 mcg or 21.6 mcg/kg for a 50 kg person.

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

Review:

This review is in response to a chemistry consult from the CMC reviewer, Dr. Vibhakar Shah, dated 9/16/04 to evaluate the proposed acceptance criteria for the following leachables in the drug product for IVAX's Volare HFA Inhalation Aerosol. The leachables and their proposed acceptance criteria are as follows:

Leachable**Proposed acceptance criteria**

/

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

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

of

Recommendation:

The proposed criteria for

, individual unspecified leachables are acceptable.

The sponsor should limit the acceptance criteria for
in the drug product to \leq MDI (equivalent to a maximum daily patient exposure of
or provide adequate qualification data to support their
proposed specifications. If a new toxicology study is deemed to be necessary, the
duration of study should be at least 90 days, the route of administration should mimic that
proposed for clinical use and the acceptance criteria should be set based upon the no
observed adverse effect level (NOAEL).

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

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/s/

Virgil Whitehurst
10/12/04 10:36:23 AM
PHARMACOLOGIST

Timothy McGovern
10/13/04 08:18:11 AM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: NDA 21-457

Review number: 002

Sequence number/date/type of submission: 000/March 15, 2004/BZ

Information to sponsor: Yes (x) No ()

Sponsor and/or agent: Ivax Research, Inc.

Manufacturer for drug substance: —

Reviewer name: VWhitehurst, Ph.D.

Division name: Division of Pulmonary and Allergy Drug Products

HFD #: HFD 570

Review completion date: October 13, 2004

Drug:

Trade name: To be determined, (albuterol sulfate) HFA Inhalation Aerosol

Generic name: Albuterol sulfate

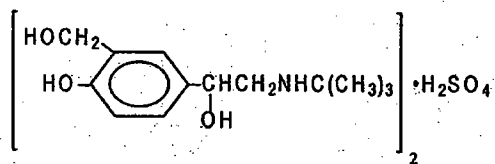
Code name: NA

Chemical name: Albuterol sulfate: α^1 -[(tert-butylamino)methyl]-4-hydroxy-m-xylene- α , α -diol sulfate (2:1) (salt)

CAS registry number: NA

Molecular formula/molecular weight: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4 / 576.7$

Structure:



Drug class: Beta 2 adrenergic agonist

Indication: Treatment or prevention of bronchospasm with reversible obstructive airway disease and older in adults and children 12 years

Clinical formulation:

Formulation Details for Albuterol Metered Dose Inhaler

MATERIAL	Function	SUPPLIER	Qty Per Actuation (nominal values)	Qty per Can	Qty per batch
Albuterol Sulfate (USP) (micronized)	Active	/	/	/	/
Alcohol	Excipient	/	/	/	/
Total Suspension Weight					
Propellant HFA 134a ²	Propellant	/	/	/	/
Total Theoretical Weight				8.5 g	/
Actuator	Actuator	/	N/A	1	/
Valve	Valve	/	N/A	1	/
Aerosol Can	Canister	/	N/A	1	/
		/	N/A	N/A	N/A

Route of administration: Oral inhalation

Proposed use: The recommended inhalation dose is 2 actuations (90 mcg albuterol base/actuation) repeated every 4-6 hours for a maximum of 12 actuations per day. Maximum daily dose is 1080 mcg or 21.6 mcg/kg for a 50 kg person.

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

Introduction:

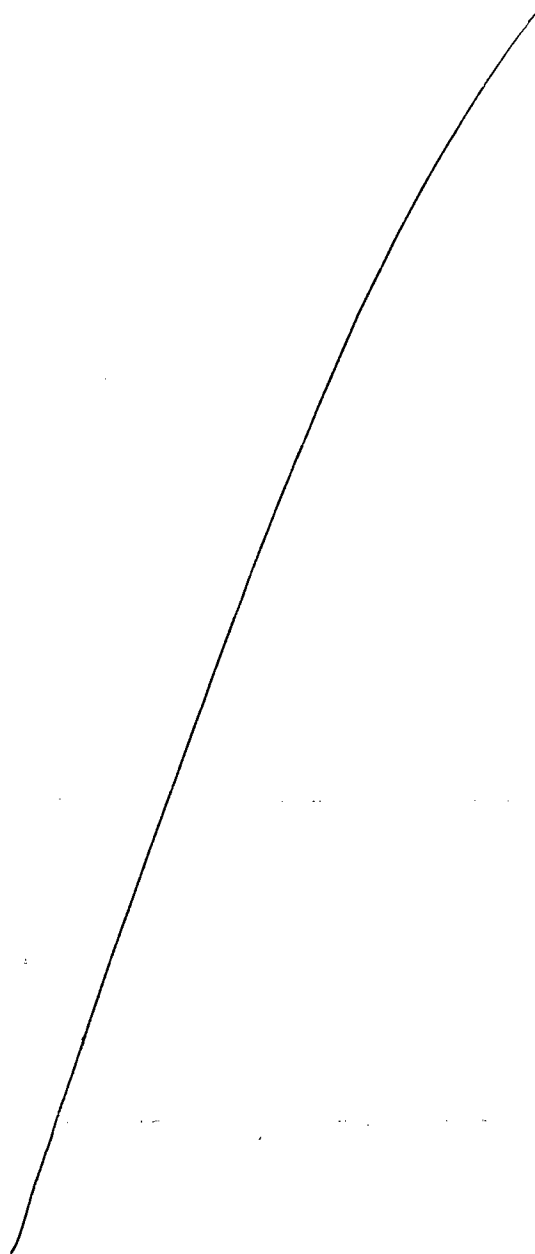
The proposed labeling for this product was reviewed in the original pharmacology/toxicology review for NDA 21-457 dated November 23, 2004. However, our comments/revisions were not submitted to the sponsor. The sponsor resubmitted the proposed labeling in their March 15, 2004 submission.

This review is of the currently proposed labeling submitted by the sponsor March 15, 2004. As previously stated in our original review the format of the product label does not adhere to that described under 21 CFR 201.57. Thus, the sponsor should reformat the overall label.

The following describes recommended revisions to the relevant non-clinical portions of

the product label. The proposed text generally parallels that for the Proventil HFA product label. However, the animal to human exposure ratios are recalculated based on the current methodology used by the division (see calculation table attached). Deletions to the sponsor's proposed text are indicated by strikeouts and insertions are indicated by underlines.

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

 § 552(b)(5) Deliberative Process

 ✓ § 552(b)(4) Draft Labeling

The above-recommended revisions have been forwarded to the sponsor.

Virgil Whitehurst

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Drug: Volare HFA (Albuterol sulfate) Inhalation

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m ²
Pediatric	6	0	2	0	20	0.00	25	0.00
Adult	>12	0.108	12	1.296	50	0.03	37	0.96

	route	mg/kg/d	conv. factor	mg/m ²	Dose Ratio		Rounded Dose Ratio	
					Adults	Children	Adults	Children
Carcinogenicity:								
mouse	dietary	500	3	1500	1564.06	---	1600	---
rat	oral	2	6	12	12.5125	---	15	---
rat	oral		6	0	---	---	---	---
rat	oral		6	0	---	---	---	---
hamster	dietary	50	4	200	208.542	---	210	---
Reproduction and Fertility:								
rat	oral	50	6	300	312.813	N/A	310	N/A
rat	oral		6	0	---	N/A	---	N/A
mouse			3	0	---	N/A	---	N/A
rabbit	oral		12	0	---	N/A	---	N/A
Teratogenicity:								
mouse	oral	0.025	3	0.075	0.0782	N/A	1/13	N/A
mouse	oral	0.25	3	0.75	0.78203	N/A	1/1	N/A
mouse	oral	2.5	3	7.5	7.82032	N/A	8	N/A
rabbit		50	12	600	625.626	N/A	630	N/A
rat	inhal	10.5	6	63	65.6907	N/A	65	N/A
Overdosage:								
mouse	oral	2000	3	6000	6256.26	---	6300	---
mouse			3	0	---	---	---	---
rat	oral	450	6	2700	2815.32	---	2800	---
rat	oral	2000	6	12000	12512.5	---	13000	---
Other:								
overdosa								
ge								
dog	oral		20	0	---	---	---	---
dog	oral		20	0	---	---	---	---
			####	#####	---	---	---	---
rabbit			12	0	---	---	---	---
rat			6	0	---	---	---	---

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/s/

Virgil Whitehurst
10/14/04 01:19:43 PM
PHARMACOLOGIST

Timothy McGovern
10/14/04 02:14:59 PM
PHARMACOLOGIST
I concur.

**Pharmacology/Toxicology Review
Chemistry Consult # 2**

NDA number: NDA 21-457

Information to sponsor: Yes, via chemist

Sponsor : IVAX Research, Inc

Manufacturer for drug substance: _____

Reviewer: VWhitehurst, Ph.D.

Team Leader: T McGovern

Division name: Division of Pulmonary and Allergy Drug Products

HFD : HFD 570

Review completion date: August 16, 2004

Drug:

Trade name: Volare HFA (albuterol sulfate) Inhalation Aerosol

Generic name: Albuterol sulfate, salbutamol

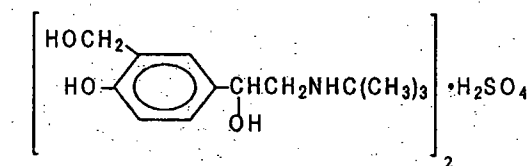
Code name: NA

Chemical name: Albuterol sulfate: α_1 -[(tert-butylamino)methyl]-4-hydroxy-mxylene- α, α -diol sulfate (2:1) (salt)

CAS registry number: NA

Molecular formula/molecular weight: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4/567.7$

Structure:



Drug class: Beta 2 adrenergic agonist

Indication: Treatment or prevention of bronchospasm with reversible obstructive airway disease
in adults and children 12 years of age and older

Clinical formulation:

Formulation Details for Albuterol Metered Dose Inhaler

MATERIAL	Function	SUPPLIER	Qty Per Actuation (nominal values)	Qty per Can	Lot/batch
Albuterol Sulfate (USP) (micronized)	Active	/	/	/	/
Alcohol	Excipient	/	/	/	/
Total Suspension Weight				/	
Propellant HFA 134a	Propellant	/	/	/	
Total Theoretical Weight				8.5 g	
Actuator Valve	Actuator Valve	/	N/A	1	
			N/A	1	
Aerosol Can	Canister	/	N/A	1	
		/	N/A	N/A	N/A

Route of administration: Oral inhalation

Proposed use: The recommended inhalation dose is 2 actuations (108 mcg albuterol sulfate/actuation or 90 mcg albuterol base/actuation) repeated every 4-6 hours. Maximum daily dose of albuterol base is 1080 mcg or 21.6 mcg/kg for a 50 kg person.

