

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-929

PHARMACOLOGY REVIEW(S)

6/19/06

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 19, 2006

TO: Alan Schroeder, Ph.D.
ONDQA

SUBJECT: Pharmacology/Toxicology Review

FROM: Timothy W. Robison, Ph.D.
Pharmacologist
Division of Pulmonary and Allergy Drug Products
HFD-570

THROUGH: Joseph Sun, Ph.D.
Supervisory Pharmacologist
Division of Pulmonary and Allergy Drug Products
HFD-570

SUMMARY: In response to a Chemistry Consult dated June 12, 2006, a non-clinical review of DMF — was written in support of NDA 21-929. This review was a safety evaluation of an impurity in —.

Reviewer signature: _____
Timothy W. Robison, Ph.D.

Supervisor signature: Concurrence - _____
Joseph Sun, Ph.D.

Non-Concurrence - _____
(see memo attached)

cc: list:
JacksonC, HFD-570
SchroederA, ONQA
SunC, HFD-570
RobisonT, HFD-570

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/s/

Timothy Robison
6/19/2006 12:11:27 PM
PHARMACOLOGIST

Joseph Sun
6/19/2006 02:31:01 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY COVER SHEET
Addendum to Chemistry Consult #2

NDA number: NDA 21-929

Date/type of submission:

Sponsor and/or Agent: AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-835

Manufacturer for drug substance: Same

Reviewer name: Timothy W. Robison, Ph.D., D.A.B.T.

Division name: Pulmonary and Allergy Products

HFD #: 570

Review completion date: June 5, 2006

Drug:

Trade name: Symbicort

Generic name (list alphabetically): Combination drug product of
Budesonide and Formoterol fumarate dihydrate

Drug class: Budesonide, corticosteroid
Formoterol, β_2 -adrenergic agonist

Response to Chemistry Consult Requested by Alan Schroeder, Ph.D.

Description of the Consult: This consult covers _____

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Specifications for the 60 actuation drug product presentation are shown in the table below. The product contains an approximate — actuation overfill. From a conservative standpoint, calculations were performed assuming — actuations per can.

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Pharm/Tox-

SUMMARY AND OVERALL EVALUATION:

Extractables and Leachables in the Drug Product:

_____ are specified at a level of _____ in the drug product. _____ possess structural alerts and are potential irritants; however, the threshold for qualification at _____ was not reached. Thus, levels of _____ in the drug product are judged to be acceptable.

Reviewer signature: _____
Timothy W. Robison, Ph.D.

Supervisor signature: Concurrence - _____
Joseph Sun, Ph.D.

Non-Concurrence - _____
(see memo attached)

cc: list:

NDA 21-929 Division File, HFD-570
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SchroederA,
SunC, HFD-570
RobisonT, HFD-570

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/s/

Timothy Robison
6/5/2006 03:04:42 PM
PHARMACOLOGIST

Joseph Sun
6/5/2006 05:05:04 PM
PHARMACOLOGIST
I concur.

INTEROFFICE MEMO

TO: NDA 21929
FROM: C. Joseph Sun, Ph. D., Supervisory Pharmacologist
Division of Pulmonary and Allergy Products
DATE: May 26, 2006

I concur with pharmacologist's recommendation that pharmacology and toxicology of Symbicort combination drug products of budesonide and formoterol and its excipients, providone K25 (PVP K25) and polyethylene glycol 1000 (PEG-1000) have been adequately studied and the drug product is approvable from a preclinical standpoint.

Pharmacology: The anti-inflammatory actions of budesonide are typical for its class and did not distinguish it from other glucocorticoids. Formoterol is a selective long-acting beta-2 agonist that possesses bronchospasmolytic activity. Several in vitro and in vivo studies using various biologic systems demonstrate that combinations of budesonide and formoterol act complementarily or additively to produced anti-inflammatory or anti-bronchoconstriction effects.

General toxicity:

Budesonide: Chronic inhalation toxicity studies (up to 12 months) in rats and dogs, subcutaneous toxicity study (6 months) in rats and oral toxicity study (6 months) in monkeys were conducted. Typical systemic glucocorticoid effects were observed. Some effects in the respiratory tree (accumulation of alveolar macrophages, pulmonary perivascular lymphocyte infiltration and increased mucus production) following inhalation administration were reported in rats whereas no local respiratory tract effects were observed in dogs.

Formoterol: One-month inhalation study in dogs and chronic inhalation toxicity study (6 months) in rats and oral toxicity study (one year) in dogs were conducted. Neither species appeared sensitive to the local effects by inhalation route. Moreover deposited doses achieved in rats exceed that could be achieved in dogs. Thus the 6-month inhalation toxicity study is adequate to assess its local effects for both species in addition to the systemic effects in the species. The target organs of toxicity were the heart in both species and testes and epididymis in rats.

Symbicort: Toxicities observe in 3-month inhalation studies in rats and dogs were primarily attributable to budesonide and tachycardia due to formoterol was observed in dogs. No potentiation of toxic effects between budesonide and formoterol was observed in these studies.

Excipients (PVP K25 and PEG-1000 and propellant, HFA-227): The sponsor has right of reference to the preclinical toxicology studies of HFA-227. Two 13-week inhalation studies in rats and dogs with a Symbicort HFA pMDI formulation containing PVP K-25, PEG-1000 were conducted. In addition, the sponsor's other chronic inhalation studies in rats and dogs with similar excipients, PVP K30 and PEG-600 and a 3-month inhalation study in rats with Formoterol HFA pMDI containing same excipients, PVP- K-25 and PEG-1000 were also considered as parts of the complete inhalation bridging program.

There was no evidence of local or systemic toxicity attributable to these excipients following inhalation administration. Thus the intended clinical formulation is considered safe for chronic inhalation administration.

Reproductive toxicity:

Budesonide has no effect on fertility by subcutaneous administration. It was teratogenic and embryocidal in rabbits and rats by subcutaneous administration. However, it was not teratogenic or embryocidal in rats by inhalation administration. Furthermore, epidemiological data indicated no risk to human during pregnancy. Decreased fertility was observed for male rats treated with oral doses of formoterol. It was teratogenic in rats and rabbits treated with oral doses. Embryolethality and rats pup loss at birth and during lactation were observed with oral doses. However, no teratogenic effects were reported with rats with inhalation exposure. Symbicort was teratogenic in rats with inhalation exposure. Thus, pregnancy category C is appropriate.

Genotoxicity:

Budesonide was not genotoxic in Ames test, mouse micronucleus assay, mouse lymphoma test, chromosome aberration test in human lymphocytes, recessive lethal test in *Drosophila melanogaster* and DNA repair analysis in rat hepatocyte. Formoterol was negative in Ames test, chromosome aberration assay in human lymphocytes, mouse lymphoma assay and rat micronucleus assay.

Carcinogenicity:

Three 2-year oral carcinogenicity studies with budesonide were conducted in rats. Budesonide caused increases in the incidence of glioma in one study which was not confirmed in two subsequent studies. It produced hepatocellular tumors, typical of other glucocorticoids. No effects were reported in a 91-week oral carcinogenicity study in mice.

In 2-year carcinogenicity studies with mice (oral) and rats (inhalation) treated with formoterol, there were typical findings of ovary and/or uterine leiomyomas with other beta-agonist drugs.

Labeling: Carcinogenesis, mutagenesis and impairment of fertility and pregnancy category C sections have been revised to incorporate the above-mentioned preclinical findings.

There are no outstanding preclinical issues.

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/s/

Joseph Sun
5/26/2006 03:50:47 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY COVER SHEET
Chemistry Consult #2

NDA number: NDA 21-929

Date/type of submission:

Sponsor and/or Agent: AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-835

Manufacturer for drug substance: Same

Reviewer name: Timothy W. Robison, Ph.D., D.A.B.T.

Division name: Pulmonary and Allergy Products

HFD #: 570

Review completion date: May 23, 2006

Drug:

Trade name: Symbicort

Generic name (list alphabetically): Combination drug product of
Budesonide and Formoterol fumarate dihydrate

Drug class: Budesonide, corticosteroid
Formoterol, β_2 -adrenergic agonist

Response to Chemistry Consult Requested by Alan Schroeder, Ph.D.

Description of the Consult: This consult covers Extractables and Leachables. —

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Specifications for the 60 actuation drug product presentation are shown in the table below. The product contains an approximate — actuation overfill. From a conservative standpoint, calculations were performed assuming — actuations per can.

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Withheld Track Number: Pharm/Tox-

SUMMARY AND OVERALL EVALUATION:

Impurities, Degradants, Leachables and Extractables in the Drug Product:

Examination of the leachables content in the drug product specifications indicated that — compounds and/or classes of compounds exceed the — threshold for qualification as follows:

None of these compounds possess structural alerts or irritant potential. Further, other leachables at levels less than — do not possess structural alerts and are not potential irritants. — content are also considered.

Three month inhalation toxicology studies with Symbicort pMDI administered to rats and dogs used batch P5993 as shown in the table below. This lot was 4 months old at the start of the 3-month dog study, 6-months old at the start of the 3-month rat study, and 12 months old at the start of the rat teratology study. The leachables content in batch 5993 at 3 months was used to calculate doses of leachables administered to rats and dogs; however, deposited doses provide no safety margins for human doses based upon the drug product specifications as rat to human and dog to human ratios were all significantly less than 1 (see table below). Safety margins of approximately 10 and 6 are normally expected for rat to human and dog to human ratios, respectively.

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Withheld Track Number: Pharm/Tox-

Recommendation: Symbicort pMDI is considered qualified for _____

Furthermore, _____ should be controlled by limiting the
extractable _____ and it is recommended that
the sponsor be encouraged to improve the LOQ for the _____ assay(s).

Reviewer signature: _____
Timothy W. Robison, Ph.D.

Supervisor signature: Concurrence - _____
Joseph Sun, Ph.D.

Non-Concurrence - _____
(see memo attached)

cc: list:

NDA 21-929 Division File, HFD-570
JacksonC, HFD-570
SchroederA,
SunC, HFD-570
RobisonT, HFD-570

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/s/

Timothy Robison
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PHARMACOLOGIST

Joseph Sun
5/23/2006 05:35:25 PM
PHARMACOLOGIST
I concur.

5/22/06

PHARMACOLOGY/TOXICOLOGY COVER SHEET
Chemistry Consult # 1

NDA number: NDA 21-929

Date/type of submission: September 23, 2005/#000

Request date: March 14, 2006

Sponsor and/or agent: AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-835

Manufacturer for drug substance: Same

Reviewer name: Timothy W. Robison, Ph.D., D.A.B.T.

Division name: Pulmonary and Allergy Products

HFD #: 570

Review completion date: May 22, 2006

Drug:

Trade name: Symbicort

Generic name (list alphabetically): Combination drug product of
Budesonide and Formoterol fumarate dihydrate

Drug class: Budesonide, corticosteroid
Formoterol, β_2 -adrenergic agonist

Response to Chemistry Consult Requested by Alan C. Schroeder, Ph.D.

Description of the Consult: Safety assessments for items listed in the table below are provided in this consult. See the Request for Chemistry Consult in the Appendix.

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Test Procedure	Acceptance Criteria	Drug substance		Drug product			
		Specification for FFD USA Not micronized	Specification for FFD USA Micronized	Specification for Symbicort 80/4.5, 60 Actuations	Specification for Symbicort 160/4.5, 60 Actuations	Specification for Symbicort 80/4.5, 120 Actuations	Specification for Symbicort 160/4.5, 120 Actuations
Formoterol impurities and degradation products:		NMT w/w	NMT (w/w	NMT w/w	NMT w/w	NMT w/w	NMT w/w
		NMT w/w	NMT (w/w	NMT w/w	NMT w/w	NMT w/w	NMT w/w
		NMT w/w	NMT (w/w	NMT w/w	NMT w/w	NMT w/w	NMT w/w
		NMT w/w	NMT w/w	NMT w/w	NMT w/w	NMT w/w	NMT w/w
		NMT w/w	NMT w/w	NMT w/w	NMT w/w	NMT w/w	NMT w/w
		NMT w/w					
Residual Solvents:		NMT	NMT				
		NMT ppm					
Budesonide impurities and degradation products:				NMT w/w	NMT w/w	NMT w/w	NMT w/w
				NMT w/w	NMT w/w	NMT w/w	NMT w/w
				NMT w/w	NMT w/w	NMT w/w	NMT w/w
				NMT w/w	NMT w/w	NMT w/w	NMT w/w
				NMT w/w	NMT w/w	NMT w/w	NMT w/w
				NMT w/w	NMT w/w	NMT w/w	NMT w/w
				NMT w/w	NMT w/w	NMT w/w	NMT w/w
Foreign particles µm				NMT actuat	NMT actuat	NMT actuat	NMT actuation
				NMT actuat	NMT actuat	NMT actuat	NMT actua
				NMT actuat	NMT actuat	NMT actuat	NMT actuation

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SUMMARY AND OVERALL EVALUATION:

Formoterol impurities and degradation products:

Formoterol impurities and degradants include

_____ Specifications for these compounds in the drug product are less than the threshold of _____ for qualification.

Formoterol and several of its impurities contain an _____ structural. _____ contains an aromatic amine structural alert, which is relatively similar to that found in the parent compound, formoterol. Formoterol was not mutagenic or clastogenic in the in vitro bacterial reverse mutation assay, in vitro mouse lymphoma assay, in vitro human lymphocyte chromosomal aberration assay, and in vivo rat micronucleus assay. _____ was negative in the in vitro bacterial reverse mutation assay. It should be noted that bacterial stain selections for in vitro bacterial reverse mutation assays with both formoterol and desformoterol were inadequate. Formoterol in 2-year carcinogenicity studies with mice and rats produced tumors characteristic of the β_2 adrenergic agonist class. Thus, the structural alerts in formoterol and related impurities as well as _____ are considered to have minimal genotoxic potential.

_____ were measured in formoterol batch 131/90 used in the 3-month inhalation toxicology study with rats (Report number T2433) at levels of _____ respectively. The NOAEL of the 3-month study with rats was identified as the deposited dose of 22 $\mu\text{g/kg/day}$. Doses of _____ at the NOAEL were _____ $\mu\text{g/kg/day}$, respectively. Doses of _____ and _____ in the clinical dose of formoterol at 18 $\mu\text{g/day}$ (0.36 $\mu\text{g/kg/day}$) are _____ $\mu\text{g/kg/day}$, respectively. Safety margins for _____ are _____, respectively, and are judged to be qualified.

_____ were not present at substantial levels in any formoterol batches used in inhalation toxicology studies with rats or dog of duration ≥ 3 months; however, qualification is not required.

_____ are specified in the drug substance at a level of _____. _____ were measured in formoterol batch 131/90 used in the 3-month inhalation toxicology study with rats (Report number T2433) at a level of _____. The NOAEL of the 3-month study with rats was identified as the deposited dose of 22 $\mu\text{g/kg/day}$. The dose of _____ at the NOAEL was _____ $\mu\text{g/kg/day}$. The dose of _____ at the proposed specification of NMT _____ in the clinical dose of formoterol at 18 $\mu\text{g/day}$ (0.36 $\mu\text{g/kg/day}$) is _____ $\mu\text{g/kg/day}$. The safety margin for _____ is _____ and is judged to be qualified.

Residual Solvents:

The residual solvent, _____ is specified in the formoterol drug substance at a level of _____. _____ is a Class 3 solvent (i.e., low toxic potential to man). The PDE for _____ is 138 mg/day, which is equivalent to 2.76 mg/kg/day for a 50-

kg person. The dose of _____ at the proposed specification of NMT _____ in the clinical dose of formoterol at 18 µg/day (0.36 µg/kg/day) is _____ µg/kg/day, which is significantly less than the PDE.

_____ is present in the formoterol drug substance at NMT _____. _____ is a member of the _____ group metals. These metals are generally nontoxic in their metallic state, but have been noted to be toxic in particular circumstances (i.e., _____ forms such as _____). Toxicology studies have reported allergic occupational diseases of the respiratory passages, allergic dermatitis, and carcinogenicity that generally appear to be associated with the _____ and _____. For the clinical dose of formoterol at 18 µg/day, the amount of _____ at the proposed acceptance criteria of NMT _____ Dietary intake _____ has been estimated at approximately 1 to 2 µg/day (Food Standards Agency, Scotland), which is 5555 to 11111 times the daily dose. TWA values from the American Conference of Governmental Industrial Hygienists (2004) for _____ are _____, respectively _____-asthma, irritation, sensitization). These TWA values are _____ times the human dose _____, respectively. In a life-time study, mice given _____ as _____ in their drinking water exhibited decreased growth, increased longevity, and malignant lung tumors (Journal of Nutrition 101: 1431-1438, 1971 and Venugopal and Luckey. Metal Toxicity in Mammals, Volume 2. New York: Plenum Press, 1978. Page 301). The dose of 5 ppm in drinking water is equivalent to a dose of 1 mg/kg in mice. For a 10^{-6} risk, the acceptable dose would be _____. This is _____ times the human dose _____. _____ at NMT _____ appears to be qualified.

Budesonide impurities and degradation products:

Budesonide-related impurities and degradants include _____

_____ budesonide-related degradation product.

The drug substance specifications for budesonide-related impurities and degradants, with the exception of _____ are identical to those approved for Pulmicort Turbuhaler (NDA 20-441) and are considered acceptable. For budesonide-related impurities and degradants in the drug product, specifications are slightly higher than those for the drug substance, but less than the qualification threshold of _____ in each case.

_____ of budesonide) is a degradation product, which increases on storage of the drug product. It does not contain a structural alert. The drug product specification for the sum of all individual unspecified impurities, which includes _____ is NMT _____. This is less than the qualification threshold of _____

Since quantitative data was not provided, a conservative approach was used whereby the total number of particles was to be composed of — of each of the following substances shown in the table below.

The safety of exposure to each substance was determined by comparing the daily exposure level with that derived from 8 hr Threshold Limits Values (TLV). These TLVs were recommended by the American Conference of Governmental Industrial Hygienists (2004). A safety factor of 14 has been incorporated to account for differences in population sensitivity (factor of 10) and exposure frequency (factor of 4).

