

estimate of systemic exposure of formoterol in the drinking water study in rats.

Table 6. Pharmacokinetics of Oral Gavage Formoterol in Rats (Study B4/1991)¹

Dose (mg/kg)	AUC 0-48 h (nmol.h/L)			Cmax (nmol/L)		
	Male	Female	Mean	Male	Female	Mean
12.5	268 ± 46	317 ± 49	293	53.2 ± 22.5	69.6 ± 41.5	61.4
25	560 ± 90	814 ± 214	687	126 ± 19	329 ± 197	228
50	1420 ± 15	4857 ± 2779	3138	422 ± 277	1318 ± 132	870

1. Extracted from vol. 64, p 185 of the original submission.

A re-evaluation of AUCs in rats reveals that the systemic exposure in the 2-year dietary carcinogenicity study may be a reasonably good indicator of the systemic exposure in the drinking water study. However, based on the observed toxicity, exposure per mg/kg may have been somewhat greater in the drinking water study (see below). Nonetheless, it appears that all treated rats in the drinking water study would likely have plasma drug exposures at least 25 fold greater than human exposure.

2. Tumor Data and AUCs

Table 7 presents the tumor incidence and plasma formoterol levels, when available, in the 2-year carcinogenicity studies in rats. Because the plasma drug levels were not monitored in the drinking water study and AUC data were not generated in the dietary study, a direct comparison of AUC values in relation to tumor rate between studies is not possible. Nonetheless, at similar nominal doses, the drinking water study showed higher incidences of tumors than the dietary study. For example, the incidence of uterine leiomyomas was 4% (3/69) for the 20 mg/kg/day group in the dietary study and 28% for the 15 mg/kg/day group in the drinking water study. Although AUC values cannot be directly compared in these studies, the evaluation of overall toxicity shows that all doses in the drinking water study exceeded the maximum tolerated dose (MTD, Appendix 1). Thus, the increase in the tumor incidence in the drinking water study probably is a reflection of increased systemic exposure. It is possible, however, that other factors were also involved. For example, the difference in animal strain could have played a role. Rat strains were Sprague-Dawley in the drinking water study and Tif:RAIf(SPF) in the dietary study.

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Table 7. Tumor Incidence in the Rat Studies

Study	Strain	Dose (mg/kg/day)	C _{max} (nmol/L)	AUC (nmol.h/L)	Uterine/ovary leiomyomas, ♀	Thyroid tumors, ♂	Mammary Adenoma, ♀
Diet	Tiff	0	-	-	0/70		
		0.5	-	-	0/70		
		2	7.2	-	1/69		
		5	11.2	-	1/69		
		20	19.9	-	3/69		
Drinking water	SD	0	ND ²	-	1/48	8/50	4/50
		15	ND	ND	14/50 ^{*.1}	3/50 ¹	7/49 ¹
		32	ND	ND	14/50 ^{*.1}	12/50 ¹	12/50 ^{*.1}
		64	ND	ND	16/50 ^{*.1}	16/49 ^{*.1}	12/50 ^{*.1}

1. Exceeding MTD

2. ND = Not determined.

*. Statistically significantly different from the control (P < 0.05).

3. Conclusion for the AUC data and Tumor incidence

No AUC data for the drinking water study in rats is available. An indirect comparison of the drinking water study with the dietary study indicates that animals in the former were exposed to formoterol at higher levels than animals in the latter because the latter study exceeded the MTD at all dose levels. No direct comparison of the two studies with regard to AUC and tumor incidence is possible because of the lack of data. Nonetheless, both studies apparently have achieved systemic exposure in excess of 25-fold human exposure.

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OVERALL SUMMARY

The re-evaluation of the AUC data and tumor incidence in mice and rats has been completed. No precise AUC data were available in any of the studies. However, plasma levels of reasonable quality were available in the dietary studies in both mice and rats. Because of lack of monitoring of the plasma drug levels during the study, the AUC and plasma level data previously reported for the drinking water studies in mice or rats were actually extrapolated from studies with different modes of administration, durations and doses. The values may have overestimated the actual systemic exposure in the drinking water studies in both mice and rats. Despite the shortcomings, there is sufficient data to be reasonably confident that animals in the drinking water studies were exposed to formoterol in excess of 25-fold human exposure. Lastly, a comparison of AUC data with tumor incidence between studies in rats is not possible or appropriate because of the lack of AUC data.

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cc: NDA 20-831/570 Divisional File
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Appendix 3

PHARMACOKINETICS AND TOXICOKINETICS¹ (Drafted by Tracey Zoetis, February 16, 2000):

The absorption, distribution, metabolism, and elimination properties of Formoterol fumarate were studied in rats, mice, and dogs using radiolabeled and non-radiolabeled analytical methods. Analytical methods evolved over time to quantify unchanged Formoterol fumarate in plasma and urine collected from animals. Results were obtained using

Pharmacokinetic Parameters

Plasma AUC of unchanged Formoterol fumarate in rats accounted for approximately 8% of the total ¹⁴C after an intravenous dose and about 1% after oral administration. Plasma clearance of Formoterol fumarate occurred after metabolism and was similar between rats ($t_{1/2} =$ _____), and mice ($t_{1/2} = 0.7$ h) (DM 1/1991, _____ F-1-4-5, Sasaki et al. 1983).