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

Review:

This review is a follow-up chemistry consult to evaluate the proposed acceptance criteria for impurities in the drug substance, albuterol sulfate. This consult is in response to a request from Dr. Craig Bertha (dated June 15, 2004) to evaluate the sponsor's response to comment 1(d)(3) from the AE letter dated November 28, 2003 with regard to the safety of the acceptance criterion of not more than — for the — drug substance impurity.

Comment 1(d)(3) from the AE letter reads as follows:

Limit the levels of — in the drug substance to ≤ —, or provide qualification data to support the current proposed specifications (e.g., a toxicology study of at least 90 days duration which demonstrates an adequate safety margin at a inhaled dose producing no adverse effects). The toxicological information, which is referred to DMF — for — impurities, could not be found in this DMF. In consultation with the DMF holder, provide the location of this information either by page number, and/or date of amendment to the DMF —

The original chemistry consult was dated November 13, 2003 and included the following:

The impurities and their originally proposed acceptance criteria are as follows:

NMT —
NMT — There are no structural alerts associated with these impurities.

A 90-day toxicology study was conducted in dogs and was reviewed in the original Pharmacology/Toxicology NDA review. The levels of the impurities in the drug substance (lot # AAW13A) used in the 90 day dog study are — for — and — for —. The highest dose tested in the 90 day toxicity study is — ng/kg; dosing was via a facial mask with an oropharyngeal tube. Although some cardiac findings (gross observations of foci) were noted in females at the two lowest doses in this study, there was no toxicity observed that was not previously associated with albuterol. Thus, the highest dose was used to perform a safety assessment for the impurities. The levels of — in the drug lot used for the 3-month dog study provided safety margins of only 3.6 and 4.5-fold, respectively, in comparison to the originally proposed specifications. Thus, the impurities in the drug substance were not considered to have been adequately qualified since a safety margin of 10 is considered adequate. As noted above, the sponsor was recommended to limit the levels of — impurities in the drug substance to — as per ICH Guidance Q3A (revision 1, February, 2003) or provide adequate qualification information.

In a teleconference dated March 2, 2004, the Division again delineated these recommendations to the sponsor. The sponsor was informed that the available data would support drug substance specifications up to —. The sponsor stated that they had performed additional research and gathered additional information, i.e, human and LD 50 data in animals from the drug substance manufacturer regarding —. They stated that the concentration in the clinical trials was found to be —. The Division said the additional data probably would not support raising the acceptable level of — however the sponsor should submit the data for review. The sponsor also noted that they have been selling albuterol in one or more products since 1994 with levels of — as high as — and questioned whether this information would be helpful in raising the acceptable levels of —. Additionally, the sponsor stated that the European Pharmacopoeia recognizes — levels up to — and they wanted to know if these data would also be helpful. The Division asked the sponsor to submit these data for review.

On March 15, the sponsor submitted their response and the abovementioned data to their NDA. The sponsor agreed to limit the level of — to —. Thus, the proposed level of this impurity is acceptable.

The sponsor proposed a level of _____. Their decision was based on the

A reevaluation of the safety margins provided by the previously conducted 90-day dog inhalation study in comparison to the newly proposed drug product specification of _____ was conducted. The highest dose tested in the dog study (_____ ng/kg) was used to perform the safety assessment since no unexpected toxicities were observed at that dose. The maximum daily dose for humans is _____. The table below indicates that the level of _____ in the drug lot used for the 3-month dog study provide a safety margin of 6-fold. This 6-fold safety margin is considered acceptable when the dog is used as the supporting nonclinical species (NOTE: the original consult incorrectly stated that a 10-fold safety margin was necessary in this case).

Impurity	Proposed Specification % µg/kg	Preclinical dose % (mcg/kg)*	Species	Duration	Route	Safety margin
_____	_____	_____	Dog	3 mos	IH	6

* Assumes 100% deposition in dogs (due to dosing with oropharyngeal tube) and humans.

Therefore, the sponsor's proposed drug product impurity specification of _____ is acceptable based upon the 6-fold safety margin provided by the 3-month dog study.

Supporting calculations:

Maximum clinical dose:

$$_____ \times 90 \mu\text{g/actuation} \times 12 \text{ actuations/day} / 50 \text{ kg person} = _____ \mu\text{g/kg/day}$$

Preclinical dose:

$$_____ \text{ mg/kg (high dose from 3 mos dog study)} = _____ \mu\text{g/kg}$$

$$\begin{aligned} \text{Safety margin} &= \text{preclinical dose} / \text{clinical dose} \\ &= \frac{_____ \mu\text{g/kg/d}}{_____ \mu\text{g/kg/d}} \\ &= 6 \end{aligned}$$

Overall conclusions and recommendations:

Conclusions:

A previous CMC consult had recommended that the sponsor limit the levels of _____ in the drug substance to \leq _____ or provide qualification data to support their proposed specifications. The sponsor has reduced the specification for _____ to an acceptable level of \leq _____.

A safety evaluation was performed regarding the sponsor's revised specification for _____ of \leq _____. Although the sponsor's supporting rationale was not considered acceptable, the previously conducted 3-month dog study was deemed adequate to support the specification by providing a 6-fold safety margin.

Recommendation:

The sponsor's proposed drug substance specifications for _____ are acceptable.

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/s/

Virgil Whitehurst
8/16/04 10:07:12 AM
PHARMACOLOGIST

Timothy McGovern
8/16/04 10:12:36 AM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY REVIEW
CHEMISTRY CONSULT #1

NDA number: NDA 21-457

Information to sponsor: Yes (x) No () via chemist

Sponsor and/or agent: Ivax Research, Inc.

Manufacturer for drug substance:

Reviewer name: VWhitehurst, Ph.D.

Division name: Division of Pulmonary and Allergy Drug Products

HFD #: HFD 570

Review completion date: November 13, 2003

Drug:

Trade name: Volare (albuterol sulfate) Inhalation Aerosol

Generic name: Albuterol sulfate

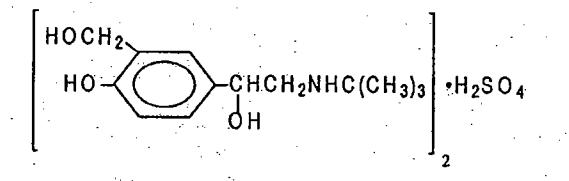
Code name: NA

Chemical name: Albuterol sulfate: α^1 -[(tert-butylamino)methyl]-4-hydroxy-m-xylene- α , α' -diol sulfate (2:1) (salt)

CAS registry number: NA

Molecular formula/molecular weight: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4 / 576.7$

Structure:



Drug class: Beta 2 adrenergic agonist

Indication: Treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years and older

Clinical formulation:

Formulation Details for Albuterol Metered Dose Inhaler

MATERIAL	Function	SUPPLIER	QTY Per Actuation (nominal values)	Qty per Can	Qty per batch
Albuterol Sulfate (USP) (micronized)	Active	/	/	/	/
/ Alcohol	Excipient	/	/	/	/
Total Suspension Weight				/	
Propellant HFA-134a	Propellant			/	
Total Theoretical Weight				8.5 g	/
Actuator	Actuator	/	N/A	1	/
Valve	Valve	/	N/A	1	/
Aerosol Can	Canister	/	N/A	1	/
	/	/	N/A	N/A	N/A

Route of administration: Oral inhalation

Proposed use: The recommended inhalation dose is 2 actuations (90 mcg/actuation) repeated every 4-6 hours. Maximum daily dose is 1080 mcg or 21.6 mcg/kg for a 50 kg person.

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

Review:

This review is in response to a chemistry consult from Dr Vibhakar Shah to evaluate the proposed acceptance criteria for impurities in the drug substance albuterol sulfate. The impurities and their proposed acceptance criteria are as follows:

NMT

NMT

According to Dr. Shah, there are no structural alerts associated with these impurities.

A 90-day toxicology study was conducted in dogs as part of the development program for NDA 21-457. This study was reviewed in the original Pharmacology/Toxicology NDA review. The levels of the impurities in the drug substance (lot # AAW13A) used in the 90 day dog study are

The highest dose tested in the 90 day toxicity study is 1.0 mg/kg ; dosing was via a facial mask with an oropharyngeal tube. Although some cardiac findings (gross observations of foci) were noted in females at the two lowest doses in this study, there was no toxicity observed that was not previously associated with albuterol. Thus, the highest dose can be used to perform a safety assessment for the impurities. The maximum daily dose for humans is 20 mcg/kg . Using these data, the level of the impurities in the drug substance used in the animal study were compared with the maximum daily human exposure at the proposed specifications. The table below indicates that the levels of 0.001% in the drug lot used for the 3-month dog study provide safety margins of only 3.6 and 4.5-fold, respectively. A safety factor of 10 is generally required.

Impurity	Proposed Specification % $\mu\text{g/kg}$	Preclinical dose % (mcg/kg)*	Species	Duration	Route	Safety margin
1	0.001	0.001	Dog	3 mos	IH	3.6
2	0.001	0.001	Dog	3 mos	IH	4.5

* Assumes 100% deposition in dogs (due to dosing with oropharyngeal tube) and humans.

Thus, the impurities in the drug substance have not been adequately qualified. The sponsor should, therefore, limit the levels of the impurities in the drug substance to $\leq 0.0001\%$ as per ICH Guidance Q3A (revision 1, February, 2003).

Supporting calculations:

Maximum clinical dose:

$$1.0 \text{ mg/kg} \times 90 \text{ } \mu\text{g/actuation} \times 12 \text{ actuations/day} / 50 \text{ kg person} = 2.16 \text{ } \mu\text{g/kg/day}$$

Preclinical dose:

$$1.0 \text{ mg/kg} \times 10 \text{ ng/kg (high dose from 3 mos dog study)} = 10 \text{ } \mu\text{g/kg}$$

$$\begin{aligned} \text{Safety margin} &= \text{preclinical dose} / \text{clinical dose} \\ &= 10 \text{ } \mu\text{g/kg/d} / 2.16 \text{ } \mu\text{g/kg/d} \\ &= 3.6 \end{aligned}$$

Maximum clinical dose:

$$- \times 90 \mu\text{g/actuation} \times 12 \text{ actuations/day} / 50 \text{ kg person} = - \mu\text{g/kg/day}$$

Preclinical dose:

$$- \times - \text{ mg/kg (high dose from 3 mos dog study)} = - \mu\text{g/kg}$$

$$\begin{aligned} \text{Safety margin} &= \text{preclinical dose / clinical dose} \\ &= - \mu\text{g/kg/d} / - \mu\text{g/kg/d} \\ &= 4.5 \end{aligned}$$

Overall conclusions and recommendations:

Conclusions:

A safety evaluation was performed regarding the proposed drug substance specifications — impurities based upon levels observed in a 3 month dog study and the maximum expected daily human exposure through use of the drug product. The impurities — have not been adequately qualified. The sponsor should reduce the proposed specifications for the impurities to \leq — or submit adequate data which show that these impurities are reasonably safe at the proposed specifications. In order to support the proposed specifications, the sponsor should carry out a toxicity study of at least 90 days duration in animals using impurity levels which show that the proposed levels are reasonably safe (qualified). The animal study should include complete histopathology.