Compound	8-hr TLV mg/m ³	8 hr TLV mg ^a	1/14 th of 8 hr TLV mg	— mg of Particulate as % of 1/14 th of 8-hr TLV ^b	Density	% of 8-hr TLV based on density of particulate
----------	-------------------------------	-----------------------------	---	--	---------	---

a. Determined by multiplying the TLV in mg/m³ by the 8 hr respiratory volume of air (10 m³) for a 70 kg adult.

b. Based on considering the density of particles to be —

Daily exposure to foreign particles — from Symbicort pMDI represents from — of the 8-hr TLV. This was determined from the total weight of the particles — the 8-hr TLV, the respiratory volume of 10 m³ over an 8-hr period for a 70-kg adult, and the density assuming that particles were —. The value for — is considered acceptable given that it is unlikely that it is present as — of particles —. Percentages were lower — if the density of particles was considered — as shown in the table above.

The EPA has health based national air quality standards for particulate matter (PM). For PM-2.5 (particulate matter $\leq 2.5 \mu\text{m}$), the standards were set at $15 \mu\text{g}/\text{m}^3$ (measured as an annual mean concentration) and $65 \mu\text{g}/\text{m}^3$ (measured as a daily concentration). For PM-10 (particulate material $\leq 10 \mu\text{m}$), the standards were set at $50 \mu\text{g}/\text{m}^3$ (measured as an annual mean concentration) and $150 \mu\text{g}/\text{m}^3$ (measured as a daily concentration).

EPA

EPA Acceptable mass (μg) of particulate matter for a respirable volume of 14m^3 over a 24 hr period based PM-2.5 and PM-10 Standards			
PM-2.5		PM-10	
$15 \mu\text{g}/\text{m}^3$	$65 \mu\text{g}/\text{m}^3$	$50 \mu\text{g}/\text{m}^3$	$150 \mu\text{g}/\text{m}^3$

a. 24-hr respirable volume for a 50 kg adult based on the 24-hr respiratory volume of 20m^3 for a 70 kg adult.

Based on the EPA's standards for acceptable levels of particles over a 24-hr period, the exposure to _____ (based on a density _____) and _____ (based on the density of _____; particle with the highest density) of particulate matter from the Symbicort pMDI formulation was determined relative to the EPA standards. Results are presented in the following table.

EPA

Weight of particulate over 24-hr μg	% of EPA 24-hr Acceptable Particulate Material Set by the PM-2.5 and PM-10 Standard			
	PM-2.5		PM-10	
	$15 \mu\text{g}/\text{m}^3$	$65 \mu\text{g}/\text{m}^3$	$50 \mu\text{g}/\text{m}^3$	$150 \mu\text{g}/\text{m}^3$
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____

Assuming a density _____ the mass of particulate material ranged from _____ of acceptable levels by the PM-2.5 standard and _____ of acceptable levels by the PM-10 standard. Assuming a density of _____ (assuming all particles were _____ with the heaviest density), the mass of particulate material ranged from _____ of acceptable levels by the PM-2.5 standard and from _____ of acceptable levels by the PM-10 standard.

Daily exposures to foreign particles _____ from the Symbicort pMDI are considered safe relative to the 8-hr threshold limit values for selected individual components and 24-hr particulate concentrations set by the PM-2.5 and PM-10 standards. For the calculations of the volume and weight of the particles, it was assumed that all the particles were _____ in diameter. The total weight of the particles only included the number of particles _____. In determining the exposure to individual components, calculations were made on the assumption that particles were _____ although there was actually a mixture of particles. For the Symbicort pMDI, daily exposure to _____ foreign particles _____ is considered acceptable.

Recommendation: Symbicort pMDI is considered qualified for formoterol-related impurities and degradants, _____ residual solvents _____ NMT _____ and foreign particles _____

Reviewer signature: _____
Timothy W. Robison, Ph.D.

Supervisor signature: Concurrence - _____
Joseph Sun, Ph.D.

Non-Concurrence - _____
(see memo attached)

cc: list:

NDA 21-929 Division File, HFD-570
JacksonC, HFD-570
SchroederA,
SunC, HFD-570
RobisonT, HFD-570

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Appendix: Chemistry Consult dated March 14, 2006

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-929
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	09/23/05
PRODUCT:	Symbicort (budesonide/formoterol fumarate dihydrate)
INTENDED CLINICAL POPULATION:	Long-term maintenance treatment of asthma in patient 12 years of age and older
SPONSOR:	AstraZeneca LP 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355
DOCUMENTS REVIEWED:	Electronic submission
REVIEW DIVISION:	Division of Pulmonary and Allergy Products (HFD-570)
PHARM/TOX REVIEWER:	Timothy W. Robison, Ph.D., D.A.B.T.
PHARM/TOX SUPERVISOR:	C. Joseph Sun, Ph.D.
DIVISION DIRECTOR:	Badrul Chowdhury, M.D., Ph.D.
PROJECT MANAGER:	Colette Jackson

Date of review submission to Division File System (DFS): May 22, 2006

TABLE OF CONTENTS

EXECUTIVE SUMMARY	3
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW.....	6
2.6.1 INTRODUCTION AND DRUG HISTORY.....	6
2.6.2 PHARMACOLOGY.....	22
2.6.2.1 Brief summary.....	22
2.6.2.2 Primary pharmacodynamics.....	22
2.6.2.3 Secondary pharmacodynamics.....	32
2.6.2.4 Safety pharmacology.....	32
2.6.2.5 Pharmacodynamic drug interactions.....	33
2.6.3 PHARMACOLOGY TABULATED SUMMARY.....	33
2.6.4 PHARMACOKINETICS/TOXICOKINETICS.....	33
2.6.4.1 Brief summary.....	33
2.6.4.2 Methods of Analysis.....	33
2.6.4.3 Absorption.....	34
2.6.4.4 Distribution.....	34
2.6.4.5 Metabolism.....	36
2.6.4.6 Excretion.....	38
2.6.4.7 Pharmacokinetic drug interactions.....	45
2.6.4.8 Other Pharmacokinetic Studies.....	45
2.6.4.9 Discussion and Conclusions.....	45
2.6.4.10 Tables and figures to include comparative TK summary.....	46
2.6.5 PHARMACOKINETICS TABULATED SUMMARY.....	46
2.6.6 TOXICOLOGY.....	46
2.6.6.1 Overall toxicology summary.....	46
2.6.6.2 Single-dose toxicity.....	60
2.6.6.3 Repeat-dose toxicity.....	67
2.6.6.4 Genetic toxicology.....	87
2.6.6.5 Carcinogenicity.....	89
2.6.6.6 Reproductive and developmental toxicology.....	90
2.6.6.7 Local tolerance.....	101
2.6.6.8 Special toxicology studies.....	101
2.6.6.9 Discussion and Conclusions.....	101
2.6.6.10 Tables and Figures.....	102
2.6.7 TOXICOLOGY TABULATED SUMMARY.....	102
OVERALL CONCLUSIONS AND RECOMMENDATIONS	102
APPENDIX/ATTACHMENTS	118

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From a nonclinical pharmacology and toxicology standpoint, the application is recommended for approval.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

Labeling to describe nonclinical study findings conducted with the budesonide component has been adjusted to conform to the labeling for Pulmicort Respules. Labeling for the formoterol component under the Pregnancy category has been extensively adjusted to more accurately reflect findings from reproductive toxicology studies.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Symbicort is a combination drug product consisting of monoproducts, budesonide and formoterol. The sponsor has several approved drug products with budesonide (i.e., Pulmicort Turbuhaler®, Rhincort®, Pulmicort Respules®, Entocort®). Development of these products was supported by their nonclinical pharmacology and toxicology program for budesonide. These studies were submitted and reviewed under NDAs 20-441, 20-747, 20-929, and 21-324. The sponsor has no approved drug products with formoterol in the United States. However, they have a complete nonclinical pharmacology and toxicology program for formoterol. These studies were submitted under IND _____ and have also been provided in the present NDA.

The sponsor has conducted subchronic and chronic toxicology studies with formoterol in both rats and dogs. Studies with rats include 3-, 6-, and 24-month inhalation toxicology studies. A 1-year oral toxicology study has been conducted with dogs. The longest inhalation toxicology study in dogs was 1 month, but the 6-month inhalation toxicology study in rats is sufficient to bridge the systemic toxicology studies of formoterol because deposited doses achieved in rats greatly exceed those that could be achieved in dogs, and neither species seemed particularly sensitive to the local effects of formoterol. Studies have adequately evaluated the toxicity of formoterol in terms of local (respiratory) and systemic effects.

In toxicology studies with dogs, the target organ of toxicity as the heart. NOAELs were not established for formoterol-induced cardiac effects in dogs; however, these effects were attributed to increased heart rate, which is monitorable in a clinical setting.

In toxicology studies with rats, target organs of toxicity were the heart, testes, and epididymides. NOAELs were identified for these organs and tissues. Safety margins for the clinical dose of formoterol at 18 µg/day based upon deposited dose or systemic exposure at the NOAEL identified in the 6-month inhalation toxicology study with rats are 6.4- and 20.9-fold, respectively.

Formoterol was negative in the in vitro bacterial reverse mutation assay, in vitro human lymphocytes chromosomal aberration assay, in vitro L5178Y mouse lymphoma cell thymidine kinase forward mutation assay, and in the in vivo rat micronucleus assay.

In 2-year carcinogenicity studies with mice and rats treated with formoterol, there were findings of ovary and/or uterine leiomyomas. Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Decreased fertility and/or reproductive performance were observed for male rat treated with a high oral dose of formoterol. The duration of pregnancy was prolonged with a high oral dose of formoterol, which might be attributed to relaxation of the uterine musculature, a known class effect of β_2 -agonists. Teratogenic effects were observed in both rats and rabbits treated with oral doses of formoterol. Embryo lethality and rat pup loss at birth and during lactation were observed with oral doses of formoterol. With inhalation exposure, no teratogenic effects were observed with rats. Formoterol is Pregnancy Category C.

For the combination Symbicort pMDI HFA drug product, 3-month inhalation bridging toxicology studies with rats and dogs and a teratology study with rats were provided. Toxicities observed in 3-month bridging studies with Symbicort HFA pMDI in rats and dogs appeared to be primarily attributable to the pharmacological effects of budesonide. In addition, tachycardia, attributable to formoterol, was observed in dogs. There was no evidence in these studies of additive or synergistic toxic effects between budesonide and formoterol.

The Symbicort HFA pMDI drug product contains excipients, PVP K-25 and PEG-1000, and the propellant, HFA-227. There are no approved inhalation drug products that contain PVP K-25, PEG-1000, or HFA-227. Extensive preclinical toxicology studies have been conducted with HFA-227 by IPACT-II, for which the sponsor has rights of reference. HFA-227 is considered safe for use in the Symbicort HFA pMDI drug product. A 6-month inhalation

toxicology study is generally required to bridge excipients, PVP K-25 and PEG-1000, from the oral to inhalation route. The sponsor conducted 13-week inhalation toxicity studies with rats and beagle dogs that were treated daily with a Symbicort HFA pMDI formulation (batch P5993) containing budesonide, formoterol, PVP K-25, PEG-1000, and HFA-227. The sponsor's bridging program principally consisted of chronic studies conducted with similar excipients, povidone K-30 (PVP K-30) and polyethylene glycol 600 (PEG-600), respectively. The results of a 3-month inhalation toxicology study (Study 96195) conducted with rats that received Formoterol HFA pMDI containing excipients, PVP K-25 and PEG-1000, as found in the Symbicort drug product, were also considered. There was no evidence of local or systemic toxicity attributable to these excipients following administration by the inhalation route.

B. Pharmacologic activity

Symbicort® is a combination inhalation drug product consisting of a glucocorticoid (budesonide) and a long acting β_2 agonist (formoterol). The sponsor is attempting to prove that the combination of budesonide and formoterol in asthma therapy delivers a greater benefit than either drug alone.

Formoterol is a highly selective long-acting β_2 -agonist that possesses potent bronchospasmolytic activity. Budesonide is a potent glucocorticoid.

Studies conducted by the sponsor using various biological systems suggest that combinations of budesonide and formoterol act complementarily, additively, or synergistically to produce enhanced anti-inflammatory, anti-remodeling, or anti-bronchoconstriction effects. These include inhibition of the following activities: granulocyte macrophage-colony stimulating factor (GM-CSF) release in human bronchial epithelial cells, the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in human lung fibroblasts, oxidative burst in human eosinophils stimulated by bronchial epithelial cell-derived condition medium, inflammation-induced lung edema, proliferation of airway smooth muscle cells, production of proteoglycans by lung fibroblasts, and the bronchoconstriction response to provocation. These mechanistic studies provide potential explanations that the combination of budesonide and formoterol in asthma therapy delivers a greater benefit than either drug alone.

C. Nonclinical safety issues relevant to clinical use

None.

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2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 21-929

Review number: #01

Sequence number/date/type of submission:

#000/September 23, 2005/Initial Submission

March 17, 2006/BM

April 26, 2006/BP

Information to sponsor: Yes () No (X)

Sponsor and/or agent: AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-835

Manufacturer for drug substance: Same

Reviewer name: Timothy W. Robison, Ph.D., D.A.B.T.

Division name: Pulmonary and Allergy Products

HFD #: 570

Review completion date: May 22, 2006

Drug:

Trade name: Symbicort

Generic name (list alphabetically): Combination drug product of Budesonide and Formoterol fumarate dihydrate

Chemical name:

Budesonide, 16 α ,17 α -butylidenedioxypregna-1,4-diene-11 β , 21-diol-3,20-dione
Formoterol fumarate dihydrate, (R*,R*)-($\pm$)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]phenyl]formamide, (E)-2-butendioate (2:1), dihydrate (asterisks denote asymmetric carbon atoms)

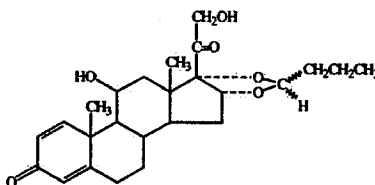
Molecular formula/molecular weight:

Budesonide, C₂₅H₃₄O₆ / 430.5 g/mole

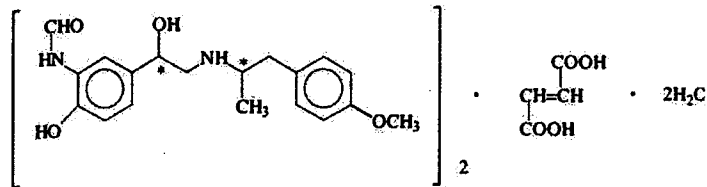
Formoterol fumarate dihydrate, C₄₂H₅₆N₄O₁₄ / 840.9 g/mole

Structure:

Budesonide



Formoterol fumarate dihydrate



Relevant INDs/NDAs/DMFs:

IND 63,394 (Symbicort HFA, AstraZeneca)

IND — (Formoterol fumarate dihydrate, AstraZeneca)

NDA 20-441 (Pulmicort, AstraZeneca)

NDA 20-746 (Rhinocort, AstraZeneca)

NDA 20-929 (Pulmicort Respules, AstraZeneca)

NDA 21-324 (Entocort, AstraZeneca)

NDA 20-831 (Foradil[®], Novartis)

DMF 10378 (1,1,1,2,3,3,3-heptafluoropropane (HFA-227), IPACT-II)

Drug class: Budesonide, corticosteroid
Formoterol, β_2 -adrenergic agonist

Intended clinical population: Symbicort pMDI is intended for the long-term maintenance treatment of asthma (160/9 μg or 320/9 μg twice daily) in adult and adolescent subjects 12 years of age and older.

Clinical formulation: Symbicort — pressurized metered dose inhaler (Symbicort — pMDI) is a combination product containing budesonide and formoterol fumarate dihydrate.

Two strengths of Symbicort — pMDI have been developed, each designed to deliver a minimum of 120 actuations, and delivering either:

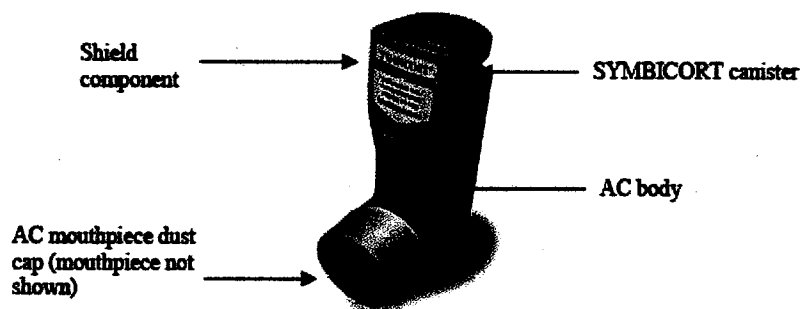
- 80 μg budesonide micronized and 4.5 μg formoterol fumarate dihydrate micronized per actuation, ex-actuator (Symbicort — pMDI 80/4.5), or;
- 160 μg budesonide micronized and 4.5 μg formoterol fumarate dihydrate micronized per actuation, ex-actuator (Symbicort — pMDI 160/4.5).

Table 1 Composition of SYMBICORT μ MDI 80/4.5, 120 actuations

Component	Manufacturing concentration (% w/w)	Canister concentration (% w/w)	Quantity per canister ^a	Quantity per actuation, ex-valve	Quantity per actuation, ex-actuator	Function	Standard
Budesonide micronised						Active	AstraZeneca
Formoterol fumarate dihydrate micronised						Active	AstraZeneca
Povidone K25						Suspending agent	USP
PEG 1000						Lubricant	NF
HFA 227						Propellant	

Table 2 Composition of SYMBICORT μ MDI 160/4.5, 120 actuations

Component	Manufacturing concentration (% w/w)	Canister concentration (% w/w)	Quantity per canister ^a	Quantity per actuation, ex-valve	Quantity per actuation, ex-actuator	Function	Standard
Budesonide micronised						Active	AstraZeneca
Formoterol fumarate dihydrate micronised						Active	AstraZeneca
Povidone K25						Suspending agent	USP
PEG 1000						Lubricant	NF
HFA 227						Propellant	

Figure 1 SYMBICORT μ MDI (label text is for representation purposes only)

Route of administration: Inhalation

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Studies reviewed within this submission:

Study Title:	Study or Document number:
PHARMACOLOGY:	
PHARMACOKINETICS/TOXICOKINETICS:	
Distribution:	
Whole-body autoradiographic study on the distribution of radioactivity in rats after single intravenous injection, oral administration, or intratracheal installation of ³ H-Formoterol.	843-TO-0242 (95007)
Uptake of the RR and SS enantiomers of formoterol in the isolated perfused guinea pig lungs.	843-RD-0359
Metabolism:	
Metabolism of RR-Formoterol. Identification of metabolites formed in liver microsomes from different species, and in vivo in the mouse.	843-RD-0370
Metabolism of R,R- and S,S-Formoterol in liver microsomes from different species.	843-RD-0360
Excretion:	
Excretion and biotransformation of R,R and S,S-Formoterol after intravenous, intratracheal, and oral administration of Rac-formoterol to mice.	843-RD-0361
TOXICOLOGY:	
Single-Dose Toxicity:	
Symbicort (Budesonide + Formoterol): Single dose inhalation (powder) toxicity study in the rat.	02218
Symbicort (Budesonide + Formoterol): Single dose inhalation (powder) toxicity study in the dog.	02219
Repeat-dose Toxicity:	
Testicular effects of formoterol fumarate (D2522) given orally to young rats for 3 months, using salbutamol sulphate as a reference compound.	T3160
Symbicort (budesonide + formoterol): 3-month inhalation (pMDI) toxicity study in the dog – Addendum to review of the initial submission of IND 63,394.	SR99023-01
Reanalysis of lung histopathology slides in inhalation toxicology studies with rats, Study numbers 96195 and 96010	0370KY and 0388KY
Genetic Toxicology:	
Mutagenicity evaluation of _____ in the Ames Salmonella/Mammalian microsome mutagenicity test.	91117
Reproductive and Developmental Toxicology:	
Symbicort (Budesonide-Formoterol): Embryofetal development study after administration to pregnant rats via the inhalation route.	SR00581-01

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Studies reviewed in present and past submissions:

MODULE 4 NONCLINICAL STUDY REPORTS

Module/CTD Description	Archive Copy Location Folder/File
4.1 Table of Contents	pharmtox/pharmtox.pdf
4.2 SYMBICORT pMDI Study Reports	
4.2.1 Pharmacology	
4.2.1.1 Primary Pharmacodynamics	
SYMBICORT pMDI	
Study 843-RD-0419-01 (850-92): Effects of formoterol and budesonide on GM-CSF and IL-8 secretion in human primary bronchial epithelial cells.	pharmtox/pharm/843-RD-0419-01.pdf
Study D5890RD0005-01: Effects of formoterol, budesonide and their combination of TNF (alpha) Induced GM-CSF levels in human bronchial epithelial cells in vitro.	pharmtox/pharm/D5890RD0005-01.pdf
Study D5890RD0004-01: AZ10959319. GR activation in human bronchial epithelial cells by formoterol in the presence or absence of budesonide in vitro.	pharmtox/pharm/D5890RD0004-01.pdf
Study D5890RD0006-01: Budesonide. Effects of various regimens of adjusted budesonide/formoterol dosing on airway hyperresponsiveness, inflammation and tissue oedema in an allergic rat model in vivo.	pharmtox/pharm/D5890RD0006-01.pdf
Study 850-RD-0474-01 (BLK-1999-00072): On the interaction between formoterol and budesonide in the Guinea-Pig: Effects on Airway Beta-Adrenoceptors after repeated inhalation of powder aerosols.	pharmtox/pharm/850-RD-0474-01.pdf
Formoterol	
Study 843-RD-0366: Steric aspects on formoterol and terbutaline: Is there an adverse effect of the distomer on airway smooth muscle function.	pharmtox/pharm/843-RD-0366.pdf
Study 843-RD-0289: Steric aspects of agonism and antagonism at B-adrenoceptors: Synthesis of and pharmacological experiments with the enantiomers of formoterol and their diastereomers.	pharmtox/pharm/843-RD-0289.pdf
Study 843-RD-0372: Lack of adverse effects of (S,S)-formoterol on airway reactivity in the isolated guinea-pig lung.	pharmtox/pharm/843-RD-0372.pdf
Study D5890RD0003-01: Effects of Formoterol, Budesonide or the Combination thereof on Superoxide Release from Isolated Human Eosinophils.	pharmtox/pharm/D5890RD0003-01.pdf

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Module/CTD Description	Archive Copy Location Folder/File
Study SC-100608-02 (843-RD-0397-02): The potency and duration of action of the B2-related effect of formoterol against intravenous histamine-induced bronchoconstriction in the guinea-pig when delivered by aqueous aerosol: A comparison with salbutamol and salmeterol.	pharmtox\pharm\SC-100608-02 (843-RD-0397-02).pdf
Study 843-RD-0399: The beta-2 related effect of formoterol on histamine-induced bronchoconstriction in the dog when delivered intratracheally by aerosol: A comparison with salmeterol.	pharmtox\pharm\843-RD-0399.pdf
Study 843-RD-0013: Long duration and high potency of antixudative effects of formoterol in guinea-pig tracheobronchial airways.	pharmtox\pharm\843-RD-0013.pdf
Study 843-RD-0373 : Pharmacologic activity of metabolites of formoterol.	pharmtox\pharm\843-RD-0373.pdf
4.2.1.2 Secondary Pharmacodynamics	NA
4.2.1.3 Safety Pharmacology	NA
4.2.1.4 Pharmacodynamic Drug Interactions)	NA
4.2.2 Pharmacokinetics	
4.2.2.1 Analytical Methods and Validation Reports	
SYMBICORT pMDI	NA
Formoterol	
Study 843-RD-0312: Determination of D2522 in mouse plasma using coupled column liquid chromatography with electrochemical detection.	pharmtox\pharm\843-RD-0312.pdf
Study 843-RD-0292: Determination of D2522 in rat plasma using coupled column liquid chromatography with electrochemical detection study no 90076.	pharmtox\pharm\843-RD-0292.pdf
Study 843-RD-0293: Determination of D2522 in rat plasma using coupled column liquid chromatography with electrochemical detection.	pharmtox\pharm\843-RD-0293.pdf
Study 843-RD-0310: Determination of D2522 in rat plasma (2.00 mL) using coupled column liquid chromatography with electrochemical detection.	pharmtox\pharm\843-RD-0310.pdf
Study 843-RD-0330: Determination of D2522 in rat plasma, after oral administration, using coupled column liquid chromatography with electrochemical detection.	pharmtox\pharm\843-RD-0330.pdf

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Module/CTD Description	Archive Copy Location Folder/File
Study 843-RD-0414-01: Determination of formoterol base in dog and rat plasma using coupled column liquid chromatography and electrospray tandem mass spectrometry.	pharmtox/pharm/843-RD-0414-01.pdf
Study 843-RD-0327: Determination of D2522 in rabbit plasma using coupled column liquid chromatography with electrochemical detection.	pharmtox/pharm/843-RD-0327.pdf
Study 843-RD-0311: Determination of D2522 in dog plasma using coupled column liquid chromatography with electrochemical detection.	pharmtox/pharm/843-RD-0311.pdf
Study 843-RD-0313: Determination of formoterol base, after administration of D2522, in human plasma using coupled column liquid chromatography with electrochemical detection.	pharmtox/pharm/843-RD-0313.pdf
Study 843-RD-0406-01: Determination of formoterol base in human plasma using coupled column liquid chromatography with electrochemical detection.	pharmtox/pharm/843-RD-0406-01.pdf
Study 843-RD-0413-01: Determination of formoterol base in human plasma using coupled column liquid chromatography and electrospray tandem mass spectrometry.	pharmtox/pharm/843-RD-0413-01.pdf
Study Q-20027: Validation of a method for the determination of formoterol in human plasma using SPE and LC-ESI-MS/MS.	pharmtox/pharm/Q-20027.pdf
Study 843-RD-0304: Determination of D2522 in human urine using coupled column liquid chromatography with electrochemical detection.	pharmtox/pharm/843-RD-0304.pdf
Study 843-RD-0353: Determination of the enantiomeric ratio of formoterol base in human urine using coupled column liquid chromatography for sample workup preceding chiral separation on alfa1-acid glycoprotein (AGP) column.	pharmtox/pharm/843-RD-0353.pdf
4.2.2.2 Absorption	
SYMBICORT pMDI	
Study 70045RD0002-01: Symbicort (budesonide+formoterol): General toxicity study after daily administration via the inhalation (pMDI) route to rats for 3 months; plasma concentration study.	pharmtox/pk/70045RD0002-01.pdf
Study 850-RD-0424-01 (98022): budesonide + formoterol: 3-month inhalation toxicity study in rats - plasma concentration study.	pharmtox/pk/850-RD-0424-01.pdf
Study 70045RD0003-01 (00581): Symbicort (budesonide-formoterol): Embryofetal development study after administration to pregnant rats via inhalation routes. Toxicokinetic evaluation. Study No. 00581.	pharmtox/pk/70045RD0003-01.pdf

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Module/CTD Description	Archive Copy Location Folder/File
Study 70045RD0001-01 (00047): Symbicort (budesonide+formoterol): 3-month inhalation (pMDI) toxicity study in the dog; plasma concentration study.	pharmtox/pk/70045RD0001-01.pdf
Study 850-RD-0423-01 (99023): Symbicort (budesonide + formoterol): 3-month inhalation (powder) toxicity study in the dog - plasma concentration study.	pharmtox/pk/850-RD-0423-01.pdf
Formoterol	
Study 843-RD-0318 (91118): General toxicity of D2522 given orally to mice for three months. Plasma concentration study.	pharmtox/pk/843-RD-0318.pdf
Study 843-RD-0349 (BRL 85133): An oral carcinogenicity study of D2522 in the albino mouse. Plasma concentration study.	pharmtox/pk/843-RD-0349.pdf
Study 70046RD0003-01: The disposition of [3H]-formoterol in the rat following intratracheal and intravenous administration.	pharmtox/pk/70046RD0003-01.pdf
Study 70046RD0001-02 (96195): Formoterol: 3-month inhalation (HFA-227 pMDI) toxicity study in the rat. Plasma concentration study.	pharmtox/pk/70046RD0001-02.pdf
Study 843-RD-0295 (90106): General toxicity study of D2522 given by the inhalation route to rats for three months. Plasma concentration study.	pharmtox/pk/843-RD-0295.pdf
Study 843-RD-0335 (92110): General toxicity study of D2522 in lactose given to rats by the inhalation route for 6 months. Plasma concentration study.	pharmtox/pk/843-RD-0335.pdf
Study 843-RD-0336: Plasma levels of D2522 lactose in rats. Satellite study to study no. 91055. Oncogenicity study in rats given D2522 lactose by the inhalation route for 104 weeks.	pharmtox/pk/843-RD-0336.pdf
Study 843-RD-0350 (ARA/192): A study of the effect on fertility and general reproductive performance of the rat - oral administration. Plasma concentration study.	pharmtox/pk/843-RD-0350.pdf
Study 843-RD-0358 (94031): General toxicity of formoterol fumarate (D2522) given orally to young rats for three months. Plasma concentration study.	pharmtox/pk/843-RD-0358.pdf
Study 843-RD-0367 (94143): Effects on the respiratory tract and male reproductive organs in young rats given formoterol fumarate (D2522) in lactose by the inhalation route for 3 months. Plasma concentration study.	pharmtox/pk/843-RD-0367.pdf
Study 843-RD-0369 (94146): Testicular effects of formoterol fumarate (D2522) given orally to rats for three months, using salbutamol sulphate as a reference compound. Plasma concentration study.	pharmtox/pk/843-RD-0369.pdf

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Module/CTD Description	Archive Copy Location Folder/File
Study 843-RD-0347 (ARA 193): D 2522: A study of the effect of pregnancy of rabbit - oral administration. Plasma concentration study.	pharmtox\pk\843-RD-0347.pdf
Study 843-RD-0394 (96235): Plasma potassium and glucose levels in dogs given formoterol fumarate dihydrate (D2522) in Lactose monohydrate by the inhalation route for 4 day. Plasma concentration study.	pharmtox\pk\843-RD-0394.pdf
Study 843-RD-0342 (93058): Dose finding study of D2522 in lactose given to the dogs by the inhalation route for 5 days. Plasma concentration study.	pharmtox\pk\843-RD-0342.pdf
Study 70046RD0004-02 (00447): Formoterol: One month inhalation (pMDI) toxicity study in the dog: Toxicokinetic evaluation.	pharmtox\pk\70046RD0004-02.pdf
Study 843-RD-0343 (93087): General toxicity study of formoterol fumarate dihydrate (D2522) in lactose given to dogs by the inhalation route for one month. Plasma concentration study.	pharmtox\pk\843-RD-0343.pdf
Study 843-RD-0320 (91125): General toxicity of D2522 given orally to dogs for one month. Plasma concentration study.	pharmtox\pk\843-RD-0320.pdf
Study 843-RD-0337 (92032): General toxicity of D2522 given orally to dogs for 12 months. Plasma concentration study.	pharmtox\pk\843-RD-0337.pdf
4.2.2.3 Distribution	
SYMBICORT pMDI	N/A
Formoterol	
Study 843-RD-0354: Plasma protein binding of formoterol enantiomers in different species.	pharmtox\pk\843-RD-0354.pdf
Study 843-TO-0242 (95007): Whole-body autoradiographic study on the distribution of radioactivity in rats after single intravenous injection, oral administration or intratracheal installation of D2522-3H.	pharmtox\pk\843-TO-0242 (95007).pdf
Study 843-RD-0359: Uptake of the RR and SS enantiomers of formoterol in the isolated perfused guinea pig lungs.	pharmtox\pk\843-RD-0359.pdf
4.2.2.4 Metabolism	
SYMBICORT pMDI	N/A
Formoterol	
Study 843-RD-0370: Metabolism of R,R-formoterol. Identification of metabolites formed in liver microsomes from different species, and in vivo in mouse.	pharmtox\pk\843-RD-0370.pdf

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Module/CTD Description	Archive Copy Location Folder/File
Study 843-RD-0360: Metabolism of R,R and S,S-Formoterol in liver microsomes from different species.	pharmtox/pk/843-RD-0360.pdf
Study 843-RD-0361 (A37-8154): Excretion and biotransformation of R,R and S,S-formoterol after intravenous, intratracheal and oral administration of rac-formoterol to mice.	pharmtox/pk/843-RD-0361.pdf
Study 843-RD-0410 (KM98022): Metabolite pattern of formoterol in the rat after intratracheal administration.	pharmtox/pk/843-RD-0410 (KM98022).pdf
4.2.2.5 Excretion	N/A
4.2.2.6 Pharmacokinetic Drug Interactions	
SYMBICORT pMDI	N/A
Formoterol	
Study 843-RD-0395: Biotransformation of RR- and SS-formoterol by O-demethylation. Liver enzyme identification and effect of formoterol on selected CYP substrates.	pharmtox/pk/843-RD-0395.pdf
4.2.2.7 Other Pharmacokinetic Studies	N/A
4.2.3 Toxicology	
4.2.3.1 Single-Dose Toxicity	
SYMBICORT pMDI	
Study 02218: Symbicort (budesonide + formoterol): Single dose inhalation (powder) toxicity study in the rat.	pharmtox/tox/02218.pdf
Study 02219: Symbicort (budesonide + formoterol): Single dose inhalation (powder) toxicity study in the dog.	pharmtox/tox/02219.pdf
Formoterol	
Study 93082 (T2807): Single dose toxicity in mice of formoterol fumarate (D2522) given by the inhalation route.	pharmtox/tox/93082 (T2807).pdf
Study 93089 (T2843): Single dose toxicity of formoterol fumarate (D2522) in mice after oral administration.	pharmtox/tox/93089 (T2843).pdf
Study 91115 (T2514): Acute toxicity in rats of D2522 given as single exposure by the inhalation route.	pharmtox/tox/91115 (T2514).pdf
Study 93088 (T2842): Single dose toxicity of formoterol fumarate (D2522) in rats after oral administration.	pharmtox/tox/93088 (T2842).pdf

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Module/CTD Description	Archive Copy Location Folder/File
4.2.3.2 Repeat-Dose Toxicity	
SYMBICORT pMDI	
Study SR00342-03: Symbicort (budesonide + formoterol): General toxicity study after daily administration via the inhalation (pMDI) route to rats for 3 months.	pharmtox\tox\SR00342-03.pdf
Study SR99022-01(659469): Budesonide + formoterol 3-month inhalation toxicity study in rats.	pharmtox\tox\SR99022-01.pdf
Study SR00047-02: Symbicort (budesonide + formoterol): 3-month inhalation (pMDI) toxicity study in the dog.	pharmtox\tox\SR00047-02.pdf
Study SR99023-01: (Report No. 850-TO-0430-01): Symbicort (budesonide + formoterol): 3 month inhalation (powder) toxicity study in the dog.	pharmtox\tox\SR99023-01.pdf
Formoterol	
Study 90076 (T2460): Dose finding study of D2522 given by the inhalation route to rats for 5 days.	pharmtox\tox\90076 (T2460).pdf
Study 96195-1: Formoterol: 3-month inhalation (HFA pMDI) toxicity study in the rat.	pharmtox\tox\96195-1.pdf
Study 90106 (T2433): General toxicity study of D2522 given by the inhalation route to rats for three months.	pharmtox\tox\90106 (T2433).pdf
Study 92110 (T2860): General toxicity study of formoterol fumarate (D2522) in lactose given to rats by the Inhalation route for 6 months.	pharmtox\tox\92110 (T2860).pdf
Study 96235-01: Plasma potassium and glucose levels in dogs given formoterol fumarate dihydrate (D2522) in lactose monohydrate by the inhalation route for 4 days.	pharmtox\tox\96235-01.pdf
Study 93058 (T3006): Dose finding study of formoterol fumarate (D2522) in lactose given to dogs by the inhalation route for five days.	pharmtox\tox\93058 (T3006).pdf
Study SR00447-01: Formoterol: One month inhalation (pMDI) toxicity study in the dog: toxicokinetic evaluation.	pharmtox\tox\SR00447-01.pdf
Study 93087 (T3120): General toxicity study of formoterol fumarate dihydrate (D2522) in lactose given to dogs by the inhalation route for one month.	pharmtox\tox\93087 (T3120).pdf
Study 91125 (T2579): General toxicity of D2522 given orally to dogs for one month.	pharmtox\tox\91125 (T2579).pdf
Study 92032 (T3077): General toxicity of formoterol fumarate (D2522) given orally to dogs for 12 months.	pharmtox\tox\92032 (T3077).pdf