Recommendation:

The sponsor should limit the levels of — in the drug substance to \leq — or provide qualification data to support their proposed specifications (e.g., a toxicology study of at least 90 days duration which demonstrates an adequate safety margin at a pulmonary dose producing no adverse effects).

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

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/s/

Virgil Whitehurst
11/14/03 09:35:43 AM
PHARMACOLOGIST

Timothy McGovern
11/14/03 10:45:35 AM
PHARMACOLOGIST
I concur.

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA #: 21-457

Drug Name: Volare (Albuterol Sulfate) Inhalation Aerosol

Sponsor: Ivax Research, Inc.

Indication: Treatment or prevention of bronchospasm with reversible obstructive airway disease — in adults and children 12 years of age and older

Division: Pulmonary and Allergy Drug Products

Reviewer: Virgil E. Whitehurst, Ph.D.

Regulatory Recommendation: AP

Date: November 14, 2003

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability

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

1.2 Recommendation for nonclinical studies

No further studies are recommended.

1.3 Recommendations on labeling

The product label should be reformatted to conform to that described in the CFR. The “Carcinogenesis, mutagenesis, impairment of fertility”, “Pregnancy” and “OVERDOSAGE” sections should also be revised in terms of the estimated animal to human dose comparisons.

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings

The objective of the nonclinical studies conducted by the sponsor was to compare the toxicological profile for Albuterol /HFA and Albuterol /CFC. A 90-day study was conducted in dogs based upon findings in short-term studies in rats and dogs. Albuterol/HFA was administered to Beagle dogs using inhalation achieved doses of 0.042, 0.082 and 0.162 mg/kg daily for 90 days. Albuterol/CFC was included as the positive control, 0.169 mg/kg. The results of this study are difficult to interpret. There were no microscopic changes in the papillary muscles of the dogs in either the Albuterol/HFA or Albuterol/CFC dose groups. The sponsor utilized a special collagen stain, Masson’s Trichrome, in an attempt to delineate myocardial lesions. It is well-established that albuterol and other beta-2 adrenergic agonists have the potential to induced myocardial toxicity, i.e., tachycardia, EKG changes and myocardial necrosis. Gross pathology examinations in the 90-day study revealed pale, focal areas on the papillary muscles in one of four female dogs in the low dose and two of four female dogs in the mid dose but no focal areas in the high dose HFA group. Additionally, there were no gross pathology findings in the male dogs or in animals administered the CFC formulation. There were increases in heart rates in all dogs in the mid and high dose groups, especially during the first 2 weeks of the study. Prolonged and/or repeated increases in heart rates may result in changes (increase in unmet energy demands leading to death of the cells) in the most susceptible areas, the papillary muscles. The NOAEL in the 90 day study is difficult to define in the female dogs due the gross myocardial findings at the lower doses that are related to known albuterol effects. The NOAEL in the male dogs is 0.162 mg/kg. In a 28 day study in the dog, inhaled doses of 0.16 mg/kg and above of albuterol/HFA induced fibrosis and mineralization in the papillary muscles; fibrosis was also noted in one albuterol/CFC animal at a dose of 0.5 mg/kg. NOAELs for the HFA formulation in the 28 day study were 0.044 mg/kg in males and 0.16 mg/kg in females.

Although the Division recommended that the sponsor take blood samples for possible future kinetics assessment should any toxicity of concern occur and to compare the kinetics of the HFA and CFC formulations, a kinetic assessment was not conducted. Experience with HFA products reveals that systemic exposure is greater when compared to CFC drug products at comparable doses. Assessment of the kinetic data is not necessary at this time since the observed toxicities are expected with albuterol, the findings in the 90-day dog study are not definitive given the lack of a dose-response, and due to the extensive marketing history with albuterol products with and without HFA.

Overall, the toxicity profile of albuterol/CFC and albuterol/HFA in dogs is similar, and is primarily related to cardiac toxicity.

2.2 Pharmacologic activity

Albuterol is a beta-2 adrenergic agonist. The fundamental action of albuterol is its ability to relax bronchial smooth muscle. Albuterol interacts with beta receptors causing an increase in intracellular cAMP leading to bronchodilation of smooth muscle tissues.

2.3 Nonclinical safety issues relevant to clinical use

No nonclinical safety issues relevant to clinical use have been identified.

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PHARMACOLOGY/TOXICOLOGY REVIEW**3.1 INTRODUCTION AND DRUG HISTORY****NDA number:** NDA 21-457**Review number:** 001**Sequence number/date/type of submission:** N-000/January 30, 2003/original NDA submission**Information to sponsor:** Yes (x) No ()**Sponsor and/or agent:** Ivax Research, Inc., Miami, FL**Manufacturer for drug substance:** —**Reviewer name:** V Whitehurst**Division name:** Division of Pulmonary and Allergy Drug Products**HFD #:** HFD 570**Review completion date:** November 14, 2003**Drug:**

Trade name: Volare HFA (albuterol sulfate) Inhalation Aerosol

Generic name: Albuterol sulfate, salbutamol

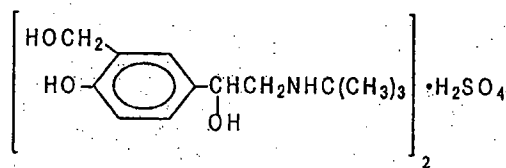
Code name: NA

Chemical name: Albuterol sulfate: α^1 -[(tert-butylamino)methyl]-4-hydroxy-m-xylene- α , α' -diol sulfate (2:1) (salt)

CAS registry number: NA

Molecular formula/molecular weight: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4/567.7$

Structure:



Relevant INDs/NDAs/DMFs: Albuterol: INDs 60,549 — , and
 DMF — NDA 20-503: Proventil HFA (3M)
 HFA 134a: DMFs —)

Drug class: Beta 2 adrenergic agonist

Indication: Treatment or prevention of bronchospasm with reversible obstructive
 airway disease —
 in adults and children 12 years of age and older

Clinical formulation:**Formulation Details for Albuterol Metered Dose Inhaler**

MATERIAL	Function	SUPPLIER	QTY Per Actuation (nominal values)	Qty per Can	Qty per batch
Albuterol Sulfate (USP) (micronized)	Active	/	/	/	/
Alcohol	Excipient	/	/	/	/
Total Suspension Weight					
Propellant HFA-134a	Propellant	/	/	/	/
Total Theoretical Weight					
Actuator	Actuator		N/A	1	/
Valve	Valve	/	N/A	1	/
Aerosol Can	Canister		N/A	1	
		/	N/A	N/A	N/A

Route of administration: Oral inhalation

Proposed use: The recommended inhalation dose is 2 actuations (108 mcg albuterol sulfate/actuation or 90 mcg albuterol base/actuation) repeated every 4-6 hours. Maximum daily dose of albuterol base is 1080 mcg or 21.6 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:

1. 4 Week Inhalation study in Rats (655815), Module 4, Volume 1.
2. 28 day Repeat Dose Inhalation Toxicity study in the Dog (NHL 4/952816), Module 4, Volume 2.
3. Comparative 3 Month Inhalation Toxicity study of an HFA-Propelled Albuterol Inhalation Aerosol and a CFC-Propelled Albuterol Formulation in Beagle Dogs (21107), Module 4, Volume 3.

Studies not reviewed within this submission: None

3.2 PHARMACOLOGY

3.2.1 Brief summary

Albuterol has bronchodilation and anti-anaphylactic activities. Albuterol acts via beta 2 receptors in bronchial smooth muscle and via beta 1 receptors in cardiac muscle. Both effects are inhibited by propranolol, a beta blocking agent.

3.2.2 Primary pharmacodynamics

Mechanism of action:

No specific studies were conducted for this drug product. Albuterol acts via beta 2 receptors to increase the concentration of intracellular cAMP resulting in bronchodilation of the bronchial smooth muscle. cAMP is generated from ATP by the enzyme adenylyl cyclase. Albuterol is active after parenteral, oral or inhalational administration to dogs, rats, cats and guinea pigs.

Drug activity related to proposed indication:

No specific studies were conducted for this drug product. Airway obstruction in asthma is caused by several factors: spasm of airway smooth muscle, edema of the airway mucosa, increased mucus secretion, cellular infiltration of the airway and injury and desquamation of airway epithelium. Albuterol-induced increases in cAMP results in relaxation of the airway bronchial smooth muscle and helps to alleviate the above mentioned symptoms. Albuterol's mechanism of action is by means of decreases in pulmonary resistance as well as improvement in pulmonary compliance.

3.2.3 Secondary pharmacodynamics

No studies were conducted for this NDA submission. In studies in the dog, albuterol causes increases in the rate and force of contraction of the heart. Albuterol also produces arrhythmias in the cat but at doses well above those required for bronchodilation. Albuterol has the potential to induce EKG changes in the dog. Prolonged tachycardia as well as increased force of contractions of the heart can result in myocardial necrosis. These effects are thought to be mediated mainly via beta 1 receptors. However, beta 2 receptors also play a role in these myocardial effects. Albuterol induces bronchodilation of the smooth muscle in the uterus. This effect plays a role in the formation of leiomyomas in the rat.

3.2.4 Safety pharmacology

No specific safety pharmacology studies were conducted for this drug product. The data contained in the safety pharmacology section were obtained from the original pharmacology reviews for NDA 17-559 (Proventil Inhaler) and NDA 20-503 (Proventil HFA).

Neurological effects:

Albuterol administered orally had no CNS effects in rats, cats, dogs or rabbits but caused ataxia and decreased spontaneous activity in mice. Albuterol does not pass the blood-brain barrier and had no effect on tremors or hypothermia induced by intracerebral injection of oxotremorine in mice. Albuterol interacts with the serotonergic system in the rat brain and stimulates central 5-hydroxytryptamine turnover. Continuous administration of albuterol aerosol at doses of 600-800 mcg/kg to dogs without benefit of oxygen caused convulsions.

Cardiovascular effects:

In minipigs, rodents and dogs, albuterol induces hypotension, tachycardia, cardiac arrhythmias and sudden death with histologic evidence of myocardial necrosis. At the maximum inhaled dose proposed for clinical use, approximately 21.6 mcg/kg albuterol, hypotension and tachycardia occur in rats and dogs but albuterol did not cause myocardial necrosis.

Pulmonary effects:

In *in vitro* and *in vivo* studies albuterol produced relaxation of tracheobronchial smooth muscle. At an iv dose of 100 mg/kg in the dog, albuterol increased respiratory rate, volume, O₂ consumption and CO₂ production. At an iv dose of 5 mg/kg, albuterol increased the respiratory rate in the dog. Inhaled albuterol doses of 600-800 mcg/kg had no effect on respiratory mucous flow in the cat.