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Module/CTD Description	Archive Copy Location Folder/File
4.2.3.3 Genotoxicity	
4.2.3.3.1 In Vitro	
SYMBICORT pMDI	N/A
Formoterol	
Study 91011 (T2388): Mutagenicity evaluation of D2522 batch 131/90 in the ames salmonella/mammalian microsome mutagenicity test.	pharmtox\tox\91011 (T2388).pdf
Study 91067 (T2389): Mutagenicity evaluation of D2522 batch 100/91 in the ames salmonella/mammalian microsome mutagenicity test.	pharmtox\tox\91067 (T2389).pdf
Study 91002 (T2397): Mutagenicity evaluation of D2522 in the L5178Y mouse lymphoma cell thymidine kinase locus mutagenicity test.	pharmtox\tox\91002 (T2397).pdf
Study 91137 (T2510): Analysis of structural chromosome aberrations in human lymphocytes treated with D2522 in vitro.	pharmtox\tox\91137 (T2510).pdf
4.2.3.3.2 In Vivo	
SYMBICORT pMDI	N/A
Formoterol	
Study 91132 (T2513): Rat micronucleus test of D2522 given by inhalation route as a powder aerosol.	pharmtox\tox\91132 (T2513).pdf
4.2.3.4 Carcinogenicity	
4.2.3.4.1 Long-Term Studies	
SYMBICORT pMDI	N/A
Formoterol	
Study 85133a (T3086): An oral carcinogenicity study of D2522 in the albino mouse.	pharmtox\tox\85133a (T3086).pdf
Study 85133b (T3086): An oral carcinogenicity study of D2522 in the albino mouse.	pharmtox\tox\85133b (T3086).pdf
Study 85133(T3086) - Datasets	pharmtox\datasets\85133 (T3086)\define.pdf
Study 91055 and 91056 (T2884): Oncogenicity study in rats given formoterol fumarate (D2522) in lactose by the inhalation route for 104 weeks.	pharmtox\tox\91055-91056 (T2884).pdf
Study 91055 (T2884) Datasets	pharmtox\datasets\91055 (T2884)\define.pdf

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Module/CTD Description	Archive Copy Location Folder/File
4.2.3.4.2 Short or Medium-Term Studies	
SYMBICORT pMDI	N/A
Formoterol	
Study 91118 (T2578): 843-32-T2578: General toxicity of D2522 given orally to mice for three months.	pharmtox/tox/91118 (T2578).pdf
4.2.3.4.3 Other Studies	N/A
4.2.3.5 Reproductive and Developmental Toxicity	
4.2.3.5.1 Fertility and Early Embryonic Development	
SYMBICORT pMDI	N/A
Formoterol	
Study ARA-192 (T3015): A Study on the effect on fertility and general reproductive performance of the rat - oral administration.	pharmtox/tox/ARA-192 (T3015).pdf
4.2.3.5.2 Embryo-Fetal Development	
SYMBICORT pMDI	
Study SR00581-01: Symbicort (budesonide-formoterol): embryofetal development study after administration to pregnant rats via the inhalation route.	pharmtox/tox/SR00581-01.pdf
Formoterol	
Study 92064 (T2628): Effects upon pregnancy in rats of D2522 given by the inhalation route.	pharmtox/tox/92064 (T2628).pdf
Study 93025 (T2710): Effects upon pregnancy in rabbits of D2522 given orally - a dose finding study.	pharmtox/tox/93025 (T2710).pdf
Study ARA-193 (T3014): Effects upon pregnancy in rats of D2522 given by the inhalation route.	pharmtox/tox/ARA-193 (T3014).pdf
4.2.3.5.3 Prenatal and Postnatal Development, including maternal function	
SYMBICORT pMDI	N/A
Formoterol	
Study 93081 (T2905): Effects upon pregnancy, delivery and offspring development in rats given formoterol fumarate (D2522) orally.	pharmtox/tox/93081 (T2905).pdf

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Module/CTD Description	Archive Copy Location Folder/File
4.2.3.5.4 Studies in which the Offspring (juvenile animals) are Dosed and/or Further Evaluated	
SYMBICORT pMDI	N/A
Formoterol	
Study 93069 (T2815): Single dose toxicity of formoterol fumarate (D2522) in young rats after oral administration.	pharmtox/tox/93069 (T2815).pdf
Study 94031 (T3136): General toxicity of formoterol fumarate (D2522) given orally to young rats for three months.	pharmtox/tox/94031 (T3136).pdf
Study 94143 (T3137): Effects on the respiratory tract and male reproductive organs in young rats given formoterol fumarate (D2522) in lactose by the inhalation route for 3 months.	pharmtox/tox/94143 (T3137).pdf
Study 94146 (T3160): Testicular effects of formoterol fumarate (D2522) given orally to young rats for three months, using salbutamol sulphate as a reference compound.	pharmtox/tox/94146 (T3160).pdf
4.2.3.6 Local Tolerance	
SYMBICORT pMDI	N/A
Formoterol	
Study 90041 (T2296): Hemolysis and protein flocculation in human blood of D2522 studied in vitro.	pharmtox/tox/90041 (T2296).pdf
Study 90033 (T2302): Vaso- and tissue irritation study in dogs of D2522 given intravenously and subcutaneously for 5 days.	pharmtox/tox/90033 (T2302).pdf
4.2.3.7 Other Toxicity Studies (if available)	
4.2.3.7.1 Antigenicity	N/A
4.2.3.7.2 Immunotoxicity	N/A
4.2.3.7.3 Mechanistic Studies	N/A
4.2.3.7.4 Dependence	N/A
4.2.3.7.5 Metabolites	N/A

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Module/CTD Description	Archive Copy Location Folder/File
4.2.3.7.6 Impurities	
SYMBICORT pMDI	N/A
Formoterol	
Study 91117 (T2488): Mutagenicity evaluation in the ames salmonella/mammalian microsome mutagenicity test.	pharmtox/tox/91117 (T2488).pdf
4.2.3.7.7 Other	
SYMBICORT pMDI - Excipients	
Authorization to refer to Drug Master File Letter 10378	pharmtox/tox/Letter DMF 10378.pdf
Study 96010: : 6-month inhalation (HFA-227 MDI) / subcutaneous toxicity study in the rat.	pharmtox/tox/96010.pdf
Study 96012: : 6-month inhalation (HFA-227 MDI) / subcutaneous toxicity study in the dog.	pharmtox/tox/96012.pdf
Study 98292: 12-month inhalation (HFA-227 pMDI) and subcutaneous toxicity study in beagle dogs.	pharmtox/tox/98292.pdf
Study 98027a: Life-time Inhalation (HFA 227 pMDI) carcinogenicity study in the rat.	pharmtox/tox/98027a.pdf
Study 98027b: Life-time inhalation (HFA 227 pMDI) carcinogenicity study in the rat.	pharmtox/tox/98027b.pdf

Studies not reviewed within this submission:

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2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Formoterol is a highly selective long-acting β_2 -agonist that possesses potent bronchospasmolytic activity. Formoterol is 20 to 70 times more potent than albuterol in relaxing guinea pig tracheal strip preparations. It is 70 to 400 times more potent than albuterol in relaxing isolated human bronchus in vitro. Formoterol is over 200 times more selective for the β_2 receptor than isoproterenol, a non-selective beta-adrenoceptor agonist. The affinity of formoterol for the β_2 receptor is 700 times higher than salbutamol. However, formoterol (like salbutamol) is a partial agonist for the β_2 receptor. The intrinsic activity of formoterol for activating adenylate cyclase is slightly lower than that of isoproterenol. Formoterol is a racemate of the RR and SS enantiomers with a ratio of one to one. The RR isomer is 1000 times more potent than the SS in relaxing guinea pig trachea in vitro.

Budesonide is a potent glucocorticoid. Inhalation or intratracheal administration of budesonide inhibited the increase in lung resistance during both the immediate and late asthmatic reactions. Budesonide inhibited the production and release of a variety of mediators and cytokines from inflammatory cells, the increases in airway eosinophil and vascular permeability, and the development of inflammatory lung edema, all of which play important roles in airway inflammatory reactions of asthma. Data may suggest that the reversible esterification of budesonide with fatty acids prolongs its retention in the airways, improves its selectivity for the airway, and contributes to a long duration of action within the airways/lung.

Studies using various biological systems suggest that combinations of budesonide and formoterol act complementarily, additively, or synergistically to produce enhanced anti-inflammatory, anti-remodeling, or anti-bronchoconstriction effects. These include the inhibition of the following activities: granulocyte macrophage-colony stimulating factor (GM-CSF) release in human bronchial epithelial cells, the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in human lung fibroblasts (Thorax 2002; 57:237-41), oxidative burst in human eosinophils stimulated by epithelial cell-derived condition medium, inflammation-induced lung edema in an allergic rat model in vivo, proliferation of primary cell cultures of human bronchial smooth muscle cells (The Lancet 2002; 360:1293-9), production of proteoglycans by lung fibroblasts (Eur Respir J 2003;22 (suppl 45): 286s), and the bronchoconstriction response to provocation in dogs. These mechanistic studies provide potential explanations that the combination of budesonide and formoterol in asthma therapy delivers a greater benefit than either drug alone.

2.6.2.2 Primary pharmacodynamics

See attached reviews of pharmacology studies conducted with formoterol under IND

See NDA 20-441 for studies conducted with budesonide.

Mechanism of action:

Effects of Formoterol and Budesonide and their Combination of TNF(alpha)-Induced GM-CSF Levels in Human Bronchial Epithelial Cells in Vitro (Study D5890RD0005-01): This study examined the effects of formoterol and budesonide alone and in combination on tumor necrosis factor α (TNF α , 10 ng/mL) induced granulocyte-macrophage colony stimulation hormone (GM-CSF) release from normal human bronchial epithelial cells over an 18-hr period. GM-CSF promotes the differentiation and survival of certain inflammatory cells that play a role in asthma. Cells were treated with budesonide or formoterol alone at concentrations ranging from 10^{-12} to 10^{-6} M. Cells were treated with budesonide and formoterol in combination as follows: 10^{-12} , 10^{-10} , 10^{-8} , or 10^{-6} M budesonide + either 10^{-12} , 10^{-10} , 10^{-8} , or 10^{-6} M formoterol. Budesonide alone dose-dependently reduced TNF α induced release of GM-CSF. Formoterol alone also decreased GM-CSF release, although the dose-response curve was flat. Formoterol alone showed efficacy up to 10^{-10} M as contrasted to the effect of budesonide, which was not significant at 10^{-9} M. When cells were treated with the combination of budesonide and formoterol, a further decrease in GM-CSF levels was observed. Maximal inhibition was achieved with budesonide at 10^{-8} M combined with formoterol 10^{-8} or 10^{-6} M and budesonide at 10^{-6} M + formoterol at $\geq 10^{-10}$ M. The results suggested an additive effect of budesonide and formoterol on TNF α induced GM-CSF release.

The duration of the effect of budesonide and/or formoterol on TNF α -induced GM-CSF release was examined by incubating cells with TNF α in the presence of these agents for 24, 32, 48, 56 or 72 hrs. Treatment with either budesonide at 10^{-6} M or formoterol at 10^{-6} M alone inhibited GM-CSF release to almost basal levels; however, inhibitory effects decreased over time (from 80% to 60%). Treatment with the combination of budesonide + formoterol (both at 10^{-6} M) resulted in a significantly greater inhibition of GM-CSF release (~90-95%) with a sustained effect up to 72 hrs. The inhibitory activity of the combination was apparently more effective and longer lasting than either agent alone.

Cells were treated with TNF α for 24, 48 or 72 hrs in the presence and absence of the combination of budesonide and formoterol at the 35 to 1 ratio (i.e., 10^{-8} M budesonide + 2.8×10^{-10} M formoterol or 10^{-9} M budesonide + 2.8×10^{-11} M formoterol) found in the Symbicort product. At all time points, the combination of budesonide and formoterol resulted in a more effective inhibition of TNF α -induced GM-CSF release than mono-components alone. A comparison of the combination of 10^{-9} M budesonide + 2.8×10^{-11} M formoterol to 10^{-9} M budesonide + 2.8×10^{-10} M salbutamol found no significant differences as both combinations produced maximal inhibition of GM-CSF release.

GR Activation in Human Bronchial Epithelial Cells by Formoterol in the Presence or Absence of Budesonide In Vitro (Study D5890RD0004-01): The ability of formoterol to induce nuclear translocation and activation of the glucocorticoid receptor (GR) was examined in human bronchial epithelial cells. GR nuclear translocation was

assessed by Western blotting on nuclear and cytoplasmic protein pools. GR activity was measured by reporter gene activity (i.e., pSV- β -galactosidase reporter vectors) and GM-CSF analysis. Treatment of cells with budesonide at 10^{-10} to 10^{-6} M for 30 min produced a dose-dependent translocation of GR into the nucleus. Treatment of cells with budesonide at 10^{-6} M produced a translocation of GR into the nucleus within 15 min and the effect remained for at least 4 hr. Treatment of cells with formoterol at 10^{-10} to 10^{-6} M for 15, 30, 60, and 120 min did not produce any translocation of GR into the nucleus. Similarly, treatment of cells with salmeterol at 10^{-6} M for 60, 120, 180, or 240min also did not produce any translocation of GR into the nucleus. Treatment of cells with budesonide at 10^{-12} to 10^{-6} M for 24 hr dose-dependently increased GR activity with a maximal increase of 230%; however, formoterol at identical concentration had no effect. Treatment of cells with budesonide or formoterol at 10^{-12} to 10^{-6} M produced a dose-dependent inhibition of PMA-induced TRE-regulated gene reporter activity (TRE-reporter gene activity is regulated by the pro-inflammatory transcription factor AP-1). The ability of budesonide to reduce TRE activity was reversed when cellular GR levels were reduced; however, the ability of formoterol to reduce TRE-activity was independent of GR levels. Formoterol had no effect on budesonide-induced GR translocation or activity. The combination of budesonide and formoterol inhibited PMA-induced TRE activity as well as TNF α -induced GM-CSF levels by a greater extent than either monoproduct alone. The anti-inflammatory activity of formoterol was independent of the glucocorticoid receptor.

Steric Aspects of Formoterol and Terbutaline: Is there an Adverse Effect of the Distomer on Airway Smooth Muscle Function (Report number 843-RD-0366):

Effects of enantiomers of formoterol and terbutaline on isolated airway smooth muscle from guinea pigs during various experimental conditions was assessed. Trachea or main bronchi, with or without adhering vagus nerves, were obtained from male Dunkin-Hartley guinea pigs. Organ bath preparations consisted of tracheal rings contracted with 1 μ M carbachol, 3 cartilage rings from the trachea or main bronchi with transmural field stimulation induced by trains of biphasic pulses, and the electrically-stimulated vagus nerve-trachea tube. Effects of enantiomers of formoterol and terbutaline in these preparations were assessed. (R,R)-Formoterol and (R)-terbutaline were potent inhibitors of cholinergic-induced contractions. In contrast, (S,S)-formoterol and (S)-terbutaline were significantly less potent by almost 3 orders of magnitude. (R,R)-formoterol and racemic formoterol were also potent inhibitors of vagus nerve-induced contraction. (S,S)-formoterol was less potent by almost 3-orders of magnitude. Recovery of cholinergic-induced contraction during continuous stimulation with a β_2 -adrenoreceptor agonist may have been due to down regulation of the β_2 -adrenoreceptor, up-regulation of the muscarinic receptor function, or changes in another regulatory mechanism. There were no indications of hyperreactivity induced by β_2 -adrenergic agonists.

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TABLE 1. pEC₅₀-values and eudismic ratios for the inhibition by the enantiomers of terbutaline and formoterol of nerve-induced contractions of airway smooth muscle from guinea-pig^a

Tissue Response	Terbutaline			Formoterol		
	pEC ₅₀ (R)-	(S)-	Eudismic ratio	pEC ₅₀ (R,R)-	(S,S)-	Eudismic ratio
<i>Trachea</i>						
Cholinergic	7.13±0.32(7)	<4.0(5)	>1,350	9.52±0.24(5)	6.44±0.13(5)	1,202
e-NANC	8.14±0.33(6)	5.27±0.42(6)	741	10.47±0.17(5)	7.56±0.28(5)	812
<i>Main bronchus</i>						
Cholinergic	7.15±0.20(9)	<4.0(8)	>1,400	9.09±0.17(5)	6.20±0.28(5)	724
e-NANC	7.97±0.19(9)	4.76±0.37(8)	1,621	10.12±0.16(5)	7.42±0.23(5)	501

^aThe data are the means±SE of (n) experiments. More details are given in fig. 3 and 4.

TABLE 2. pEC₅₀-values for the inhibition by the enantiomers of formoterol of contractions induced by stimulation of the vagus nerve in the guinea-pig trachea tube preparation^a

Chiral form	Mode of administration	
	Extratracheal	Intratracheal
(R,R)-formoterol	9.89±0.06(6)	8.65±0.13(7)
(S,S)-formoterol	6.42±0.14(5)	5.45±0.15(5)
<i>rac</i> -formoterol ^b	9.23±0.11(4)	8.51±0.25(4)

^a The data are the means±SE of (n) experiments. For more details see fig. 5.