Renal effects:

In an inhalation study in the Sprague-Dawley, albuterol at doses of 0.78, 1.56 and 3.16 mg/kg resulted in significant increases in absolute kidney weights in all dose groups. In an inhalation study in squirrel monkeys, albuterol at doses of 0.78, 1.58 and 2.28 mg/kg had no effects on absolute kidneys weights or any other organ weight. There were no histopathology-related lesions observed in these animals. No functional effects have been reported.

Gastrointestinal effects:

In *in vitro* studies, albuterol, 1 mg/L, had no effect on the smooth muscle of the rabbit duodenum, human stomach and guinea pig colon. Albuterol, at concentrations up to 100 mg/L, had no effect on histamine, acetylcholine, bradykinin or BACL-induced contractions of the guinea pig ileum.

Abuse liability:

No abuse liability effects related to albuterol have been reported.

3.2.5 Pharmacodynamic drug interactions

No specific studies have been conducted for this drug product. Pretreatment of mice with 5 mg/kg of oral albuterol did not significantly alter the ED₅₀ value for hexobarbital and alcohol sleeping time, amphetamine motor activity and chlorpromazine avoidance response. The concurrent use of beta 2 adrenergic agonists and phosphodiesterase inhibitors has been shown to exacerbate the myocardial toxicity in the rat and rabbits

(Whitehurst, VE, et al: (1983), Cardiotoxic Effects in Rats and Rabbits Treated with Terbutaline Alone and in Combination with Aminophylline. J Amer. Coll. Toxicol. 2, 147-153) and Joseph X et al: (1981), Enhancement of cardiotoxic Effects of Beta – Adrenergic bronchodilators by Aminophylline in Experimental Animals. Fundam. Appl. Toxicol. 1, 443-447. It has also been reported that additive cardiotoxicity may occur in the asthmatic patient who is receiving theophylline and high doses of beta 2 agonists (Wilson, JD, et al: (1981), Has the Change to Beta Agonist Combination with Oral Theophylline Increased Cases of Fatal Asthma. Lancet 1, 1235-1237).

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief summary

No studies were conducted for this NDA. The lung distribution and clearance of radiolabeled (albuterol-³H) given by inhalation was measured in the dog. Of the given dose, 10-20% reached the lungs and 0.4-1.5% was found in the trachea and main bronchi. When measured in the rabbit, dog and rat, albuterol given orally is rapidly absorbed and excreted mainly via the urine (60-70%). Albuterol administered by inhalation to animals including humans is also rapidly absorbed, metabolized and eliminated. Inhaled albuterol is metabolized via glucuronidation in rodents and dogs and eliminated mainly in the urine. The metabolism of inhaled albuterol in humans has not been delineated. The drug is eliminated mainly in the urine. The distribution of albuterol after inhaled or oral in animals is found mainly in the lungs, kidney and the liver. However, albuterol administered by inhalation to pregnant rats crossed the placenta and was found in the tissues of the fetuses.

3.3.3 Absorption

Albuterol is rapidly absorbed in rodents and man after oral and inhalation administration. Maximum plasma concentrations were obtained 2 hours post dosing in Sprague-Dawley rats following oral administration. Peak plasma levels were observed in rabbits and dogs 1-2.5 hours after oral administration.

3.3.4 Distribution

In studies in the rat, albuterol was found in significant concentrations in the kidney, the liver and the plasma only 24 hours after oral dosing. There was no drug accumulation in the tissues of animals following repeated dosing. The Proventil HFA label indicates that albuterol-related material was transferred to the fetus following administration to pregnant rats.

3.3.5 Metabolism

In rats, rabbits and dogs, albuterol is metabolized via glucuronidation pathways. The glucuronide derivative accounted for 65-85 % of total drug related material in the rat, 90 % in the rabbit and 10% in the dog. Unchanged drug accounted for 90% in the dog and 5-20% in the rat and the rabbit. The half-life in animals including man is approximately 1.5-4 hours. In humans, unchanged drug and a metabolite accounted for 40 and 60 % of the urinary activity. In man, when albuterol was introduced directly into the lung via a

bronchoscope, the majority of the dose in the plasma and urine samples was present as unchanged drug suggesting that the drug is not metabolized in the lung. The main metabolite in humans is thought to be albuterol-4-O-sulfate.

3.3.6 Excretion

Albuterol is excreted mainly in the urine in rats, dogs and humans. In the rat, urinary excretion accounted for 52-59% and fecal excretion 25-40%. In humans, approximately 60-70% is excreted in the urine.

3.3.7 Pharmacokinetic drug interactions

No studies were conducted for this NDA.

3.3.10 Tables and figures to include comparative TK summary

No toxicokinetic data were produced for this NDA submission.

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology:

Acute studies were conducted in rodents and dogs in which albuterol was given orally, intraperitoneously (ip) and intravenously (iv). The oral LD₅₀ for rodents and dogs was greater than 2000 and 1000 mg/kg, respectively. The iv LD₅₀ was approximately 70 and 60 mg/kg in rodents and dogs, respectively. The LD₅₀s were similar in male and female animals. The toxicity of the base and the sulfate was similar. Symptoms include ataxia, clonic convulsions and shallow respiration.

Repeat dose inhalation studies of 28 days duration in rats and dogs were conducted by the sponsor to determine the most appropriate animal species for a 90 day toxicity study to compare the toxicities of Salbutamol/CFC and Salbutamol/HFA. Salbutamol/ HFA was administered to rats daily by inhalation using achieved inhalation doses of 0, 0.07, 0.17 and 0.52 mg/kg (pulmonary deposited doses were 0.005, 0.012 and 0.036 mg/kg, respectively) for 28 days. Salbutamol/HFA did not induce any major toxicity in the rat. The NOAEL was 0.52 mg/kg (0.036 mg/kg mg/kg pulmonary deposited dose). Salbutamol/HFA was also administered to Beagle dogs using inhalation doses of 0.044, 0.16 and 0.49 mg/kg daily for 28 days. Salbutamol/CFC was administered as a positive control, 0.50 mg/kg. The results of this study reveal that Salbutamol/HFA at doses of 0.16 mg/kg and higher induced fibrosis and mineralization in the papillary muscles of the dog. The study results also show that both Salbutamol formulations may be irritating to the tracheal bifurcation. The NOAEL in this study was 0.044 mg/kg in males and 0.16 mg/kg in females.

Based on the cardiac toxicity, the dog was selected for a 90-day toxicity study bridging the known effects of albuterol/CFC formulation with that of albuterol/HFA formulation.

albuterol /HFA was administered to Beagle dogs using inhalation achieved doses of 0.042, 0.082 and 0.162 mg/kg daily. Albuterol /CFC was included as the positive control, 0.169 mg/kg. In contrast to the 28-day dog study, there were no microscopic changes in the papillary muscles of the dogs in either the albuterol /HFA or albuterol /CFC dose groups even though the sponsor utilized a special collagen stain, Masson's Trichrome, to identify myocardial necrosis. This is likely due to the reduced dose levels in the 90-day study; also, only one male showed microscopic changes in the 28-day study at the dose of 0.16 mg/kg. Gross pathology examinations did reveal pale, focal areas on the papillary muscles in a non-dose-related manner (1 of 4 low dose female dogs and 2/4 mid dose female dogs but no focal areas in the high dose group); no gross pathology findings were observed in the male dogs or in albuterol/CFC dosed animals. Toxicokinetic analyses were not conducted in the 90 day study. The Division previously recommended that samples be taken and stored for future analysis should any toxicity of concern occur and to allow for comparative exposure assessment of the HFA and CFC formulations; blood samples were stored by the sponsor. Based on the findings, the NOAEL in females in the 90 day study is difficult to define since only gross cardiac findings were noted in the low and mid dose with no associated microscopic findings. The NOAEL in the male dog is the high dose of 0.162 mg/kg. Overall, the toxicity profile in the dog is similar when Salbutamol/HFA is compared with Salbutamol/CFC. Further, there were no toxicities identified that were not previously associated with albuterol.

Genetic toxicology:

Albuterol sulfate was not mutagenic in the Ames test with and without metabolic activation. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with and without metabolic activation. Fluctuation assays in *S.typhimurium* TA98 and *E.coli* WP2, both with metabolic activation, was negative. Albuterol sulfate was not clastogenic in the human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assays at intraperitoneal doses up to 200 mg/kg.

Carcinogenicity:

Albuterol sulfate was not carcinogenic in an 18 months oral (diet) chronic /carcinogenicity study in CD1 mice. The doses were 0, 50, 150 and 500 mg/kg. In a 2 year oral (feeding) study in the CD rat, albuterol sulfate at doses of 0, 2, 10 and 50 mg/kg was not carcinogenic. Albuterol sulfate induced significant, dose-related increases in smooth muscle tumors, leiomyomas, in the mesovarium at all doses; an effect that was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. A 99 week (696 days) oral oncogenic study was carried out in the female Syrian hamster. The albuterol sulfate doses were 10 and 50 mg/kg. There was no tumorigenicity in this study.

Reproductive toxicology:

A segment I study was carried out in the Wistar rat using oral doses of 2 and 50 mg/kg. The rats were dosed prior to mating and the females were dosed until weaning. The 21 day pup survival was significantly decreased in the high dose. There were no effects on fertility. The study was extended to the F₁ generation. The males and females were dosed

for 110 and 130 days, respectively. They were then mated and the dams were sacrificed 20 days post-partum. No adverse effects were observed on fertility and there were no abnormalities in the pups. A segment II study was carried out in the Wistar rat using oral albuterol doses of 0.0.5, 2.32, 10.75 and 50 mg/kg, day 1-19 of pregnancy. No teratogenic effects were observed. A total of 9 segment II studies were carried out in the Stride Dutch rabbit. The oral doses were 0, 0.5, 2.32, 10.75, 50 and 100 mg/kg. In some of the studies, there was a small number of rabbits/dose (2-4/dose/study). The duration of the studies varied from days 1-29, 6-20 or 8-16. Results reveal doses at 2.32 mg/kg and above consistently depressed body weight gain in the dams. The mean weight of the live fetuses showed no drug-related changes. There was a decreased number of live fetuses/litter and resorption sites at 50 mg/kg and higher. Another segment II study was carried out in the New Zealand rabbit. Albuterol sulfate was given orally, day 16-18 using doses of 0, 0.05, 0.5, 5 and 50 mg/kg. There were no fetal abnormalities in this study. Proventil HFA label describes development of cranioschisis in rabbits. In a segment III study in the Wistar rabbit, albuterol was administered orally using doses of 0, 2 and 50 mg/kg from day 14 post coitus to day 20 post-partum. There was a dose-related decrease in 21 day survival, 64.3, 57.2 and 31.2 %, respectively in the control, low and high dose pups. Carbuterol, Salbutamol and Isoproterol were injected subcutaneously into CD1 mated mice using doses of 0.1, 0.5, 2.5, 10 and 25mg/kg in 12 studies (NDA 17-800; Carbuterol). The study data do not include number of days or when during pregnancy the drugs were administered. All three drug increased resorptions, decreased the number of liver fetuses and decreased fetal weights at doses of 0.1 mg/kg and higher. The incidence of gross malformations was significantly increased at and above 0.5 mg/kg Carbuterol and Isoproterol and 2.5 mg/kg Salbutamol. The most common finding was cleft palate which was significant more frequent at 0.1 mg/kg Carbuterol and 0.5 mg/kg Isoproterol and Salbutamol. Teratogenic effects of the three drugs were evident at doses that produced adverse effects on the dams. Because of the above noted findings, albuterol is a pregnancy category C.