^b Data from Jeppsson et al.¹⁵

Steric Aspects of Agonism and Antagonism at β -Adrenoreceptors: Synthesis of and Pharmacological Experiments with the Enantiomers of Formoterol and Their Diastereomers (Report number 843-RD-0289): The enantiomers of formoterol (R,R and S,S) and their diastereomers (R,S and S,R) were assessed for their *in vitro* interactions with β -adrenoreceptors in tissues isolated from male Dunkin-Hartley guinea pig. Effects measured were relaxation of carbachol- or histamine-induced contraction of the tracheal smooth muscle, depression of subtetanic contractions of the soleus muscle, and increases in the force of papillary muscle of the left ventricle of the heart. All enantiomers produced a concentration-dependent and complete relaxation of tracheal smooth muscle that was inhibited by propranolol. The order of potency was (R,R) >> (R,S) = (S,R) > (S,S) with a 1000-fold difference in potency between the most and least

potent isomers. The presence of the (S,S) enantiomer had no effect on the relaxing capacity of the (R,R) enantiomer. Formoterol caused a concentration-dependent depression of subtetanic contractions of the soleus muscle. The (R,R) enantiomer was approximately 15 times more potent than the (R,S) enantiomer. In the electrically driven papillary muscle, the (R,R) and (R,S) enantiomers increased the force of contraction. This effect was concentration-dependent and reached the same maximum as that achieved by 10 μ M isoprenaline; however, the (R,R) enantiomer was 10 times more potent than the (R,S)-isomer. The (S,R) and (S,S) enantiomers increased the force of contraction at 1 μ M, but this effect at higher concentrations was counteracted by a negative inotropic effect.

Relaxation by the four stereoisomers of formoterol of the guinea-pig trachea. Contraction was induced either by 0.1 μ mol/l carbachol or 0.5 μ mol/l histamine with or without 0.1 μ mol/l propranolol. The data are the mean $pD_2 \pm SE$ with the number of experiments in parenthesis.

	Batch no	(R;R)	(R;S)	(S;R)	(S;S)
Carbachol	1	9.63 $\pm$ 0.04 (6)	8.11 $\pm$ 0.15 (6)	7.30 $\pm$ 0.10 (9)	7.90 $\pm$ 0.06 (5)
	2	10.03 $\pm$ 0.02 (6)	8.19 $\pm$ 0.13 (5)	-	-
	3	9.89 $\pm$ 0.04 (6)	7.87 $\pm$ 0.06 (6)	7.83 $\pm$ 0.06 (5)	6.96 $\pm$ 0.02 (6)
Histamine	1	9.79 $\pm$ 0.12 (5)	8.36 $\pm$ 0.10 (5)	7.98 $\pm$ 0.12 (5)	8.06 $\pm$ 0.14 (5)
+propranolol	1	7.87 $\pm$ 0.10 (5)	6.64 $\pm$ 0.12 (5)	5.68 $\pm$ 0.19 (5)	6.18 $\pm$ 0.09 (5)

Depression of subtetanic contractions of the soleus muscle and increase in force of the electrically driven papillary muscle from guinea-pig by two stereoisomers of formoterol. The data are the mean $pD_2 \pm SE$ with the number of experiments in parenthesis.

Tissue	Batch no	(R;R)	(R;S)
Soleus muscle	1	9.26 $\pm$ 0.08 (8)	7.77 $\pm$ 0.28 (5)
	3		8.08 $\pm$ 0.10 (6)
Papillary muscle	1	6.81 $\pm$ 0.15 (5)	
	2	6.79 $\pm$ 0.09 (5)	6.10 $\pm$ 0.10 (5)
	3		5.78 $\pm$ 0.17 (6)

Lack of Adverse Effects of (S,S)-Formoterol on Airway Reactivity in the Isolated Guinea Pig Lung (Report number 843-RD-0372): The potential of the (S,S) enantiomer of formoterol to induce airway hyperreactivity was assessed using an isolated, perfused, ventilated lung preparation from male Dunkin Hartley guinea pigs. Metacholine was infused in increasing doses (0.27+0.45+0.9+1.35+1.71 nmol). For each dose level, the depressive effect of metacholine on airway conductance was allowed to reach its maximum before the next dose was administered. After two sequences of provocation with metacholine, an aerosol of the test compound or vehicle was inhaled for 5 min, just before commencement of the third challenge. The aerosols were generated from solutions containing the vehicle or 10 µM racemic formoterol, (R,R)-formoterol, or (S,S)-formoterol. Inhalation of racemic or (R,R)-formoterol increased basal conductance by about 80% compared to the control. (S,S)-formoterol tended to increase conductance, although it was not statistically significant. Both racemic and (R,R)-formoterol inhibited the response to metacholine. (S,S)-formoterol did not significantly attenuate the response to metacholine; however, it also did not increase reactivity. (S,S)-formoterol was comparable to the vehicle. There was no indication of (S,S)-formoterol-induced hyperreactivity to metacholine.

Effects of Formoterol, Budesonide, or the Combination Thereof on Superoxide Release from Isolated Human Eosinophils (Study D5890RD0003-01): Effects of the combination of budesonide and formoterol as compared to monoproducts were assessed on in vitro superoxide production by human eosinophils treated with conditioned medium obtained from normal human bronchial epithelial cells. Eosinophils were isolated from human peripheral blood from healthy volunteers following a magnetic cell separation protocol. The main component in epithelial cell conditioned medium responsible for mediating superoxide release from eosinophils was GM-CSF. GM-CSF dose-dependently increased superoxide release from human eosinophils; however, background superoxide release from eosinophils of some donors was very high resulting in a lack of a dose-response. GM-CSF dose-dependent superoxide production was included as a control in all subsequent experiments. Experiments displaying less than 3-fold increase in superoxide release after GM-CSF stimulation were excluded. Formoterol at concentrations of 10^{-10} to 0.5×10^{-7} M produced a dose-dependent inhibition of superoxide production. Budesonide did not produce a dose-dependent inhibition of superoxide production. Combinations of formoterol and budesonide generally resulted in additive effects toward superoxide release. Large variations between experiments were recorded. Due to lack of reproducibility and large variability, the study was terminated.

Pharmacologic Activity of Metabolites of Formoterol (Study 843-RD-0373): Three compounds (_____), structurally related to formoterol and potential metabolites/impurities, were assessed for relaxation of guinea pig tracheal smooth muscle. _____ was formed by the demethylation of formoterol in the methoxy group to form a 4-hydroxyphenyl derivative. _____ was formed when the formamide group of formoterol was converted to an amino group (_____). _____ was a derivative of formoterol with an unbranched (_____). Tracheal smooth muscle strips were prepared from male Dunkin-Hartley guinea pigs and mounted in organ baths

for isometric recording of tension. Tone was induced by 1 μ M carbachol. All three compounds produced a concentration-dependent relaxation of tracheal smooth muscle. — with a pD₂ value of — was comparable to (R,R)-formoterol. — is a racemate comprising two diastereomer pairs. One of the four possible stereoisomers, possibly the (R,R)-enantiomer, may be more potent than formoterol as a bronchodilator. — with a pD₂ of — was about 100 times less potent than — a potential impurity, with a pD₂ of — was of intermediate potency between — and —.

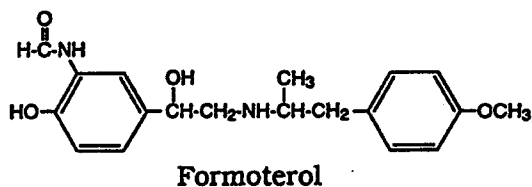


Fig. 1. Chemical structure of formoterol and the compounds investigated.

Drug activity related to proposed indication:**Rats****Budesonide: Effects of Various Regimens of Adjusted Budesonide/formoterol Dosing on Airway Hyperresponsiveness, Inflammation, and Tissue Edema in an Allergic Rat Model In Vivo (Study D580RD0006-01):**

Effects of a flexible or adjusted budesonide/formoterol dosing protocol were compared to fixed doses of budesonide/formoterol on methacholine-induced airway constriction, lung edema, and interleukin (IL)-1 release in ovalbumin-sensitized Brown Norway rats. Rats were sensitized to ovalbumin on days 1 and 7 and challenged by intratracheal instillation of ovalbumin on days 14 and 21. Twenty-four hr after the last provocation with ovalbumin, rats were exposed to an aerosol of 0.2% methacholine for 4 min. Rats were subsequently terminated for measurement of excised lung gas volume (ELGV) or lung weight as an index of edema. Bronchoalveolar lavage fluid was collected for measurement of leukocyte influx. Rats were randomly allocated into 10 treatment groups as shown in the table below. The most effective treatment was B/F at 1/0.028 µg/kg for maintenance + B/F at 10/0.28 µg/kg on challenge days (Group 4) which produced a 90% inhibition of ELGV, 44% inhibition of lung edema, and 30% inhibition of leukocyte influx. Treatment with B/F at 10/0.28 µg/kg all days (Group 8) produced a 54% inhibition of ELGV, 32% inhibition of lung edema, and 29.1% inhibition of leukocyte influx. Treatment with B/F at 1/0.028 µg/kg for maintenance + B/F at 10/0.28 µg/kg twice for challenge days (Group 9) day produced a 66% inhibition of ELGV and 45% inhibition of lung edema; however, the effect on leukocyte influx was minimal. Treatment with B/F at 1/0.028 µg/kg for maintenance plus with B/F at 1/0.28 µg/kg twice for challenge days (Group 10) produced a 70% inhibition of ELGV; however, effects on lung edema and leukocyte influx were minimal. Treatment with B/F at 1/0.028 µg/kg for maintenance + B/F at 1/0.28 µg/kg for challenge days (Group 5) produced at 25% inhibition of lung edema; however, effects on ELGV and leukocyte influx were minimal. B/F at 1/0.028 µg/kg for maintenance + B/F at 10/0.28 µg/kg on challenge days was the most effective treatment for control of methacholine-induced airway hyperresponsiveness, lung edema, and leukocyte influx. Treatments with fixed low or high doses of budesonide and formoterol on all days were generally not as effective.

Experimental design

Group	Treatment	Comments
1	Animals were sensitized and provoked with saline and treated with vehicles	
2	Animals were sensitized with OVA and provoked with saline and treated with vehicles.	
3	Animals were sensitized and provoked with OVA and treated with vehicles.	
4	Animals were sensitized and provoked with OVA and treated with B/F at 1/0.028 µg/kg for maintenance + B/F at 10/0.28 µg/kg on challenge days	Adjustable regimen
5	Animals were sensitized and provoked with OVA and treated with B/F at 1/0.028 µg/kg for maintenance + B/F at 1/0.28 µg/kg on challenge days.	High dose formoterol
6	Animals were sensitized and provoked with OVA and treated with B/F at 1/0.028 µg/kg for maintenance + B/F at 10/0.028 µg/kg on challenge days.	High dose budesonide
7	Animals were sensitized and provoked with OVA and treated with B/F at 1/0.028 µg/kg for all days.	Fixed low doses

8	Animals were sensitized and provoked with OVA and treated with B/F at 10/0.28 µg/kg for all days.	Fixed high dose
9	Animals were sensitized and provoked with OVA and treated with B/F at 1/0.028 µg/kg for maintenance + B/F at 10/0.28 µg/kg twice for challenge day.	More B/F on challenge days
10	Animals were sensitized and provoked with OVA and treated with B/F at 1/0.028 µg/kg for maintenance plus with B/F at 1/0.28 µg/kg twice for challenge day.	High dose formoterol

Effects of treatment with combinations of budesonide and formoterol on excised lung gas volume (ELGV), lung edema, and leukocyte influx in the bronchoalveolar lavage fluid.

Group	ELGV, % Inhibition	Lung edema, % Inhibition	Leukocyte in the BAL Fluid, % Inhibition
1			
2			
3			
4	89.79%	44.26	29.54%
5	13.75%	25.40	16.95%
6	13.72%	18.15	13.56%
7	28.97%	-12.82	-22.03%
8	53.54%	32.07	29.06%
9	65.79%	45.33	12.35%
10	70.27%	3.56	-8.76%

Guinea Pigs

The Potency and Duration of Action of the β_2 -Related Effect of Formoterol Against Intravenous Histamine-Induced Bronchoconstriction in the Guinea Pig when Delivered by Aqueous Aerosol: A Comparison with Salbutamol and Salmeterol (Study SC-100608-2): The potency and duration of action of formoterol against intravenous histamine-induced bronchoconstriction in the guinea pig were examined following dosing using an aqueous aerosol. Effects were compared with salbutamol and salmeterol. Animals were exposed for 15 min to aerosols of aqueous solutions of formoterol, salmeterol, or salbutamol by nebulizer. At 1, 3, and 5 hr following inhalation exposure to a β_2 -agonist, animals were anesthetized and prepared for measurement of tracheal back pressure. Histamine was administered by the intravenous route at doses of 1, 3, 5, 10, and 20 µg/kg with 4 min between doses. Intravenous histamine produced a dose-dependent bronchoconstriction. Formoterol (3 to 100 µg/mL), salmeterol (3 to 300 µg/mL), and salbutamol (0.1 to 3 mg/mL) all inhibited histamine-induced bronchoconstriction in a dose-dependent manner. Maximal effects were observed with formoterol at 30 µg/mL, salmeterol at 100 µg/mL, and salbutamol at 1 mg/mL. Formoterol at 30 µg/mL and salmeterol at 50 µg/mL significantly inhibited histamine-induced bronchoconstriction up to 5 hr postdose; however, the bronchodilator effect obtained with salmeterol at 5 hr was significantly greater than that obtained with formoterol. Salbutamol significantly inhibited histamine-induced bronchoconstriction at 1-hr postdose, but not at 3 and 5 hr postdose. The order of potency was formoterol > salmeterol > salbutamol. The order of duration of action was salmeterol > formoterol > salbutamol.

Long Duration and High Potency of Anti-Exudative Effects of Formoterol in Guinea Pig Tracheobronchial Airways (Study 843-RD-0013): The potency and duration of action of anti-exudative effects of formoterol and salbutamol were compared in guinea pig tracheobronchial airways. To assess the acute anti-exudative effects of formoterol or salbutamol, male guinea pigs were anesthetized and a catheter was introduced into the tracheal lumen. ^{125}I -labeled human serum albumin was administered by the intravenous route. Formoterol (10^{-9} to 10^{-7} M) or salbutamol (10^{-6} to 10^{-4} M) was superfused onto the tracheal mucosa for 5 min. This was immediately followed by superfusion with bradykinin at 1.25×10^{-4} M. To assess the duration of action, guinea pigs were treated with formoterol (10^{-9} to 10^{-7} M) or salbutamol (10^{-6} to 10^{-4} M) and then allowed to recover. At 280 min postdose, animals were anesthetized and intubated. Ten min later, ^{125}I -labeled albumin was administered by the intravenous route. At 300 min postdose, bradykinin (1.25×10^{-4} M) was superfused onto the tracheal mucosa. The duration of action was also assessed with 10^{-7} M formoterol at 450 and 600 min postdose. Experiments were terminated 5 min after addition of bradykinin and airway luminal fluid was sampled. Formoterol at 10^{-9} to 10^{-7} M inhibited exudation of ^{125}I -labeled albumin by 35.5 to 88.5%. Salbutamol at 10^{-5} and 10^{-4} M inhibited exudation of ^{125}I -labeled albumin by 87.7 and 85.6%, respectively. These anti-exudative effects of formoterol and salbutamol were attributed to their β_2 -adrenergic activities given that effects were eliminated by treatment with propranolol. Formoterol at 10^{-8} and 10^{-7} M inhibited exudation at 10 and 300 min postdose. Salbutamol at 10^{-5} and 10^{-4} M inhibited exudation at 10 min postdose, but not at 300 min postdose. Formoterol was shown to have an anti-exudative effect, with a relatively long duration of action.

Dogs

The β_2 Related Effect of Formoterol on Histamine-induced Bronchoconstriction in the Dog when Delivered Intratracheally by Aerosol: A Comparison with Salmeterol (Study 843-RD-0399): Dose-related effects of formoterol administered by aqueous aerosol against histamine-induced bronchoconstriction were assessed in anesthetized female beagle dogs. Salmeterol was used as a comparator. Flow, volume, and transpulmonary pressure were measured and used to calculate dynamic lung compliance (C_L) and lung resistance (R_L). Histamine was administered by aerosol using a nebulizer. Test compound were administered as an aerosol of 100 breaths of the appropriate concentration directly into the tracheal cannula 30 min before histamine challenge. This was repeated at 60 min intervals with test compounds being administered 15-30 min before each histamine challenge. Compounds were administered in a cumulative fashion until a plateau effect was achieved. Formoterol at concentrations of 3, 10, 30, and 100 $\mu\text{g/mL}$ inhibited histamine-induced increases of R_L by 46, 68, 90, and 92%, respectively. Formoterol at concentrations of 3, 10, 30, and 100 $\mu\text{g/mL}$ blocked histamine-induced decreases of C_L by 12, 34, 76, and 91%, respectively. Formoterol in a dose-dependent manner inhibited histamine-induced increases of lung resistance and decreases of lung compliance with ED_{50} values of approximately 4 and 10 $\mu\text{g/mL}$, respectively. Salmeterol in a dose-dependent manner also inhibited histamine-induced increases of lung resistance and decreases of lung compliance with ED_{50} values of 98 and 224 $\mu\text{g/mL}$, respectively. Inhibition of histamine-induced

bronchoconstriction by formoterol and salmeterol were consistent with β_2 -adrenergic activities as effects could be reversed by propranolol. Formoterol at 100 $\mu\text{g/mL}$ produced tachycardia in 2 of 3 dogs.

2.6.2.3 Secondary pharmacodynamics

See attached reviews of studies conducted with formoterol under IND ———. See NDA 20-441 for studies conducted with budesonide.

2.6.2.4 Safety pharmacology

See attached reviews of safety pharmacology studies conducted with formoterol under IND ———. See NDA 20-441 for studies conducted with budesonide.