Special toxicology:

There were no data submitted in this NDA submission.

3.4.2 Single-dose toxicity

No studies were conducted for this drug product. The acute toxicity of albuterol was determined in rats and mice by the intravenous, oral and intraperitoneal routes. The results are shown below:

Species	Route	LD ₅₀ (mg/kg)	
		Male	Female
Mice	Iv	70.5	75.3
Rat	Iv	61.5	59
Rat	Oral	<2000	<2000
Mice	Oral	<2000	<2000
Rat (fed)	Oral	8600	7600

Rat (fasted)	Oral	2900	4100
Rat (10 and 20 days old)	Oral	<1000	<1000
Rat (10 day old)	IP	213	169
Rat	IP	372	415

iv-intravenous/IP-intraperitoneous

Symptoms in rats and mice include ataxia, reduced activities, tremors, convulsions, arrhythmias and sudden death.

3.4.3 Repeat-dose toxicity

Study title: 4 Week Inhalation Toxicity Study in Rats

Key study findings: There was no significant toxicity observed in the rats in this study. The NOAEL was the achieved high dose of 0.52 mg/kg albuterol/HFA (0.036 mg/kg mg/kg pulmonary deposited dose). The HFA and CFC formulations produced comparable effects except the CFC formulation produced laryngeal squamous metaplasia that was not observed in animals exposed to the HFA formulation.

Study no: 655815

Volume #, and page #: Module 4, volume 1, page 400001

Conducting laboratory and location: _____

Date of study initiation: August 23, 1996

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, radiolabel, and % purity: Salbutamol HFA Inhaler/SAL-061/ _____
%; Salbutamol CFC/ batch # 96703

Formulation/vehicle: Salbutamol/ HFA, Salbutamol/CFC

Methods (unique aspects): Exposure to aerosols were achieved using a _____
_____ inhalation exposure system. The aerosol generating system was optimized prior to each exposure by assessing the aerosol concentration achieved following actuation of varying numbers of MDI units over differing time periods. The exposure chamber air flow rate was ~ 15 L/min. The aerosol concentration of salbutamol was determined by chemical analysis; sampling on _____ and samples were analyzed by HPLC. Particle size characterization was performed using a _____ Cascade Impactor (_____)

Dosing:

Species/strain: Rat, Sprague-Dawley

#/sex/group or time point (main study): 10/sex/group

Satellite groups used for toxicokinetics or recovery: NA

Age: 10 weeks

Weight: 161-287 g

Doses in administered units: 0.07, 0.17 and 0.52 mg/kg are the achieved doses for Salbutamol/HFA. Salbutamol/CFC was used as a positive control at an achieved dose of 0.49 mg/kg. These are the delivered doses. The nominal dose levels were estimated as follows:

$$\text{Dose (mg.kg}^{-1}\text{)} = \frac{\text{RV} \times \text{T} \times \text{CC}}{\text{BW}}$$

where: RV = Respiratory Volume^l/minute (ml) = $2.10 \times \text{weight}^{0.75}$

T = Duration of exposure

CC = Chamber Concentration (mg.litre⁻¹, protocol deviation)

BW = Most current group mean body weight (expressed in g - mean of males and females calculated separately)

Given the achieved doses, the estimated pulmonary deposited doses based on particle size is approximately 7 % which equates to doses of 0.005, 0.012 and 0.036 mg/kg.

Route, form, volume, and infusion rate: Inhalation, Salbutamol inhaler, 100 mcg, 15 liters/minute, drug was administered for 4-20 minutes daily for 28 days. The mass median aerodynamic diameter (MMAD) ranged from — µm for Salbutamol/HFA.

The age of the Salbutamol/HFA was 16 months.

Observations and times:

Mortality: Observed daily.

Clinical signs: Observed daily.

Body weights: Observed prestudy and twice weekly.

Food consumption: Observed weekly.

Ophthalmoscopy: Observed predose and week 4.

EKG: NA

Hematology: Prior to termination, week 4.

Clinical chemistry: Prior to termination, week 4.

Urinalysis: Evaluated during week 4.

Gross pathology: Observed during terminal studies.

Organs weighed: Evaluated during terminal studies. The following organs were weighted: lungs, heart, adrenals, kidneys, liver, ovaries, parathyroids, pituitary, prostate, spleen, testes, thymus, thyroids and uterus

Histopathology: Evaluated during the terminal studies. Only the tissues of the rats in the control and high dose groups were evaluated microscopically. Full tissue examinations were conducted in the rats in these dose groups.

Toxicokinetics: Blood samples were taken via the tail vein at 1 and 2 hours postdosing on days 1, 7 and 26.

Results:

Mortality: There were no mortalities in this study.

Clinical signs: There were no clinical signs.

Body weights: The body weight gain was comparable in all dose groups at study termination. However body weight gain was significantly higher (5-10 %) in the females in the mid and high dose groups after the first week of dosing. A similar result was observed in the CFC group. The summary of body weight for males and females is shown below:

Salbutamol/HFA Formulation
4 Week Inhalation Toxicity Study in Rats
Body Weights (g)
Group Mean Values: Males

Group/Dose Level (mg Salbutamol, kg ⁻¹ .day ⁻¹)		Pretrial				Treatment Period (Days)								Body Weight Gain (g) (Time 0 - Day 28)
		PT 3	PT 2	PT 1	0	3	7	10	14	17	21	24	28	
1 (0)	Number Mean SD	10 208 8	10 227 9	10 237 11	10 255 13	10 268 14	10 279 14	10 296 16	10 313 17	10 322 18	- - -	10 346 21	10 346 23	10 91 20
2 (0.06)	Number Mean SD Prob.	10 213 8	10 237 8	10 247 9	10 266 12	10 280 14	10 299 17	10 314 21	10 328 26	10 340 28	- - -	10 364 31	10 366 31	10 100 25
3 (0.16)	Number Mean SD Prob.	10 210 9	10 225 12	10 236 12	10 254 15	10 266 19	10 282 24	10 297 27	10 307 29	10 320 33	- - -	10 338 41	10 346 43	10 92 31
4 (0.52)	Number Mean SD Prob.	10 210 9	10 230 10	10 241 11	10 259 12	10 274 15	10 288 16	10 303 18	10 314 20	10 326 22	- - -	10 343 29	10 355 28	10 96 20
5 (0.48)	Number Mean SD Prob.	10 212 10	10 232 12	10 242 14	10 260 17	10 277 20	10 295 23	10 307 25	10 321 26	10 331 28	10 344 29	10 356 30	10 356 31	10 97 19

PT = Pretrial

PT = Pretrial
- = No data available

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TABLE 3 (continued)

Body Weights (g)
Group Mean Values: Females

Group/Dose Level (mg Salbutamol, kg ⁻¹ .day ⁻¹)		Pretrial				Treatment Period (Days)								Body Weight Gain (g) (Time 0 - Day 28)
		PT 3	PT 2	PT 1	0	3	7	10	14	17	21	24	28	
1 (0)	Number Mean SD	10 153 6	10 164 5	10 165 5	10 174 5	10 181 5	10 185 7	10 198 10	10 208 11	10 217 10	- - -	10 231 11	10 234 13	10 60 13
2 (0.07)	Number Mean SD Prob.	10 155 7	10 164 7	10 168 8	10 175 7	10 186 7	10 193 8	10 206 8	10 216 11	10 220 12	- - -	10 230 14	10 231 13	10 57 11
3 (0.17)	Number Mean SD Prob.	10 154 7	10 163 7	10 167 10	10 177 11	10 188 14	10 196 15	10 207 16	10 216 17	10 224 16	- - -	10 240 19	10 243 20	10 66 15
4 (0.52)	Number Mean SD Prob.	10 155 5	10 164 8	10 169 8	10 176 8	10 189 10	10 196 11	10 209 11	10 217 12	10 226 12	- - -	10 239 15	10 239 18	10 63 11
5 (0.49)	Number Mean SD Prob.	10 156 8	10 166 11	10 169 9	10 179 13	10 195 15	10 207 17	10 219 19	10 229 21	10 236 21	10 239 28	10 246 24	10 247 22	10 69 10

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

PT = Pretrial
- = No data available

Food consumption: The food consumption was comparable in all dose groups.

Ophthalmoscopy: There were no drug-related eye changes in the rats in this study.

Electrocardiography: NA

Hematology: There were statistically significant increases in the hemocrit and hemoglobin values in the males in the mid and high dose groups. The changes ranged from 4-10 %. The increases were not observed in females in these dose groups. There also small increases in the red blood cell values in the males in all dose groups. The increases of approximately 2% were not statistically significant or observed in the females in these dose groups. The hematology values were similar in the Salbutamol/CFC dosed rats.

Clinical chemistry: There were decreases in glucose values in the males and females rats in all dose groups. The decreases in the males were 6-15 % in the males and 9-11 in the females. The decreases were not dose-related or statistically significant. There were also small increases in the potassium values in the females in the mid and high dose groups. The changes were approximately 9% and were statistically significant in the high dose females. The clinical chemistry values were similar in the Salbutamol/CFC dosed rats.

Urinalysis: There were no drug-related changes in the urinalysis parameters in the rats in this study.

Organ weights: The following organs were weighted: lungs, heart, adrenals, kidneys, liver, ovaries, parathyroids, pituitary, prostate, spleen, testes, thymus, thyroids and uterus. There were no drug-related organ weight changes in the rats in this study.

Gross pathology: There was no drug-related gross pathology.

Histopathology: Only the tissues of the rats in the control and high dose groups were examined microscopically. There were no drug-related microscopic changes in the rats in this study except for the statistically significant increase in squamous metaplasia in the larynx of the rats in the Salbutamol/CFC high dose group suggesting drug-induced irritation. The metaplasia was observed in 8/10 males and 7/10 females. These changes were not observed in the rats in the high dose Salbutamol/HFA group.

Toxicokinetics: The samples were frozen and sent to the laboratory for analysis. The sponsor has not analyzed the plasma samples.

Study title: 28 Day Repeat Dose Inhalation Toxicity Study in the Dog

Key study findings: Myocardial mineralization and fibrosis in the papillary muscles of the dogs in the 0.16 (males only) and 0.49 mg/kg dose groups. The NOAEL was 0.044 mg/kg in males and 0.16 mg/kg in females. Myocardial fibrosis was also observed in the papillary muscles of one male dog in the Salbutamol/CFC dose group (0.50 mg/kg). Overall, comparable toxicity profiles were observed with the HFA and CFC formulations of albuterol.

Study no: — 4/952816

Volume #, and page #: Module 4, volume 2, page . 400001

Conducting laboratory and location: —

Date of study initiation: July 25, 1995

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, radiolabel, and % purity: Salbutamol/ HFA (lot # SAL-061),
Salbutamol/CFC (lot # 95342A)/ —

Formulation/vehicle: Salbutamol inhaler, 200 doses, 100 mcg/dose; Salbutamol inhaler placebo

Methods (unique aspects):

Dosing:

Species/strain: Dog, Beagle

#/sex/group or time point (main study): 3/sex/group

Satellite groups used for toxicokinetics or recovery: None

Age: 22-26 weeks

Weight: 7.2-11 kg

Doses in administered units: Achieved doses, 0, 0.044, 0.16 and 0.49 mg/kg, Salbutamol/HFA.

The report states that administered doses were calculated using the following formula:

$$\text{Dose (mg/kg/d)} = (\text{N} \times \text{D} \times \text{P}) / (\text{W} \times 1000)$$

where N = # of metered doses administered per day, D = mean metered dose delivery, P = mean % salbutamol delivered to the dogs and W = BW (kg).

Salbutamol/CFC was used as a positive control at an achieved dose of 0.50 mg/kg.

Route, form, volume, and infusion rate: Inhalation, inhaler used, and dose was delivered via an oropharyngeal tube inserted into the mouth. MDIs were attached to an aerosol expansion chamber. The dogs in the low dose group received 6 metered doses/day. The mid dose group received 20 metered doses/day and the high dose received 65 metered doses/day. Metered doses were delivered during a number of consecutive 40-second cycles. Each metered dose was administered at approximately 0, 10 and 20 seconds for the low dose group and 0, 5, 10, 15 and 20 seconds for the other dose groups. The dogs were dosed twice daily with a 4 hour interval between dosing periods. The drug recovery studies reveal that the estimated dose in the low dose was 53.3 % of the nominal dose, 58.8% in the mid dose, 61.8% in the HFA high dose and only 43.4 % in the CFC high dose. Particle size characterization was not conducted in this study. However, the same batches were used in the previously reviewed 28-day rat study and the mass mean aerodynamic diameter (MMAD) was reported as \sim μm for Salbutamol/HFA and \sim μm for Salbutamol/CFC. The age of salbutamol HFA is 16 months and 3 months for Salbutamol/CFC.

Observations and times:

Mortality: Observed twice daily.

Clinical signs: Observed daily

Body weights: Observed weekly beginning 2 weeks prior to dosing.

Food consumption: Observed daily beginning 2 weeks prior to dosing.

Ophthalmoscopy: Evaluated prior to dosing and week 4.

EKG: Evaluated prior to dosing and 60-90 minute postdosing during week 4.

Hematology: Evaluated predose and week 4.

Clinical chemistry: Evaluated predose and week 4.

Urinalysis: Evaluated predose and week 4.

Gross pathology: During terminal studies.

Organs weighed: During terminal studies. The following organ weights were evaluated: adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, spleen, testes with epididymes and thyroid with parathyroids.

Histopathology: During terminal studies. A full histopathology was included in all dose groups.

Toxicokinetics: Blood was drawn on days 1 and 28 for absorption studies. For control, low and mid dose groups, 10 minutes after the morning dosing session, for the high dose groups, 2, 5, 15 and 30 minutes and 1, 2 and 4 hours after the morning dosing session.

Results:

Mortality: There was no unscheduled mortality.

Clinical signs: There were no drug-related clinical signs.

Body weights: Body weight gain was similar in the males in this study. The body weight gain was also similar in the females except for the Salbutamol/HFA females in the high dose group who had statistically significant increases in body weight gain by approximately 30%. The females in the Salbutamol/CFC had decreases in bodyweight gain by approximately 20% (non-significant). The summary of body weight gain is shown below:

TABLE 3
Bodyweights - group mean values (kg)

Week	Group									
	1 (Placebo control)		2 (Low dose-H)		3 (Inter. dose-H)		4 (High dose-H)		5 (High dose-C)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
-2	8.9	8.3	8.4	9.4	7.9	8.2	8.9	9.1	8.9	8.1
-1	9.2	8.7	8.7	9.3	8.1	8.5	9.2	9.6	9.1	8.4
0	9.6	8.9	9.1	9.6	8.5	8.7	9.6	9.7	9.4	8.8
1	9.8	9.1	9.3	9.9	8.7	8.9	9.8	10.0	9.5	8.8
2	10.2	9.5	9.6	10.2	9.1	9.3	9.9	10.3	9.9	9.1
3	10.2	9.7	9.9	10.4	9.4	9.5	10.2	10.6	10.1	9.2
4	10.5	9.9	10.2	10.7	9.5	9.9	10.8	11.0	10.3	9.6
Gain Weeks 0 - 4	0.9	1.0	1.2	1.0	1.0	1.2	1.2	1.3	1.0	0.8
sd	0.21	0.20	0.31	0.21	0.15	0.06	0.17	0.15	0.64	0.36
Mean bodyweight ¹										
Weeks 0 - 4 ♂/♀										
Average			9.6	10.2	9.0	9.3	10.1	10.3		
Weeks 0 - 2 ♂/♀			9.9		9.2		10.2			
Average									9.6	8.9
Weeks 2 - 4 ♂/♀									9.2	
Average									10.1	9.3
									9.7	

sd - Standard deviation

Level of significance: # $p < 0.05$

¹ Used for the purposes of dose estimation (see Appendix 2)

NA Not applicable

Food consumption: Food consumption was similar in all dose groups.

Ophthalmoscopy: There were no drug-related lesions or changes in the eyes of the dogs dosed with salbutamol.

Electrocardiography: During week 4 evaluations, a male dog in the high dose salbutamol/HFA dose group had 2 ventricular premature complexes each with positive QRS deflection. One female in the same dose group had a CV5RL atypical flat T-wave. One female in the high dose Salbutamol/CFC also had a CV5RL atypical flat T-wave. Repeat recordings in the dogs, 24 hours later revealed no abnormalities. However, the recordings should have been repeated at or close to C_{max} in an attempt to delineate whether Salbutamol at the doses used induced EKG changes in these dogs.

Hematology: There were no statistically significant differences in the Salbutamol-dosed dogs when compared with the control dogs.

Clinical chemistry: Group mean values (mean values for males and females) for blood urea nitrogen, creatinine and cholesterol in the male and female dogs in the high dose Salbutamol/HFA group were statistically significantly higher than the values in the control group. The increases ranged from 15-30% for the blood urea nitrogen, 14 % for the creatinine and 11-39 % for the cholesterol values. In addition, the mean group chloride values were statistically significantly lower in all Salbutamol-treated groups. The decreases were approximately 18% and were not dose-related. The clinical chemistry values were similar in the Salbutamol/CFC dosed groups.

Urinalysis: The pH of the females in the Salbutamol/HFA was higher than the females in the control group. The dose-related increases were 5, 11 and 16%, respectively and were statistically significant in the high dose females. The pH in the males was decreased by 10 % in the mid and high dose males. The urinalysis values were similar in the Salbutamol/CFC dosed groups.

Organ weights: The group mean absolute heart weight (absolute group mean heart weight = male and female values combined) was reduced for males and females in all dose groups. The decreases were approximately 7, 15 and 12% in the low, mid and high dose groups, respectively. The decrease was statistically significant in the mid dose group only. The group mean absolute kidney weight was statistically significantly decreased in the male and female rats in the mid and high dose groups by 10 and 14 %, respectively (the mean absolute kidney weight values are combined for males and females). The mean absolute adrenal weight was increased in the females in all dose groups by 15, 5 and 22 % in the low, mid and high dose groups, respectively. The mean absolute adrenal weights in the males were reduced in all dose groups by 17, 22 and 27 % in the low, mid and high dose groups, respectively. The decreases were dose-related in the males. The changes were statistically significant in the high dose females and males. The mean absolute gonad weight of the males in the high dose group was reduced by 30 %. The group mean absolute thyroid weight was reduced in a dose-related manner by 2, 15 and 19 % in the low mid and high dose groups, respectively. The noted organ weight changes were not associated with histological changes with exception of the heart. The relative organ

weights were not provided. The organ weights were similar in the Salbutamol/CFC dosed dogs. The summary of the absolute organ weights is shown below:

Absolute organ weights - group mean values

Males and females combined - Week 5

Group	Body wt kg	Brain g	Pitu- itary mg	Heart g	Lungs g	Liver g	Spleen g	Kidneys g	Thyr- oids g	Gonads g	Prost- ate g
1 (Placebo control)	10.1	79.1	61	76.7	96.0	374.2	59.3	54.1	0.97	♀ 1.03 ♂ 14.93	2.78
2 (Low dose-H)	10.3	79.2	66	71.2	92.5	372.0	57.8	55.5	0.93	0.95	14.56
3 (Inter. dose-H)	9.5	76.4	61	65.5**	84.8	337.9	52.9	48.6*	0.82	0.73	13.40
4 (High dose-H)	10.7	76.3	62	67.5**	87.2	353.2	53.3	46.6**	0.79	0.80	19.43*
5 (High dose-C)	9.8	74.3	63	67.4**	86.3	346.3	48.8	49.7	0.72*	0.71	16.34

Gross pathology: Treatment-related findings included sub-endocardial areas on the papillary muscles of the heart in 1 male dog each in the mid and high dose groups and in 2 females in the high dose group. These findings were also observed in 1 male in the positive control group.