Formoterol can dose-dependently alter behavior, hemodynamics, respiratory patterns of muscle contraction, and metabolism in animals and humans. Administration of formoterol to mice at oral doses ≥ 0.1 mg/kg caused increased respiratory rate, decreased motor responses and miosis, salivation, and ptosis. Similar doses administered to rats produced decreased appetite, increased respiratory rate, exophthalmus, flush of pinna, urination, and defecation. Similar doses administered to guinea pigs caused hyperirritability, increased respiratory rate, lacrimation, and flushing. In dogs, there were observations of miosis, salivation, yawning, barking, hypersensitivity and staggering. In monkeys, there were observations of increased respiration rate, ptosis, weak piloerection, and flushing of the face. In cats, formoterol at oral doses ≥ 0.01 mg/kg elicited increased respiratory rate, yawning, tremor, flushing, nausea, vomiting, lacrimation, and ptosis. In dogs, formoterol at an oral dose of 0.001 mg/kg caused tremor, and 0.003 mg/kg caused congestion of the eye and lacrimation. Formoterol at oral doses ranging from 1 to 1000 mg/kg had no effect on convulsion induced by maximal electroshock, muscle relaxant activity, or rotarod performance. Formoterol prolonged thiopental sleeping time at oral doses ≥ 100 mg/kg. Formoterol at an oral dose of 1.0 mg/kg had no effect on electroencephalogram in immobilized cats.

In anesthetized dogs, formoterol administered by the intraduodenal route at 0.1 $\mu\text{g/kg}$ lowered diastolic pressure and at 10 $\mu\text{g/kg}$ lowered systolic pressure. In conscious dogs, formoterol at an oral dose of 10 $\mu\text{g/kg}$ or an intravenous dose of 0.1 $\mu\text{g/kg}$ lowered both diastolic and systolic pressures. Formoterol administered by the oral route induced tachycardia in dogs at 1.0 $\mu\text{g/kg}$, cats at 10 $\mu\text{g/kg}$, guinea pigs at 10 $\mu\text{g/kg}$, and monkeys and rats at 30 $\mu\text{g/kg}$. The effect of formoterol was equipotent to that of isoproterenol. Formoterol administered to anesthetized dogs at an intravenous dose of 1.0 $\mu\text{g/kg}$ produced depression of the R-wave and ST segment and decreased T-wave amplitude. Formoterol at an intravenous dose of 1.0 $\mu\text{g/kg}$ also caused a decrease in coronary arteriovenous oxygen difference and an increase in the maximum rate of the rise in left ventricular pressure, myocardial oxygen consumption, cardiac output, and stroke volume.

Formoterol at an intraduodenal dose of 10 $\mu\text{g/kg}$ (ID) inhibited epinephrine-induced hypertension (5 $\mu\text{g/kg}$, IV) and acetylcholine-induced hypotension (0.5 $\mu\text{g/kg}$, IV) in dogs. Formoterol inhibited spontaneous motility of the uterus at concentrations $\geq 10^{-10}$.

g/mL. Formoterol at doses of $\geq 0.1 \mu\text{g/kg}$ produced increased levels of pyruvic acid and lactic acid in dogs serum. Blood sugar and free fatty acid levels were also elevated after an oral dose of $10 \mu\text{g/kg}$. SS-formoterol and (S)-terbutaline did not induce airway hyperreactivity in an isolated guinea pig tracheal strip model.

2.6.2.5 Pharmacodynamic drug interactions

See attached reviews of studies conducted with formoterol under IND — . See NDA 20-441 for studies conducted with budesonide.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not provided.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

See attached reviews of ADME studies conducted with formoterol under IND — .
See NDA 20-441 for studies conducted with budesonide.

2.6.4.1 Brief summary

Toxicokinetic parameters of Symbicort (budesonide + formoterol) were assessed in 3-month bridging studies with rats and dogs and are described in the review of the initial submission of IND 63,394. ADME parameters were only determined for monoproducts in nonclinical studies.

Formoterol is readily absorbed after oral and inhalation administration. Bioavailability of formoterol following oral and intratracheal administration was high, although there was evidence of extensive metabolism. Peak concentrations are achieved 0.5-1 hr after oral and intratracheal administration. Distribution of the drug after inhalation exposure is in the following order: trachea > lung > kidney > liver > plasma > heart > brain. Half-lives of the drug after inhalation exposure range from 2 to 4 hours. Formoterol is extensively metabolized with glucuronide conjugation and O-demethylation as the major pathways. Following oral administration, there was evidence of a hepatic first pass effect. Following intratracheal administration, there was some evidence of first pass metabolic effect produced by the lung. Formoterol is primarily eliminated by urine excretion with smaller quantities eliminated by biliary excretion. There was evidence of enterohepatic recirculation in rats and dogs. Plasma protein binding of formoterol was approximately 50%. Formoterol readily crosses placenta to reach the fetus and is excreted into the milk. Pharmacokinetic profiles of formoterol in rats, dogs, and humans were relatively similar.

See NDA 20-441 for ADME studies conducted with budesonide.

2.6.4.2 Methods of Analysis

See attached reviews of studies conducted with formoterol under IND — for specific details of methods of analysis. See NDA 20-441 for studies conducted with budesonide.

2.6.4.3 Absorption

See attached reviews of studies conducted with formoterol under IND — See NDA 20-441 for studies conducted with budesonide.

2.6.4.4 Distribution

See attached reviews of studies conducted with formoterol under IND — . See NDA 20-441 for studies conducted with budesonide.

Whole-Body Autoradiographic Study on the Distribution of Radioactivity in Rats After Single Intravenous Injection, Oral Administration, or Intratracheal Installation of ^3H -Formoterol (Study 843-TO-0242 (95007)).

Methods: The distribution of radioactivity in Black Hooded rats (pigmented) was examined using a whole-body autoradiography technique after a single intravenous, oral, or intratracheal dose of ^3H -formoterol. Fourteen male rats received ^3H -formoterol by the intravenous or oral route at a dose of 1.95 $\mu\text{mol/kg}$. Following intravenous administration, animals were sacrificed at 5 and 15 min, 1, 4, and 16 hr and 2 days postdose. Following oral administration, animals were sacrificed at 5 and 15 min, 1, 4, and 16 hr, and 2, 8, and 30 days postdose. Five pregnant female rats at gestation day 19 received ^3H -formoterol by the intravenous route at a dose of 1.95 $\mu\text{mol/kg}$ and were sacrificed at 5 and 15 min, and 1, 4, and 16 hr postdose. Six young male rats (16 days old) received ^3H -formoterol by the oral route at a dose of 2.04 $\mu\text{mol/kg}$ and were sacrificed at 15 min, 1, 4, and 16 hr, and 2 and 8 days postdose. Six adult rats received ^3H -formoterol by the intratracheal route at a dose of 1.83 $\mu\text{mol/kg}$ and were sacrificed at 5 and 15 min, 1, 4, and 16 hr, and 2 days postdose. Animals were subsequently processed to determine the distribution of radioactivity by whole body autoradiography.

Results: Radioactivity detected in organs and tissues was attributed to the parent compound as well as its metabolites.

Intravenous administration to adult male rats: The highest levels of radioactivity in organs and tissues were observed at 5 min after dosing. Very high levels of radioactivity were observed in the pigmented layer of the eye, parts of the intestinal contents, choroid plexus, pituitary gland, pineal body, adrenal medulla, adrenal cortex, kidney, urine, and bile. High levels of radioactivity were observed in the myocardium, lung, gastric mucosa, submandibular salivary gland, pancreas, red and white pulp of the spleen, thyroid gland, and brown fat. The tissue distribution of radioactivity was comparable at 15 min after dosing, although levels were declining. Very high levels of radioactivity were observed in the pigmented layer of the eye at all time points up to 2 days postdose. Moderate to very high levels of radioactivity were observed in the adrenal medulla at all time points up to 2 days postdose. High to very high levels of radioactivity were observed in parts of the intestinal contents, choroids plexus, pituitary gland, urine, and bile up to 4 hr postdose and then began to decline. Moderate to high levels of radioactivity were observed in the melanin pigment in the hair roots at all time points.

Intravenous administration to pregnant female rats: A limited examination of organ and tissues was conducted for pregnant female rats. At 5 min postdose, high levels of radioactivity were observed in the ovary, corpus luteum, and amnion membrane. Moderate to high levels of radioactivity were observed in the fetal eye melanin layer from 5 min to 16 hr postdose. Moderate to high levels of radioactivity were observed in ovary and amnion membrane up to 4 hr postdose and then began to decline. High levels of radioactivity were present in the corpus luteum at 5 and 15 min and then began to decline. Moderate levels of radioactivity were present in placenta from 5 min to 1 hr and then began to decline. Moderate to high levels of radioactivity were present in the central part of the white pulp of the maternal spleen from 1 to 16 hr postdose; earlier time points were not examined.

Oral administration to adult male rats: Very high levels of radioactivity were observed in parts of the stomach and intestinal contents from 5 min to 4 hr postdose and as contamination in the oral cavity and esophagus from 5 min to 1 hr postdose. Radioactivity levels declined rapidly and were negligible at later time points. High to very high levels of radioactivity were observed in the urine from 5 min to 16 hr postdose and the bile from 5 min to 4 hr postdose. Radioactivity levels declined rapidly and were negligible at later time points. For other organs and tissues, radioactivity levels were low or not detectable.

Oral administration to young male rats: The young male rat showed higher tissue concentrations of radioactivity as compared to the adult rat. Uptake of radioactivity in the adrenal medulla and melanin tissue in the eye was observed at a moderate level at 4 or 16 hr postdose to 8 days postdose.

Intratracheal administration to adult male rats: The distribution of radioactivity after intratracheal administration was comparable to that observed with intravenous administration. The highest levels of radioactivity in organs and tissues were observed at 5 and 15 min postdose. Very high levels of radioactivity at 5 and/or 15 min postdose were observed in the administration route, lung, contamination of the nasal cavity, parts of the stomach contents, parts of the intestinal contents, choroid plexus, kidney medulla, urine, and bile. Moderate levels of radioactivity were found in the pigmented layer of the eye at 5 and 15 min and very high levels were found from 1 hr to 2 days. Moderate to very high levels of radioactivity were observed at the administration route at all time points. High to very high levels of radioactivity were found in the lungs from 5 min to 4 hr postdose and then began to decline. Very high levels of radioactivity as contamination in the nasal cavity were observed at 5 and 15 min postdose. Moderate to very high levels of radioactivity were found in parts of the stomach contents from 5 min to 4 hr postdose. High to very high levels of radioactivity were found in parts of the intestinal contents from 15 min to 4 hr postdose and then began to decline. Very high levels of radioactivity were found in the choroid plexus at 5 min to 4 hr postdose. High to very high levels of radioactivity were found in the medulla of the kidney at 15 min and 1 hr postdose. Very high levels of radioactivity were found in urine at 15 min to 4 hr postdose and then began to decline. Very high levels of radioactivity were found in the bile from 5

min to 4 hr postdose and then began to decline. High to very high levels of radioactivity were found in the melanin pigments in hair roots at 4 hr to 2 days postdose.

Uptake of the RR and SS Enantiomers of Formoterol in the Isolated Perfused Guinea Pig Lungs (Study 843-RD-0359):

Methods: The uptake of (R,R)-formoterol and (S,S)-formoterol by the lungs after administration directly into the airways or after systemic administration was examined using an isolated perfused and ventilated lung model prepared from male Dunkin-Hartley guinea pigs. Each of the two enantiomers labeled with tritium was mixed with the opposite unlabeled enantiomer at proportions similar to those of the racemic substance. Each enantiomer was studied after administration to the perfusion medium and after instillation into the trachea in parallel experiments using guinea pig lungs in the recirculating mode. The dose to the lungs was 0.5 nmol racemic formoterol of which 0.25 nmol was either ^3H -(R,R)- or ^3H -(S,S)-formoterol. Samples were collected from the recirculating medium at 10, 20, 40, 80, 100, or 120 min after administration. The lungs were homogenized for measurement of ^3H -(R,R)- or ^3H -(S,S)-formoterol. Samples from the lungs and the 2-hr perfusion buffers were analyzed by HPLC in order to quantify possible metabolites.

Results: The lung uptake of formoterol enantiomers was determined by calculation of the ratio of the concentration in the lungs over the concentration in the perfusate at the end of the 2-hr perfusion. Irrespective of route of administration, steady-state levels of enantiomers in the perfusion medium were obtained within 1 hr after the start of recirculation. The lung/perfusate concentration ratios for (R,R)-formoterol at steady-state following intravascular and intratracheal administration were 15.5 and 25.6, respectively. The lung/perfusate concentration ratios for (S,S)-formoterol at steady-state following intravascular and intratracheal administration were 10.8 and 16.6, respectively. Uptake of ^3H -(R,R)-formoterol by the lung after intravascular and intratracheal administration of racemic formoterol was 34.8 and 40.4% of the dose, respectively. Uptake of ^3H -(S,S)-formoterol by the lung after intravascular and intratracheal administration of racemic formoterol was 27.4 and 27.1% of the dose, respectively. Uptake by the lung was greater following intratracheal administration as compared to intravascular administration. No metabolism of the formoterol enantiomers was observed in the study. The overall higher uptake of (R,R)-formoterol compared to (S,S)-formoterol must be attributed to factors other than metabolism. It is noted that (R,R)-formoterol is the pharmacologically active form. Administration of racemic formoterol to the isolated lungs increased spirometric values. The lungs remained stable through the 2-hr perfusion time without marked signs of deterioration.

2.6.4.5 Metabolism

See attached reviews of studies conducted with formoterol under IND — See NDA 20-441 for studies conducted with budesonide.

Metabolism of R,R-Formoterol. Identification of Metabolites Formed in Liver Microsomes from Different Species, and In Vivo in the Mouse (Study 843-RD-0370).

Methods: Metabolism of (R,R)-formoterol was examined in vitro with liver microsomes prepared from several species and in vivo with male CD-1 mice. In vitro studies were conducted with liver microsomes prepared from male NMRI mice, male Sprague-Dawley rats, male New Zealand White rabbits, male beagle dogs as well as pooled human liver microsomes from one man and one woman. Both in vitro and in vivo metabolism studies were conducted using (R,R)-formoterol mixed with either $^2\text{H}_4$ -(R,R)-formoterol or ^3H -(R,R)-formoterol. Mice received an intravenous dose at 1.3 $\mu\text{mol/kg}$, were placed in metabolic cages for 24 hr, and urine was collected in two 12-hr periods. Metabolites were identified using a liquid chromatography system with an absorbance detector and a radioactivity detector. Structures of metabolites were determined using a liquid chromatography system with a mass spectrometer.

Results:

In vitro metabolism with liver microsomes: Metabolic activity was highest with rat liver microsomes where only 5% of formoterol remained unchanged. Rabbit and mouse microsomes also produced significant biotransformation of formoterol. Dog and human liver microsomes displayed the lowest metabolic activity. Two metabolites, formoterol O-demethylated at the 4-methoxyphenyl position (designated as Met1 or D2536) and formoterol glucuronide, were observed in all species. In rat, mouse, and rabbit, two glucuronides of D2536 (designated as Met1G1 and Met1G2) were also observed. In preliminary studies conducted in the absence of UDPGA, metabolites, formoterol glucuronide, Met1G1 and Met1G2, were not found, providing evidence that these metabolites were glucuronides. In mouse, rabbit, dog, and human, metabolite, Met2 (designated as D2537), a formoterol hydrolysis product (i.e., desformyl formoterol) was also observed. Three metabolites of low abundance were observed in various species. Low levels of Met4 were observed in rat, mouse, dog, and man. Low levels of Met4G/Met5G2 were observed in all species. Low levels of Met3 (intact methoxy group)/Met5G1 were observed in rat, dog, and man.

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Retention times (min:sec) of metabolites and reference compounds in LC systems 1 and 2, their molecular mass, and relative amounts of metabolites in incubations with liver microsomes from different species.

Sheet 4

Compound	Retention time in LC system 1	Retention time in LC system 2	Molecular mass	Radioactivity / % ^a				
				Rat	Mouse	Rabbit	Dog	Man
Met1G1	7:30	5:54	506	10*	5.5*	0.3*	-	-
Met1G2	9:30	6:56	506	5.5*	1.3*	1.3*	-	-
Met1	21	9:35	330	0.3*	1.0*	15*	0.8*	1.6*
D2536	21	9:35	330					
FG	26	10:36	520	62*	2.6*	21*	0.8*	0.2*
Met2	37	12:14	316	-	0.3	4.5*	5.9*	*
D2537	37	12:14	316					
Formoterol	40	12:37	344	4.7*	58*	47*	78*	91*
Met5G1	42-43	13:19	486	*	*	*	*	*
Met3		13:38	342	1.9	-	-	4.0	0.6
Met5G2	44-46	14:05	486	1.8	0.8	1.1	1.0	0.3
Met4G		15:25	500				*	
Met4	47	17:35	324	0.7	1.5	-	1.8*	0.9

- a) The metabolite amounts are presented as the percentage of radioactivity in the radiochromatogram obtained from each species with LC system 1.
- *) Asterisks indicate all cases where the presence of the compound was verified by MS (full scan data showing isotope doublets, and by daughter and/or parent ion experiments).
-) Not detected.

In Vivo Metabolism with Male Mice: The metabolite pattern in urine was comparable to that obtained with liver microsomal incubations *in vitro*. A total of 6 radioactive peaks were observed. Five peaks corresponded with metabolites, Met1G1, Met1G2, Met1, FG, and Met2. The five peaks constituted 6.3, 1.0, 7.9, 43, and 0.8% of the radioactivity in urine, respectively. Unchanged formoterol constituted about 34% of the radioactivity in urine. The sixth peak was not identified.

Metabolism of R,R- and S,S-Formoterol in Liver Microsomes from Different Species (Study 843-RD-0360).

Methods: Metabolism of R,R- and S,S-formoterol were examined after incubation of 0.01 and 1.0 $\mu\text{mole/L}$ of ^3H -R,R-formoterol or ^3H -S,S-formoterol in liver microsomes prepared from male NMRI mice, male Sprague-Dawley rats, New Zealand White rabbits, Beagle dogs, and frozen specimens of six human livers. Metabolism of R,R-formoterol was also examined in mouse, rat, and rabbit liver post-mitochondrial supernatant to assess if other liver enzymes, apart from microsomal enzymes, were

involved in metabolism. A HPLC with radiochromatographic detector was used to detect and measure metabolites.

Results:

The metabolite pattern of R,R-formoterol and S,S-formoterol were qualitatively similar for mouse, rat, and rabbit liver microsomes showing direct glucuronidation of formoterol and demethylation at the 4-methoxyphenyl moiety followed by glucuronidation. The most predominant metabolite from mouse, rat, and rabbit liver microsomes was formoterol glucuronide. Other metabolites observed included O-demethylated formoterol (D2536 or Met1), glucuronides of O-demethylated formoterol (Met1G1 and MetG2), and Met2 (desformyl formoterol). Unidentified metabolites were observed for mouse (Unknown 2) and rat (Unknowns 2 and 3).

For dog and human liver microsomes incubated with R,R-formoterol or S,S-formoterol, both demethylation and glucuronidation occurred, but there was a lower capacity for both pathways, particularly for human microsomes, as compared to mouse, rat, and rabbit. The most predominant metabolite from human liver microsomes was O-demethylated formoterol. Other metabolites produced by human liver microsomes included formoterol glucuronide, a glucuronide of O-demethylated formoterol (Met1G2), Met2 (desformyl formoterol), and 5 unidentified compounds (U2, U3, U4, U5, and U6). There were 5 unidentified metabolites from dog liver microsomes (U1, U2, U3, U4, and U5) present at significant levels. Other metabolites observed for dogs included O-demethylated formoterol (D2536 or Met1) and formoterol glucuronide.

Under the conditions of the experiment for substrate at a concentration of 1 $\mu\text{mol/L}$, the rate of liver microsomal biotransformation of R,R-formoterol and S,S-formoterol was as follows: rat (3371 and 3253 pmol/min/mg microsomal protein) > mouse (853 and 2420 pmol/min/mg microsomal protein) > rabbit (823 and 1119 pmol/min/mg microsomal protein) > human (74 and 98 pmol/min/mg microsomal protein). The rate of biotransformation was not determined for dogs. There was a 30-fold difference between rat and human liver microsomes. The rate of liver microsomal biotransformation of S,S-formoterol was faster than R,R-formoterol for mouse, rabbit, and human, although the degree of magnitude varied between species. For rat, the rate of liver microsomal biotransformation of S,S-formoterol and R,R-formoterol was approximately equal. Observed half-lives of R,R-formoterol and S, S-formoterol incubated liver microsomes were as follows: mouse (23-24 and 8.6-8-9 min), rat (5.7-6.5 and 6.0-6.7 min), rabbit (9.6-14 and 7.6-10 min), dog (38-41 and 33-46 min), and human (245-313 and 186-245 min).

Incubation of R,R-formoterol with liver post-mitochondrial supernatant from mouse, rat, and rabbit produced a similar profile of metabolites (i.e., formoterol glucuronide, O-demethylated formoterol, glucuronides of O-demethylated formoterol, and unknown 2) as observed with liver microsomes suggesting that biotransformation was principally performed by liver microsomes. Half-lives for R,R-formoterol in liver post-mitochondrial supernatants from mouse (14-15 min) rat (3.1-3.9 min), and rabbit (6.0-7.1 min) were shorter than observed for liver microsomes.

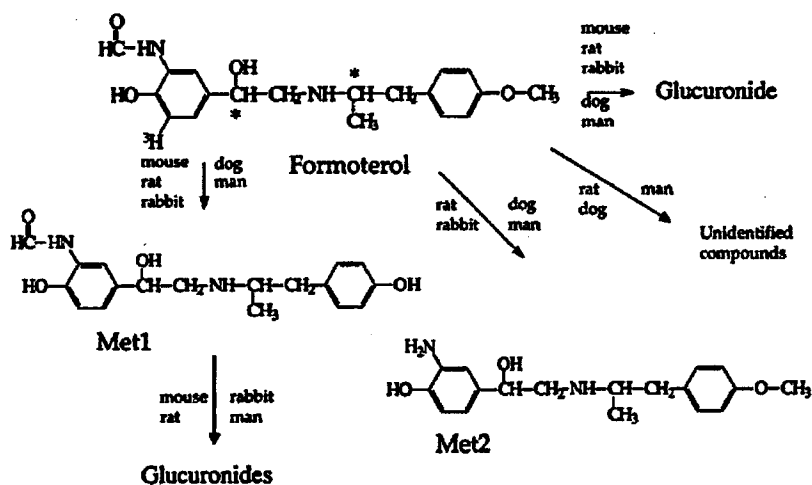


Figure 11. Proposed metabolic pathways for R,R and S,S-formoterol. Asterisks indicate centers of chirality.

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Table 2. Metabolites of R,R and S,S-formoterol formed after incubation of 1.0 $\mu\text{mol/l}$ of formoterol racemate in liver microsomes for 30 minutes.
The values are expressed as percent of initial concentration.

	F	$^3\text{H}_2\text{O}$	Met1G1	Met1G2	Met1	FG	Met2	U1	U2	U3	U4	U5	U6
Mouse													
R,R	50	4.7	8.0	1.4	0.4	32	-	-	-	-	-	-	-
R,R'	95	1.2	-	-	-	-	0.7	-	-	-	-	-	-
S,S	2.2	1.6	3.7	1.7	0.4	89	-	-	-	-	-	-	-
S,S'	97	0.8	-	-	-	-	0.5	-	0.2	-	-	-	-
Rat													
R,R	4.6	17	18	9.4	0.3	43	0.4	-	2.1	1.0	-	-	-
R,R'	93	4.0	-	-	-	-	-	-	1.1	-	-	-	-
S,S	0.8	8.5	5.2	7.4	0.9	73	0.2	-	1.0	-	-	-	-
S,S'	93	4.8	-	-	-	-	-	-	0.6	-	-	-	-
Rabbit													
R,R	47	6.7	0.1	1.3	16	21	1.3	-	-	-	-	-	-
R,R'	77	17	-	-	-	-	-	-	-	-	-	-	-
S,S	22	6.3	1.4	5.2	46	15	-	-	-	-	-	-	-
S,S'	85	11	-	-	-	-	-	-	-	-	-	-	-
Dog													
R,R	80	3.3	-	-	0.6	0.7	-	2.6	2.4	0.9	4.5	0.9	-
R,R'	90	4.7	-	-	-	-	-	-	0.4	-	-	-	-
S,S	71	5.7	-	-	1.8	0.8	-	2.0	7.1	3.0	1.6	3.1	-
S,S'	97	1.0	-	-	-	-	-	-	0.2	-	-	0.5	-
Human													
R,R	78	4.2	-	-	8.1	2.3	0.6	-	1.8	2.3	-	1.8	0.4
R,R'	97	0.8	-	-	-	-	0.6	-	0.9	-	-	-	0.2
S,S	75	3.1	-	0.1	11	3.8	0.9	-	1.7	-	1.7	0.9	0.2
S,S'	96	1.0	-	-	-	-	0.6	-	0.8	-	0.6	0.3	-

¹ Incubation without NADPH and UDPGA

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Table 3. Metabolites of R,R-formoterol formed after incubation of formoterol racemate in liver post-mitochondrial supernatants for 30 minutes.
The values are expressed as percent of initial concentration.

Species	Conc. μmol/l	F	³ H ₂ O	Met1G1	Met1G2	Met1	FG	U2
Mouse	0.01	81	3.5	2.2	-	3.1	5.4	-
	1.0	80	3.5	2.2	0.4	1.4	7.2	-
Rat	0.01	26	13	15	8.8	2.3	27	4.2
	1.0	34	10	12	6.3	2.4	28	3.9
Rabbit	0.01	71	2.2	-	-	5.9	15	-
	1.0	74	2.0	-	-	3.7	15	-

2.6.4.6 Excretion

See attached reviews of studies conducted with formoterol under IND —. See NDA 20-441 for studies conducted with budesonide.

Excretion and Biotransformation of R,R and S,S-Formoterol after Intravenous, Intratracheal, and Oral Administration of Rac-Formoterol to Mice (Study number: 843-RD-0361).

Methods: Excretion and metabolism of ³H-R,R-formoterol or ³H-S,S-formoterol were assessed in male CD-1 mice (3/group) following administration by the intravenous, intratracheal, or oral route as a single dose at 100 μg/kg. Excretion of radioactivity in the urine and feces was measured for 7 days after administration. The metabolite pattern in the urine was assessed for 2 days after administration. Urine was collected in 12-hr intervals up to 48 hr and daily thereafter up to 7 days after dosing. Feces were collected daily for 7 days. Urine and feces were processed for measurement of total radioactivity with a liquid scintillation counter. The metabolite patterns of R,R- and S,S-formoterol in urine were examined by HPLC with a radiochromatographic detector.

Results:

Following administration of ³H-R,R-formoterol or ³H-S,S-formoterol by the intravenous, intratracheal, or oral route, radioactivity was primarily eliminated by urinary excretion (73.5-83.3%). Smaller amounts were eliminated by fecal excretion (14.2-24.5%). Absorption of either ³H-R,R-formoterol or ³H-S,S-formoterol following intratracheal or oral administration was complete. The presence of similar amounts of radioactivity in the feces irrespective of route is suggestive of biliary excretion.

Bioavailability of R,R- and S,S-formoterol following intratracheal and oral administration were 51.8-61.3% and 15.3-15.6%, respectively. There was evidence of a substantial

first pass effect following oral administration. The sponsor suggested that a first pass effect by the lung may have occurred following intratracheal administration.

Following administration of ^3H -R,R-formoterol or ^3H -S,S-formoterol by the intravenous route, 16.9-17.4% of the dose was excreted in the urine unchanged. Approximately 69.8-70.8% of drug-related radioactivity was excreted in the urine during the first 12 hr after dosing. From 0-12 hr postdose, formoterol glucuronide, the predominant metabolite, constituted 56.0-65.1% of total radioactivity in the urine. The O-demethylated formoterol metabolite constituted 4.75-5.33% of total radioactivity in the urine. Glucuronides of O-demethylated formoterol (Met1G1 and Met1G2), Met2, and unknown metabolite X were also present as urinary metabolites.

Following administration of ^3H -R,R-formoterol or ^3H -S,S-formoterol by the intratracheal and oral routes, 8.99-10.3% and 2.63-2.67% of the dose was excreted in the urine unchanged, respectively. Approximately 69.8-77.7% of drug-related radioactivity was excreted in the urine during the first 12 hr after intratracheal or oral dosing. The pattern of urinary metabolites following intratracheal or oral administration was similar to that observed after intravenous administration. Met2 and unknown metabolite X were not observed following oral administration.

Table 10. Excretion of total radioactivity of R,R and S,S-formoterol after administration of (100 $\mu\text{g}/\text{kg}$) 238 nmol/kg *rac*-formoterol to mice.

Enantiomer	Route of admin.	Animal groups	Percent of dose		
			Urine	Faeces	Total
R,R	iv	5	75.7 $\pm$ 10.2	17.1 $\pm$ 7.75	92.9 $\pm$ 3.61
R,R	it	5	81.2 $\pm$ 5.87	15.0 $\pm$ 5.57	96.2 $\pm$ 3.42
R,R	po	5	79.2 $\pm$ 5.66	19.9 $\pm$ 5.58	99.1 $\pm$ 0.71
S,S	iv	5	73.5 $\pm$ 8.99	20.3 $\pm$ 8.53	93.8 $\pm$ 1.74
S,S	it	5	83.3 $\pm$ 5.08	14.2 $\pm$ 3.97	97.6 $\pm$ 1.94
S,S	po	5	73.5 $\pm$ 7.77	24.5 $\pm$ 7.48	98.0 $\pm$ 0.59

Half-lives and bioavailability of R,R-formoterol and S,S-formoterol following intravenous, intratracheal, or oral administration

Route	Half-life, hr		Bioavailability, %	
	R,R-formoterol	S,S-formoterol	R,R-formoterol	S,S-formoterol
Intravenous	7.1	6.2		
Intratracheal	9.0	7.5	51.8	61.3
Oral	5.7	6.4	15.3	15.6

Table 14. Metabolite pattern of R,R and S,S-formoterol in urine after an intravenous dose of 100 µg/kg (238 nmol/kg) *rac*-formoterol to mice. Mean ± SD of five groups.

Sampling period h	Total excretion % of dose	Fraction recovered of total radioactivity in urine (%)								
		Formo- terol	³ H ₂ O	Met1G1	Met1G2	Met1	FG	Met2	X	
<u>R,R-formoterol</u>										
0-12		69.8	23.4	2.44	7.32	1.48	5.33	56.0	0.48	0.88
	SD	9.98	4.79	0.26	0.85	0.24	0.67	5.52	0.07	0.36
12-24		2.55	35.5	14.2	4.46	0.88	4.78	34.3	1.07	0.97
	SD	0.95	17.3	6.25	1.36	0.26	1.59	8.03	0.24	0.31
24-36		0.79	30.6	26.4	4.42	0.93	3.70	27.3	0.84	0.60
	SD	0.33	19.2	11.1	1.21	0.33	1.30	6.27	0.52	0.37
36-48		0.47	22.7	42.5	2.89	0.96	2.46	20.8	0.74	0.42
	SD	0.16	16.7	14.4	0.56	0.44	0.62	2.49	0.31	0.29
<u>S,S-formoterol</u>										
0-12		70.8	23.5	1.33	1.58	1.01	4.75	65.1	0.43	0.35
	SD	8.45	3.90	0.17	0.15	0.16	0.37	4.48	0.08	0.11
12-24		1.10	29.3	7.09	1.29	0.72	4.13	51.8	0.71	0.67
	SD	0.22	16.6	1.75	0.42	0.36	1.13	15.6	0.21	0.29
24-36		0.36	22.5	19.8	1.27	0.95	3.84	42.1	1.01	0.50
	SD	0.10	14.7	4.63	0.57	0.25	1.17	15.1	0.64	0.33
36-48		0.26	16.3	21.0	1.11	0.73	3.38	43.8	0.50	0
	SD	0.21	13.9	8.75	0.72	0.43	0.80	10.6	0.58	

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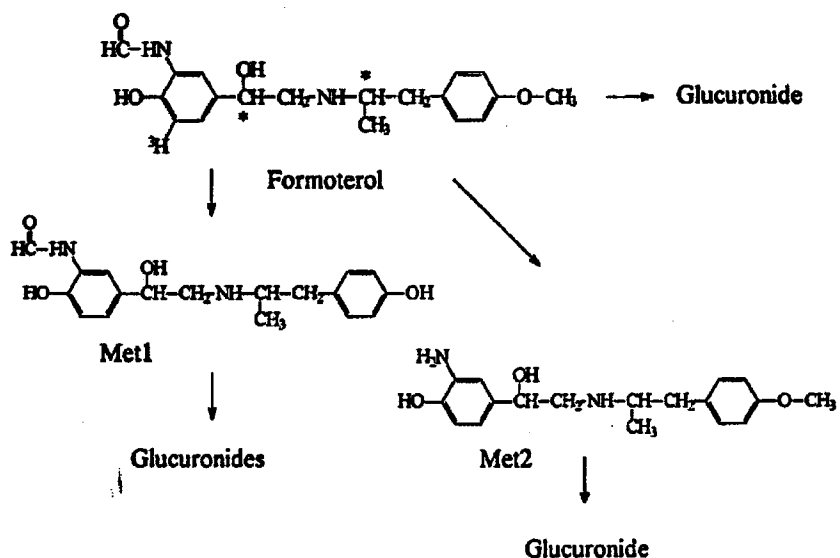


Figure 1. Proposed metabolic pathways for R,R and S,S-formoterol in mice. Asterisks indicate centers of chirality.

2.6.4.7 Pharmacokinetic drug interactions

See attached reviews of studies conducted with formoterol under IND — See NDA 20-441 for studies conducted with budesonide.

2.6.4.8 Other Pharmacokinetic Studies

See attached reviews of studies conducted with formoterol under IND — See NDA 20-441 for studies conducted with budesonide.

2.6.4.9 Discussion and Conclusions

ADME parameters were only determined for monoproducts in nonclinical studies.

Half-lives of formoterol after inhalation exposure range from 2 to 4 hours. Formoterol is extensively metabolized with glucuronide conjugation and O-demethylation as the major pathways in animals and humans. Rats have the highest rate of formoterol metabolism *in vitro*, followed by rabbits, mouse, and dogs while humans have the lowest rate. Formoterol is primarily eliminated by urine excretion with smaller quantities eliminated by biliary excretion. There was evidence of enterohepatic recirculation in rats and dogs. Plasma protein binding of formoterol was approximately 50%. Formoterol readily crosses placenta to reach the fetus and is excreted into the milk.

See NDA 20-441 for ADME studies conducted with budesonide.

2.6.4.10 Tables and figures to include comparative TK summary

Table 5 Pharmacokinetic mean data for formoterol in laboratory animals after single administration.

Species	Dose (mg/kg)	Route of adm.	T _{1/2} (h)	Cl (L/h/kg)	Vd (L/kg)	F (%)	Ref
Mouse	100	it.	9.0 ^a , 7.3 ^b	NC	NC	32 ^a , 61 ^b	843-KD-0361
	100	p.o.	5.7 ^a , 6.4 ^b	NC	NC	15 ^a , 16 ^b	
	100	i.v.	7.1 ^a , 6.2 ^b	NC	NC	NA	
Rat	50	it.	1.1	3.4	5.3	122	70046RID0003-01
	50	p.o.	NC	NC	NC	13 ^c	Sasaki et al 1982

Species	Dose (mg/kg)	Route of adm.	T _{1/2} (h)	Cl (L/h/kg)	Vd (L/kg)	F (%)	Ref
	50	i.v.	1.6, 1.8 ^c	3.9, 3.5 ^c	8.8, 6.9 ^c	NA	70046RID0003-01, Sasaki et al 1982
Dog	10	p.o. ^c	7.2	NC	NC	59	Sasaki et al 1982
	10	i.v. ^c	4.4	0.56	2.5	NA	

a=(R,R) formoterol, b=(S,S)formoterol, c=parameters calculated from Sasaki H et al 1982.
NC=Not calculated, NA=Not applicable

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not provided.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

General Toxicology Studies conducted with Symbicort (Formoterol + Budesonide):

Single Dose:

In a single dose 1- hr inhalation toxicology study, rats were exposed to air or Symbicort (dry powder consisting of 97 mg/kg budesonide+3 mg/kg formoterol) and observed for 14 days after exposure. Deposited doses of budesonide and formoterol were 7.9 and 0.24 mg/kg, respectively. There were no deaths. Body weight gains for male rats treated with Symbicort were decreased to 40% of the air-control. Female rats treated with Symbicort lost 8.3% of initial body weight gain. These effects on body weight were attributed to the action of budesonide. Decreased absolute and relative weights of the spleen, thymus, and adrenal glands were observed for male and female rats treated with Symbicort. These changes were attributed to the pharmacological action of budesonide.