Histopathology: Minimal or moderate myocardial fibrosis was observed in the papillary muscles of males in the mid and high dose group as well as the females in the high dose group. In the high dose, the fibrosis was accompanied by myocardial mineralization and/or hemorrhage in the papillary muscle. Myocardial fibrosis (moderate) was also observed in the papillary muscles of the 1 male dog in the positive control, Salbutamol/CFC. The summary of the myocardial findings are shown below:

Group	Male					Female				
	1	2	3	4	5	1	2	3	4	5
Myocardial fibrosis in papillary muscle										
Total	0	0	1	2	1	0	0	0	2	0
Minimal	0	0	0	1	0	0	0	0	0	0
Moderate	0	0	1	1	1	0	0	0	2	0
Myocardial mineralisation in papillary muscle										
Total	0	0	0	2	0	0	0	0	1	0
Minimal	0	0	0	1	0	0	0	0	1	0
Moderate	0	0	0	1	0	0	0	0	0	0
Haemorrhage in papillary muscle										
Total	0	0	0	0	0	0	0	0	1	0
Minimal	0	0	0	0	0	0	0	0	1	0
Total number of dogs examined	3	3	3	3	3	3	3	3	3	3

Minimal mucosal hyperplasia at the tracheal bifurcation was seen in 1 male in the Salbutamol/HFA and 3/3 males and 2/3 females in the positive control group, Salbutamol/CFC. The tracheal bifurcation summary data are shown below:

		Male					Female				
Group		1	2	3	4	5	1	2	3	4	5
Mucosal hyperplasia at tracheal bifurcation	Total	0	0	0	1	3	0	0	0	0	2
	Minimal	0	0	0	1	3	0	0	0	0	2
Total number of dogs examined		3	3	3	3	3	3	3	3	3	3

Epithelial hyperplasia of the ventromedial vocal cords of the larynx was seen in the females in the low (1/3), mid (1/3) and high dose groups (2/3) and 1/3 males in the high dose group. These findings were not observed in the vocal cords of the dogs in the Salbutamol/CFC dosed dogs.

Toxicokinetics: The drug plasma samples were not analyzed.

Study title: Comparative 3 Month Inhalation Toxicity Study of an HFA-Propelled Albuterol Inhalation Aerosol and a CFC-Propelled Albuterol Formulation in Beagle Dogs.

Key study findings:

- 90-day administration of albuterol sulfate in an HFA formulation did not produce significant microscopic changes in the papillary muscles of dogs at inhaled doses up to 0.162 mg/kg/day. However, gross pathology examinations revealed pale, focal areas on the papillary muscles of 1/4 female dogs in the low dose (0.042 mg/kg) and 2/4 female dogs in the mid dose (0.082 mg/kg) in the Salbutamol/HFA dose groups. There were no significant findings in males administered the HFA formulation or in animals administered the active control CFC formulation. Myocardial toxicity is a known class effect of beta adrenergic agonists.
- Because toxicokinetics were not assessed, the systemic exposure of albuterol in these dogs is unclear. It is known that the systemic exposure following dosing with drugs administered with HFA is greater than the systemic exposure following CFC administered drugs. This may explain, in part, the reason for the myocardial toxicity in the Salbutamol/HFA administered dogs compared with the lack of myocardial toxicity in the Salbutamol/CFC administered dogs.
- The NOAEL in the males is 0.162 mg/kg. The NOAEL in females is difficult to determine since gross myocardial findings were observed only at the low- and mid-doses. However, myocardial toxicity is a known effect of beta-adrenergic agonists.
- The use of a biomarker, i.e., Troponin I or T would have been helpful in delineating initial myocardial toxicity.

- With the exception of the gross myocardial findings in females, the HFA and CFC formulations produced similar toxicity profiles; no unexpected toxicities were observed.
- The sponsor concluded that the NOAEL is 0.162 mg/kg for both males and females.

Study no: 21107

Volume #, and page #: Module 4, volume 3, page 1

Conducting laboratory and location: _____

Date of study initiation: December 3, 2001

GLP compliance: Yes

QA report: yes (☒) no (☐)

Drug, lot #, radiolabel, and % purity: Salbutamol FHA, lot # AAW13A,
Salbutamol/CFC, lot # ABK26A.

Formulation/vehicle: Salbutamol/HFA/placebo-Salbutamol/HFA

Methods (unique aspects): Animals were dosed using a close fitting face mask (fitted with an oro-pharyngeal mouth tube) via oral inhalation to aerosols generated from MDIs actuated into a _____ system. Animals were exposed to a constant aerosol concentration and the duration of dosing adjusted to achieve the target dose. A target aerosol concentration of 0.75 mg/L was selected for both formulations and was achieved by using 6 MDIs actuated 4 times per minute for the HFA formulation and 6 MDIs actuated 5 times per minute for the CFC formulation. The aerosol concentration of albuterol was determined by an analytical method; sampling or _____ and samples were _____ by calculating the difference between the pre- and post- _____ . Particle size characterization was performed at least once weekly using a _____ Cascade Impactor _____

Dosing:

Species/strain: dog, Beagle

#/sex/group or time point (main study): 4/sex/group

Satellite groups used for toxicokinetics or recovery: None

Age: 7 months

Weight: 6.5-8.8 kg and 5.6-7.3 kg for males and females.

Doses in administered units: Dose selection was based upon the 28-day study in dogs in which a dose of ~ 0.16 mg/kg produced myocardial fibrosis following dosing via oropharyngeal tubing. Target delivered doses in the current study were 0, 0.04, 0.08 and 0.16 mg/kg for albuterol/HFA and 0.16 mg/kg for the albuterol/CFC formulations. Achieved delivered doses were calculated as albuterol/HFA: 0.042, 0.082 and 0.162 mg/kg; 0.169 mg/kg for the positive control, albuterol/CFC, once daily for 90 days. The doses in this study were calculated as follows:

Achieved dose levels were estimated using the following criteria:

$$\text{Dose (mg.kg}^{-1}\text{)} = \frac{\text{CC} \times \text{RV} \times \text{T}}{\text{BW}}$$

CC = Chamber concentration (analytical) of Albuterol (mg.l⁻¹)

RV = Nominal respiratory volume of 5 l.min⁻¹

T = Duration of exposure (min)

BW = Body weight (mid-week body weight expressed in kg)

Route, form, volume, and infusion rate: Inhalation, aerosol, oro-pharyngeal tube, particle size distribution data show that 86.4, 98.0 and 94.3% of aerosol particles in groups 1, 2, 3, 4 and 5, respectively were less than — in diameter. The MMAD in dose groups ranged from — μm.

Observations and times:

Clinical signs: Observed several times each day.

Body weights: Observed pretest and weekly.

Food consumption: Observed pretest and weekly.

Ophthalmoscopy: Observed weeks 7 and 13.

EKG: Evaluated 30 minutes postdosing weeks 7 and 13.

Hematology: Evaluated weeks 7 and 13.

Clinical chemistry: Evaluated 7 and 13.

Urinalysis: Evaluated weeks 7 and 13.

Gross pathology: During terminal studies.

Organs weighed: During terminal studies, the following organs were weighed: adrenal, brain, heart, kidneys, ovaries, pancreas, pituitary, prostate, spleen, sublingual glands, sumaxillary glands, testes, thymus, lungs, thyroids and uterus.

Histopathology: During terminal studies. Complete histopathology was carried out for all dogs in all dose groups. Masson's Trichrome was used to help to delineate myocardial necrosis.

Toxicokinetics: Drug plasma levels were collected days 1 and 91 prior to and 5, 15, 30 minutes and 1, 2, 4, 8 and 24 hours.

Results:

Mortality: There were no mortalities in this study.

Clinical signs: There was an increase in heart rate and carotid pulse of all albuterol-dosed dogs during the first two weeks of the study. These effects were not observed during the third week and thereafter. Increased salivation during and immediately after dosing was observed in all albuterol/HFA-dosed dogs. These effects were greater in the mid and high dose dogs but were not observed in the albuterol/CFC-dosed dogs. Headshaking was observed in the albuterol/CFC and control dogs but not in the albuterol/HFA dogs. Red materials in loose feces were noted in all dogs in this study.

Body weights: The body weight gain was increased in all albuterol-dosed dogs. The increases were 14, 142 and 100% in the males and 100, 67 and 150 % in the females. The increases were statistically significant in the mid dose in the males and low and high dose in the females. The body weight gain was statistically significantly increased in the Salbutamol/CFC-dosed dogs by approximately 100-150%. The summaries of body weight gain are shown below:

Body Weights (kg):
Group Mean Values: Males

Dose Group/Treatment		Treatment Period (Weeks)						Body Weight Gain (kg) (Week 0 - Week 13)
		8	9	10	11	12	13	
1 Placebo Control	Number	4	4	4	4	4	4	4
	Mean	7.9	7.9	8.2	8.1	8.3	8.3	0.7
	SD	0.8	0.7	0.8	0.8	0.8	0.8	0.3
2 Albuterol-HFA Low Dose	Number	4	4	4	4	4	4	4
	Mean	7.7	7.7	7.9	7.9	8.0	8.1	0.8
	SD	1.1	1.1	1.2	1.1	1.2	1.4	0.7
3 Albuterol-HFA Intermediate Dose	Number	4	4	4	4	4	4	4
	Mean	8.7	8.8	9.0	9.2	9.4	9.3	1.7 *
	SD	1.6	1.4	1.5	1.5	1.6	1.4	0.7
4 Albuterol-HFA High Dose	Number	4	4	4	4	4	4	4
	Mean	8.7	8.8	9.0	9.0	9.0	9.1	1.4
	SD	0.2	0.2	0.2	0.1	0.1	0.2	0.4
5 Albuterol-CFC High Dose	Number	4	4	4	4	4	4	4
	Mean	9.3	9.3	9.7	9.7	9.8	10.1	2.2
	SD	0.4	0.4	0.4	0.5	0.6	0.5	0.7
	Prob.							**

Prob.: Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

Prob2: Significantly different from Group 5: * P<0.05, ** P<0.01, *** P<0.001

Weight gain (weeks 0-13) derived from individual animal weight gains

Food consumption: There were no drug-related changes in food consumption in the dogs in this study.

Ophthalmoscopy: There were no drug-related changes in the dogs in this study.

Electrocardiography: Heart rates were increased in all mid- and high-dose Salbutamol/HFA dogs and Salbutamol/CFC-dosed dogs especially during the first week. After the third week of dosing, the heart rates were similar in all dose groups.

Hematology: During week 7, hematocrit values in the mid and high dose Salbutamol/HFA dosed male dogs were statistically significantly lower than the hematocrit values in the placebo dogs by 11 and 13 %, respectively. During week 13, reticulocytes in the males in the high dose group were statistically significantly higher than the reticulocyte values in the males in the control group by 83 %. The hemocrit and reticulocyte values were similar in all female dose groups in this study. The hematocrit and reticulocyte values were similar in the dogs dosed with Salbutamol/CFC.

Clinical chemistry: During week 7, sodium values were statistically significantly decreased in the males in the low and mid dose groups by approximately 2%. During week 7, potassium values in the males in the low, mid and high dose groups were statistically significantly higher than the potassium values in the control group by 10, 12 and 15 %, respectively. The sodium and potassium values were similar in the males and females in the Salbuterol/HFA and Salbuterol/CFC dose groups.

Urinalysis: There were no treatment-related changes in urinalysis parameters in this study.

Organ weights: There were no treatment-related changes in absolute or relative organ weights in the dogs in this study.

Gross pathology: A pale focus was present in the left ventricle papillary muscle of 1/4 females in the low dose group and 2/4 females in the mid dose group. These gross findings were not associated with any histologic findings.