In a single dose nose-inhalation toxicology study, one group of 2 male and 2 female beagle dogs were exposed to Symbicort (dry powder consisting of 737 µg/kg budesonide + 22 µg/kg) for 6.8 min. Deposited doses of budesonide and formoterol were 117 and 3.3 µg/kg, respectively. There were no deaths. Clinical signs after dosing included mucosal redness, body tremor, vomiting, loose stools, increased salivation, nasal catarrh, abdominal respiration, and redness of intact skin. Sinus tachycardia was observed for all dogs from immediately after dosing to 4-hr postdose. Ventricular tachycardia was observed for male #2 at 24- and 48-hr postdose and female #4 at 24-hr postdose. Male #1 was observed with 3 monofocala VES at 24-hr postdose.

Repeat Dose:

In a 13-week nose-only inhalation toxicology study, Wistar rats were treated daily with a Symbicort HFA pMDI formulation (batch P5993 was used in this study; the sponsor provided an incorrect batch number in the initial submission of IND 63,394) containing budesonide, formoterol, PVP K-25, PEG-1000, and HFA-227. Total doses of budesonide and formoterol in the low, mid, and high dose groups were 2 + 0.11, 10 + 0.56, and 51 + 2.9 µg/kg/day, respectively. Using a deposition factor of 0.086 to 0.094, deposited doses for budesonide and formoterol in the low, mid, and high dose groups were 0.2 + 0.010, 0.8 + 0.048, and 4.8 + 0.27 µg/kg/day, respectively. Two additional groups were exposed daily to either an excipient-only HFA pMDI aerosol formulation (vehicle control) or to air only (air control). The NOAEL was identified as the mid dose. Body weight gains for male and female rats in the high dose group were reduced to 67 and 56% of the air-control, respectively. Thymus weights were decreased for male and female rats at the high dose, although, there were no corresponding histopathological findings. There were no target organs of toxicity. Decreases of body weight gains and thymus weights could be attributed to the effects of budesonide. There was no evidence of additive or synergistic toxic effects between formoterol and budesonide. There were no significant differences in findings between the air- and vehicle-control groups. Thus, no toxicity can be attributed to PVP K-25, PEG-1000, and HFA-227 at deposited doses of 0.03, 8.6, and 30300 µg/kg/day, respectively.

In a 13-week nose-only inhalation toxicology study, Wistar rats were treated daily with a Symbicort formulation containing budesonide and formoterol as a micronized dry powder blend. Total target doses of budesonide and formoterol in the low, mid, and high dose groups were 2 + 0.12, 10 + 0.60, and 50 + 3.0 µg/kg/day, respectively. Using a deposition factor of approximately 10%, deposited doses for budesonide and formoterol in the low, mid, and high dose combination groups were 0.30 + 0.018, 1.3 + 0.073, and 4.8 + 0.25 µg/kg/day, respectively. Positive control groups were treated with total target doses of 50 µg/kg/day budesonide alone or 3.0 µg/kg/day formoterol alone (actual deposited doses of 7.2 and 0.24 µg/kg/day, respectively). A control group received air only. The NOAEL was identified as the mid dose combination. Target organs of toxicity were the thymus and spleen. Decreased body weight gains were observed for groups receiving budesonide only and the high dose of budesonide + formoterol. Observed changes can be primarily attributed to the effects of budesonide. The incidence of lymphocytolysis in the thymus was increased for male and female rats in the

budesonide only group and male and female rats in the high dose budesonide + formoterol group. The incidence and magnitude of extramedullary hematopoiesis was decreased for male rats in the budesonide only group and male rats in the high dose budesonide + formoterol group. There was no evidence of additive or synergistic toxic effects between formoterol and budesonide. Systemic exposures to budesonide and formoterol were generally greater with the dry powder formulation as compared to the HFA pMDI formulation.

In a 13-week inhalation toxicity study, beagle dogs were treated daily with a Symbicort HFA pMDI formulation (batch P5993) containing budesonide, formoterol, PVP K-25, PEG-1000, and HFA-227. Target doses of budesonide and formoterol in the low, mid, and high dose groups were $2.0 + 0.11$, $10 + 0.56$, and $50.0 + 2.80$ $\mu\text{g/kg/day}$, respectively. The deposition factor has been revised from the original review to 100% based upon the use of a close-fitting face mask and aerosol delivery tube system to deliver the aerosol directly into the buccal cavity of the dog. The NOAEL was identified as the low dose. Sinus tachycardia (i.e., increased heart rate) was observed in mid and high dose groups on day 1 and during week 2. No changes in heart rate were evident during week 12. Target organs of toxicity were the adrenal cortex, thymus, and bronchial lymph nodes. Observed histopathological changes appear to be primarily attributable to the effects of budesonide. Cortical atrophy of the adrenal cortex was observed for male and female mid and high dose groups. The incidence and severity of thymic atrophy was increased for the male and female mid and high dose groups. The incidence and severity of lymphoid depletion in the bronchial lymph nodes was increased for the male and female high dose groups. There was no evidence of additive or synergistic toxic effects between formoterol and budesonide. There were no significant differences in findings between the air- and vehicle-control groups. Thus, no toxicity can be attributed to PVP K-25, PEG-1000, and HFA-227 at doses of 0.420, 126, and 41835 $\mu\text{g/kg/day}$, respectively (assuming a deposition of 100% due to delivery by oral inhalation comparable to humans).

In a 13-week inhalation toxicity study, beagle dogs were treated daily with a Symbicort formulation containing budesonide and formoterol as a dry micronized powder blend with lactose. Target doses of budesonide and formoterol for the low, mid, and high dose groups were $2.0 + 0.11$, $10.0 + 0.56$, and $50 + 2.8$ $\mu\text{g/kg/day}$, respectively. The deposition factor was revised to 100% from the review of the initial submission of IND 63,994 based upon use of a close-fitting facemask and aerosol delivery tube system to deliver the aerosol directly into the buccal cavity of the dog. Comparator groups were treated with 50 $\mu\text{g/kg/day}$ budesonide alone or 3.0 $\mu\text{g/kg/day}$ formoterol alone. A control group received air only. The NOAEL was identified as the low dose combination for male dogs. Body weight gain was reduced for the male and female dogs that received budesonide only and mid and high doses of budesonide + formoterol. On day 1, elevated heart rates were evident for male and female dogs that received formoterol only or the high dose of budesonide + formoterol. During week 2, elevated heart rates were evident in male and female dogs that received formoterol only and low, mid, and high doses of budesonide + formoterol. No changes in heart rate were evident during week 12. Target organs of toxicity were the thymus, adrenal gland, and spleen, and

toxicities could be primarily attributed to the effects of budesonide. Thymic atrophy was observed for the male and female dogs that received budesonide only, female dogs that received the low dose of budesonide + formoterol, and male and female dogs that received mid and high doses of budesonide + formoterol. Atrophy of the zona fasciculata of the adrenal gland was observed for the male and female dogs that received budesonide only, female dogs that received the low dose of budesonide + formoterol, and male and female dogs that received mid and high doses of budesonide and formoterol. Vacuolation of the zona glomerulosa of the adrenal gland was observed for the male and female dogs that received budesonide only and male dogs that received the high dose of budesonide + formoterol. Lymphoid depletion in the spleen was observed for female dogs that received budesonide and male dogs that received mid and high doses of budesonide + formoterol. There was no evidence of additive or synergistic toxic effects between formoterol and budesonide.

The Symbicort HFA pMDI drug product contains excipients, PVP K-25 and PEG-1000, and the propellant, HFA-227. There are no approved inhalation drug products that contain PVP K-25, PEG-1000, or HFA-227. PVP K25 and PEG-1000 are found in several drug products approved for chronic use that are administered by the oral route. **PEG-1000 has been classified as "generally recognized as safe" (GRAS) by the oral route and is used in food (21 CFR 172.820).** Extensive preclinical toxicology studies have been conducted with HFA-227 by IPACT-II, for which the sponsor has rights of reference. These studies were reviewed under DMF 10378 (See reviews dated October 2, 1996 and January 28, 1997). HFA-227 is considered reasonably safe for inhalation use in the Symbicort HFA pMDI product.

In 13-week inhalation toxicity studies described above, Wistar rats and beagle dogs were treated daily with a Symbicort HFA pMDI formulation (batch P5993) containing budesonide, formoterol, PVP K-25, PEG-1000, and HFA-227. Safety margins for clinical doses of these excipients in Symbicort HFA determined by comparison to doses in these 3-month toxicity studies with rats and dogs are shown in the tables below. Safety margins based upon the 3-month toxicity study with rats are inadequate (see table below). Further, these studies are insufficient in terms of duration to bridge excipients, PVP K-25 and PEG-1000, from the oral to inhalation route. The minimum study duration required is 6-months.

Rat to human dose ratios for clinical doses of excipients, PVP K-25 and PEG-1000, in the Symbicort HFA pMDI drug product based upon comparison to doses of the same excipients in the 3-month inhalation bridging toxicology study with Symbicort in rats.

Compound	Rats		Clinical doses in Symbicort µg/g LW/day	Rat to human dose ratio
	Deposited dose µg/kg/day	Deposited dose µg/g LW/day		
PVP K-25	0.03	0.006	0.0028	2.1
PEG-1000	8.6	1.72	0.8492	2.0

Notes: The deposition factor for rats was approximately 8.6 to 9.4%. Lung weight values for rats and humans used in calculations were 1.5 g and 1000 g, respectively.

Dog to human dose ratios for clinical doses of excipients, PVP K-25 and PEG-1000, in the Symbicort HFA pMDI drug product based upon comparison to doses of the same excipients in the 3-month inhalation bridging toxicology study with Symbicort in dogs.

Compound	Dogs		Clinical doses in Symbicort µg/g LW/day	Dog to human dose ratio
	Deposited dose µg/kg/day	Deposited dose µg/g LW/day		
PVP K-25	0.42	0.038	0.0028	13.6
PEG-1000	126	11.455	0.8492	13.5

Notes: The deposition factor for dogs was 100%. Lung weight values for dogs and humans used in calculations were 110 g and 1000 g, respectively.

To bridge Symbicort excipients, PVP K-25 and PEG-1000, from the oral to the inhalation route, studies conducted with comparable excipients, polyvinylpyrrolidone K-30 (PVP K-30) and polyethylene glycol 600 (PEG-600) were used.

The various pharmaceutical grades of PVPs are defined by the average polymer length, given by molecular weight. PVP K-25 and PVP K-30 have molecular weights of 26000 and 42000 daltons, respectively. K-25 and K-30 both consist of a broad range of polymer sizes with molecular weights from 1000 to 1000000 (1 million) with K-25 containing slightly less of the high MW material than K-30. Therefore, the only difference between PVP K-25 and PVP K-30 is a small shift in the average polymer length.

Polyethylene glycols are polymers of the general formula, $H(OCH_2CH_2)_nOH$, where n is greater than 4. PEG 600 has an average n of 12.5-13.9 with a MW range of 570-630. PEG 1000 is estimated to have an average n of 20.8-23.2 with a MW range of 950-1050.

Differences between PVP K-25 and PVP K-30 as well as PEG-600 and PEG-1000 were expected to have minimal or no toxicological impact.

Specifically, toxicity studies conducted with excipients, PVP K-30 and PEG-600, in a formulation of _____, a D₂/B₂ agonist, studied under IND _____ (AstraZeneca) were used to bridge Symbicort excipients, PVP K-25 and PEG-1000, from the oral to inhalation route.

Studies with _____ were provided in the submission as follows: 6-month inhalation study in rats with a 3-month interim sacrifice, 6- and 12-month inhalation studies in dogs, and 24-month inhalation carcinogenicity study in rats. All studies were conducted with the _____ HFA-227 metered dose inhaler (MDI) formulation, containing _____ PVP K-30, PEG 600, and HFA-227. Based upon reviews of the 6-month study with rats, 6- and 12-month studies with dogs, and the 2-year inhalation carcinogenicity study with rats under IND _____ (see reviews dated September 17, 1998, December 2, 1998, February 21, 2001, and July 31, 2003), no apparent local or systemic toxic effects attributable to PVP K-30 and PEG 600 and HFA-227 were observed.

Accumulation of PVP K-30 in the lungs was assessed in the 6-month toxicology study with rats and 2-year inhalation carcinogenicity study with rats. In the 6-month toxicology study with rats, no accumulation of PVP K-30 was evident in vehicle-control animals after treatment for 3 months; however, after 6-months of treatment, PVP K-30 was detected in lungs from 3 of 6 rats with levels ranging from 26 to 37 µg/g of lung tissue. In the inhalation carcinogenicity study, after 2 years of treatment with the vehicle, PVP K-30 was detected in the lung tissue. No or minimal accumulation of PVP K-30 was observed in the lungs of rats treated with _____ suggesting the test article may have altered the distribution and/or elimination of PVP K-30. There was no evidence of irritation or microscopic changes in the respiratory tract associated with accumulation of PVP K-30.

Inhaled dose (µg/kg/day) and deposited doses (µg/g lung weight/day) of excipients, PVP K-30 and PEG-600, in inhalation toxicology studies with the vehicle-control and high dose groups.

Excipient	6-month rat study		24-month rat study		6-month dog study		12-month dog study	
	Inhaled dose µg/kg	Deposited dose µg/g LW	Inhaled dose µg/kg	Deposited dose µg/g LW	Inhaled dose µg/kg	Deposited dose µg/g LW	Inhaled dose µg/kg	Deposited dose µg/g LW
PVP K-25	18.4	0.36	110	1.12	2.9	0.26	1.9	0.17
PEG-1000	2209.6	44.2	13000	131.9	344.2	31.3	222.2	20.2

a. The deposition factor for rats was 10%.

b. A close-fitting face mask and aerosol delivery mouth tube system was used to deliver aerosols directly to the buccal cavity of the dog. Deposition factors for dogs in the original reviews have been revised to 100%.

Rat to human and dog to human dose ratios for clinical doses of excipients, PVP K-25 and PEG-1000, in the Symbicort HFA pMDI drug product based upon comparison to doses of similar excipients, povidone K-30 and PEG-600, in vehicle-control groups of studies

Clinical Doses of Excipients, PVP K-25 and PEG-1000 In Symbicort HFA		Dose ratios based upon nonclinical studies with PVP K-30 and PEG 600			
		6-month	24-month	6-month	12-month
Excipients	Clinical doses in Symbicort, µg/g LW/day	Rat to Human ratio	Rat to Human ratio	Dog to Human ratio	Dog to Human ratio
Povidone K25	0.0028	128.6	400	94.2	61.7
PEG 1000	0.8492	52	155.4	36.8	23.8

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General Toxicology Studies conducted with Formoterol:**Single Dose:**

Single dose acute toxicity studies with formoterol were conducted in mice and rats. Clinical signs of acute toxicity included tachycardia, decreased motor activity, labored breathing, and salivation.

Acute toxicity studies with formoterol [Maximum non-lethal dose (NLD) and minimum lethal dose (LD)]

Species #/sex/dose	Route	Doses mg/kg	Males, mg/kg		Females, mg/kg	
			Maximum NLD	Minimum LD	Maximum NLD	Minimum LD
CD-1 Mice 5/sex/dose	Inhalation	36, 100, and 276 (Inhaled)	>276	>276	>276	>276
Wistar rats 5/sex/dose	Inhalation	40, 88, and 199 (Inhaled)	<40	40	<40	40
NMRI mice 5/sex/dose	Oral	2000	>2000	>2000	>2000	>2000
S-D rats (6-12 days old) 6/sex/dose	Oral	600, 1200, 2400, and 4800 mg/kg	600	1200	600	1200
S-D rats 5/sex/dose	Oral	210, 1500, and 2000 mg/kg	1500	2000	2000	2000

Repeat Dose:

Repeat dose general toxicology studies with formoterol were conducted with rats and dogs. Studies with rats included a 3-month inhalation study, two 3-month oral studies starting with 16-day old rats, a 3-month inhalation study with a HFA pMDI formulation, and a 6-month inhalation study. Studies with dogs included a 1-month inhalation study, 1-month oral study, and 12-month oral study.

In a 3-month inhalation toxicology with rats, formoterol was administered at doses of 0, 82, 260, and 870 $\mu\text{g/kg/day}$. Deposited doses were 0, 9, 22, and 90 $\mu\text{g/kg/day}$, respectively. One male in the high dose group died on day 21 and necropsy findings consisted of cardiac and renal congestion and slight pneumonitis. Dose-dependent decreases of plasma glucose were observed for both males and females. Increased absolute and relative heart weights (hypertrophy) were observed in female treatment groups. The same trend occurred in males, although it was less pronounced. Granulating myocardial scars were observed in control males (1/10) and high dose males (2/10). The relationship of this finding to treatment was unclear based on the low incidence; however, treatment-related effects on the heart have been observed in other studies. The NOAEL was identified as the mid dose based upon mortality and histopathological findings in the heart at the high dose.

In a 3-month oral toxicology study with rats (10/sex/group), 16 days old at the start of treatment, formoterol was administered at doses of 0, 0.2, 0.8, and 3 mg/kg/day. Gross