Histopathology: No drug-related findings were noted following dosing with either the HFA or CFC formulations. Mild to moderate adrenal cortex vacuolation (focal or diffuse) involving the *zona fasciculata* was seen in 2/4 female dogs in the high dose Salbuterol/HFA dose group. The dogs with minimal adrenal cortex *zona fasciculata* vacuolation were either in pro-estrus or metaestrus while the high dose dogs with moderate adrenal cortex *zona fasciculata* vacuolation were in late metaestrus. This finding has been observed in control Beagle dogs and is considered a spontaneous change.

Toxicokinetic: The blood samples were frozen and stored but not analyzed.

3.4.4. Genetic toxicology

The sponsor did not conduct any genetic toxicology studies for this submission. However, genotoxicity studies reported in the literature (Polymer D et al. (1978), Salbutamol: Lack of Evidence of Tumour Induction in Man. Brit.J Med. 1: 46-47 and Starosciak B et al. (1983), Investigation of Mutagenic activity of Some Drugs Produced by "Polfa" with the Use of Microbial genetics Methods. Farm. Pol. 39: 399-402) reveal albuterol sulfate was not mutagenic in the Ames test with and without metabolic activation using tester strains *S.typhimurium* TA1537, TA1538 and TA98 or *E.coli* WP2uvrA and WP67. No forward mutation was seen in yeast strain *S.cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with and without metabolic activation. Fluctuation assays in *S.typhimurium* TA98 and *E.coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in the human lymphocyte assay or in an AH1 strain mouse micronucleus assays at intraperitoneous doses up to 200 mg/kg.

3.4.5. Carcinogenicity

Carcinogenicity studies were not conducted for this submission. However, three studies were conducted for Proventil Tablets (NDA 17-853). An 18 months oral (diet) chronic/carcinogenicity study with albuterol sulfate was carried out in CD1 mice. The doses were 0, 50, 150 and 500 mg/kg. There was no tumorigenicity in this study. A two year oral (feeding) chronic/ carcinogenicity study was carried out in the CD rat. The doses were 2, 10 and 50 mg/kg. Albuterol sulfate induced significant, dose-related increases in smooth muscle tumors-leiomyomas in the mesovarium at all doses; an effect that was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. A 99 week (696 days) oral oncogenic study was carried out in the female Syrian hamster. The albuterol sulfate doses were 10 and 50 mg/kg. There was no tumorigenicity in this study.

3.4.6. Reproductive and developmental toxicology

Reproductive toxicology studies were not conducted for this NDA submission. However, studies were conducted for Proventil Inhaler (NDA 17-559) and Carbuterol (NDA 17-800).

A segment I study was carried out in the Wistar rat using oral doses of 2 and 50 mg/kg. The rats were dosed prior to mating and the females were dosed until weaning. At the 13 day post coitus sacrifice, one high dose dam had 2 adjacent embryos sharing a common placenta. At term, one high dose stillborn pup had caudal agenesis and imperforate anus. The 21 day pup survival was significantly decreased in the high dose. The study was extended to the F₁ generation. The males and females were dosed for 110 and 130 days, respectively. They were then mated and the dams were sacrificed 20 days post-partum. No adverse effects were observed on fertility and there were no abnormalities in the pups. There were no effects on the fertility of rats in this study.

Segment II studies were conducted in rats, rabbits and mice. A segment II study was carried out in the Wistar rat using oral albuterol doses of 0.05, 2.32, 10.75 and 50 mg/kg, days 1-19 of pregnancy. No teratogenic effects were observed. A total of 9 studies segment II studies were carried out in the Stride Dutch rabbit. The oral doses were 0, 0.5, 2.32, 10.75, 50 and 100 mg/kg in some of the studies; there was a small number of rabbits/dose (2-4/dose/study). The duration of the studies varied from days 1-29, 6-20 or 8-16. Results reveal doses at 2.32 mg/kg and above consistently depressed body weight gain in the dams. The mean weight of the live fetuses showed no drug-related changes. There was a decreased number of live fetuses/litter and resorption sites at 50 mg/kg and higher. In the 50 mg/kg dose group, 1/8 pups in a litter had myelocystomeningocele, another pup had meningocele. In another litter 7 pups showed cranioschisis, macroglossia and carpal flexure, 3/7 with palatoschisis and 6/7 with tarsal rotation. These findings were not observed in the 100 mg/kg dose group and the sponsor stated that these malformations were had not been observed spontaneously in the Dutch rabbit. Another segment II study was carried out in the New Zealand rabbit. Albuterol sulfate was given orally, day 16-18 using doses of 0, 0.05, 0.5, 5 and 50 mg/kg. There were no fetal abnormalities in this study. Carbuterol, Salbutamol and Isoproterenol were injected

subcutaneously into CD1 mated mice using doses of 0.1, 0.5, 2.5, 10 and 25mg/kg in 12 studies (NDA 17-800; Carbuterol). The study data do not include number of days or when during pregnancy the drugs were administered. All three drug increased resorptions, decreased the number of liver fetuses and decreased fetal weights at doses of 0.1 mg/kg and higher. The incidence of gross malformations was significantly increased at and above 0.5 mg/kg Carbuterol and Isoproterol and 2.5 mg/kg Salbutamol. The most common finding was cleft palate which was significant more frequent at 0.1 mg/kg Carbuterol and 0.5 mg/kg Isoproterol and Salbutamol. Teratogenic effects of the three drugs were evident at doses that produced adverse effects on the dams.

In a segment III study in the Wistar rabbit, albuterol was administered orally using doses of 0, 2 and 50 mg/kg from day 14 post coitus to day 20 post-partum. There was a dose-related decrease in 21 day survival, 64.3, 57.2 and 31.2 % survival, respectively in the control, low and high dose pups. The pups that died in all dose groups had full bladders, empty stomachs and interscapular brown fat, due to hypothermia, suggesting parental neglect.

Based upon the results of the aforementioned studies, albuterol sulfate has been given a Pregnancy Category C designation.

3.4.7 Local tolerance

No specific local tolerance studies were conducted for this NDA submission. However, local tolerance of the albuterol HFA formulation was assessed as part of the animal toxicology studies and no findings of concern were observed.

3.4.8 Special toxicology studies

No studies were conducted for this NDA.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

This submission is a 505 (b)(2) NDA application for Volare HFA (Albuterol Sulfate) Inhalation Aerosol; the reference product is Proventil HFA (NDA 20-503). This product utilizes a hydrofluoroalkane (HFA) propellant, 1,1,1,2-tetra fluoroethane (HFA134a). The HFA formulation has been developed as a replacement for CFC (chlorofluorocarbon) propellant that is used in MDI formulations. The drug is to be use in the treatment or prevention of broncospasm with reversible obstructive airway disease in adults and children 12 years and older. Albuterol is a beta 2 adrenoreceptor agonist that has been used in the treatment of asthma for 2 decades. The primary issue of concern from a nonclinical perspective is the relative toxicity profile between albuterol HFA and CFC formulations. In a meeting, September 5, 2001 FDA informed the sponsor that for a (b) (2) program the sponsor could rely on generally available knowledge including FDA's knowledge on the drug, including preclinical data. The sponsor would, however, need to perform a 90 day inhalation

toxicology study in the most sensitive animal species based on findings from short-term studies in two species. The sponsor submitted a protocol and it was reviewed (see pharmacology review for INDs 60,549 — dated October 21, 2001). Comments related to protocol were faxed to the sponsor on October 30, 2001 and the Division recommended that toxicokinetic samples be taken during the 90 day study and stored for possible analysis should toxicity of concern occur in the study and to compare exposures achieved with the HFA and CFC formulations. The 90 day toxicity study was carried out in the Beagle dog at achieved albuterol/HFA doses were 0.42, 0.082 and 0.162 mg/kg and the positive control was albuterol/ CFC at a dose of 0.169 mg/kg. There were no significant toxicity findings in this study except gross pathology examinations revealed non-dose-dependent incidences of pale, focal areas in the papillary muscles of 1/4 female dogs in the low dose and 2/4 female dogs in the mid dose but no focal areas in the papillary muscles in the high dose albuterol/HFA group. No microscopic changes were observed in these animals and no effects were noted in males. Overall, the results of studies conducted by the sponsor show a similar toxicity profile in dogs when albuterol/HFA and albuterol/CFC inhalation formulations are compared.

In regard to the use of HFA as an excipient in the proposed formulation, the sponsor has submitted a Letter of Authorization to refer to DMFs —

In conclusion, the sponsor has completed the recommended nonclinical testing to assess the toxicity profile of the albuterol HFA formulation. Results of the conducted studies demonstrated comparative toxicity between the HFA and CFC formulations and produced no unexpected toxicities. Therefore, this application is approvable from a nonclinical perspective.

Unresolved toxicology issues (if any): None at this time.

Recommendations: The NDA is approvable from a nonclinical perspective pending recommended revised labeling.

Suggested labeling:

A preliminary review of the product label was conducted and the format of the product label does not adhere to that described under 21 CFR 201.57. Thus the sponsor should reformat the overall label.

The following describes recommended revisions to the relevant nonclinical portions of the product label. The proposed text generally parallels that for the Proventil HFA product label. However, the animal to human exposure ratios are recalculated based on the current methodology used by the division (see calculation table attached). :

2 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

3.7 APPENDIX/ATTACHMENTS

Drug: Volare
HFA

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m ²
Pediatric				0	3	0.00000	25	0.00
Adult	>12	0.108	12	1.296	50	0.02592	37	0.96

	route	mg/kg/d	conv. factor	mg/m ²	Dose Ratio		Rounded Dose Ratio	
					Adults	Children	Adults	Children
<u>Carcinogenicity:</u>								
rat	dietary	2	6	12	12.5	---	15	---
mouse	dietary	500	3	1500	1564.1	---	1600	---
hamster	dietary	50	4	200	208.5	---	210	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
<u>Reproduction and Fertility:</u>								
rat	oral	50	6	300	312.8	N/A	310	N/A
rat			6	0	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
<u>Teratogenicity:</u>								
mouse	SC	0.025	3	0.075	0.1	N/A	1/13	N/A
mouse	SC	0.25	3	0.75	0.8	N/A	1/1	N/A
mouse	SC	2.5	3	7.5	7.8	N/A	8	N/A
rat	IH	10.5	6	63	65.7	N/A	65	N/A
rabbit	oral	50	12	600	625.6	N/A	630	N/A
<u>Overdosage:</u>								
mouse	oral	2000	3	6000	6256.3	---	6300	---
rat	SC	450	6	2700	2815.3	---	2800	---
rat	SC	2000	6	12000	12512.5	---	13000	---
extra			---	---	---	---	---	---
(Describe studies here)								
<u>Other:</u>								
rat			6	0	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Virgil Whitehurst
11/14/03 04:45:29 PM
PHARMACOLOGIST

Timothy McGovern
11/14/03 04:48:15 PM
PHARMACOLOGIST
I concur.