Following intravenous administration, plasma levels of unchanged Formoterol fumarate decreased in a biphasic manner with elimination half lives of 1.4 hr for rats and 2.9 hours for dogs (_____ F-1-4-5). In rats, the volume distribution was approximately 9.2 L/kg, total plasma clearance was $6.3 \text{ L h}^{-1} \text{ kg}^{-1}$, and the elimination half life ($t_{1/2}$) was 1.4 hours (_____ F-1-4-5).

Oral dosing yielded lower plasma concentrations for the rat (2.3 to 5.5% oral bioavailability) when compared with the dog (40 to 62 % oral bioavailability) (_____ F-1-4-5). The Sponsor attributed the response in the rat to first pass metabolism and enterohepatic circulation (_____ F-1-4-1). The absolute oral bioavailability of Formoterol fumarate was estimated to be between 10 and 15% in the mouse. The Sponsor postulated that the low bioavailability was attributed to extensive first pass glucuronidation.

Mean pharmacokinetic values obtained at study termination from various species and routes of administration are summarized in the following table.

Mean Pharmacokinetics of Formoterol fumarate									
Species n/sex/group	N/sex/ group	Duration (days)	Dose (mg/kg)	Route	Timepoint (h)	AUC	C _{max}	t _{1/2} (h)	Reference (vol:page)
Mouse	2/♂	1	6	IV	0 - 6	30.8 $\mu\text{mol}\cdot\text{h/L}$		1.0	DM 1/1991 (64:277)
			6	Oral	0 - 4	33.48 $\mu\text{mol}\cdot\text{h/L}$			
			60	Oral	0 - 6	315.5 $\mu\text{mol}\cdot\text{h/L}$			
Rat	3/sex	1	12.5	IV	0.1 - 72	60.25 $\mu\text{mol}\cdot\text{h/L}$			DM 2/1991 (65:32)
			12.5	Oral	0 - 72	51.1 $\mu\text{mol}\cdot\text{h/L}$			
			25	Oral	0 - 72	95.8 $\mu\text{mol}\cdot\text{h/L}$			
			50	Oral	0 - 72	246.5 $\mu\text{mol}\cdot\text{h/L}$			
Rat	3/sex	1	12.5	Oral	0 - 48	292.5 nmol·h/L	61.4 nmol/L		B 4 1991 (64:183)

8. Email message from Mrs. Tracey Zoetis to Dr. Luqi Pei dated February 16, 2000

Mean Pharmacokinetics of Formoterol fumarate

Species n/sex/group	N/sex/ group	Duration (days)	Dose (mg/kg)	Route	Timepoint (h)	AUC	C _{max}	t _{1/2} (h)	Reference (vol:page)
			25	Oral	0 - 48	687.2	227.6		
			50	Oral	0 - 48	1420.49	864.3		
						nmol·h/L	nmol/L		
						nmol·h/L	nmol/L		
Rat	3/♂	1	2	IV	0 - 24	319.2 ng·h/L		1.4	F-1-4-5 (64:80)
		1	2	Oral	0 - 24	7.31 ng·h/L	0.82	5.5	
		1	5	Oral	0 - 24	19.67 ng·h/L	2.16	3.5	
		1	10	Oral	0 - 24	92.10 ng·h/L	8.47	2.8	
Rat	Not stated	1	50 µg/kg	Oral	0 - 24			1.7	Sasaki et al. 1982 (64:70)
Rat	3/♂	94	12.5	Oral ¹⁰	0 - 48	687.9	96.3		B 8/1991 (65:1)
			25	Oral	0 - 48	1658.2	319.2		
			50	Oral	0 - 48	2659.4	707.3		
						nmol·h/L			
						nmol·h/L			
	5/sex	94	12.5	Oral ¹¹	0 - 48	419.5	133		R 16/1992 (65:78)
			25			1075.0	494		
			50			2415.0	1350		
						nmol·h/L			
						nmol·h/L			
Rat	10/♂	~365	.05	Inhal- ation	0 - 8	10.25	6.72		1996/061 (67:22)
			.08			7.51 nmol·h/L	4.38		
			.37			78.03	56.9		
						nmol·h/L			
Rat	10/♀		.08			8.21 nmol·h/L	4.92		
			.11			8.22 nmol·h/L	5.56		
			.54			68.45	43.34		
						nmol·h/L			

9 Data from males only. Data from females were unreliable due to extreme variability (AUC = _____ nmol·h/L) and low sample size (n=2).

10 Three month drinking water study followed by a single gavage dose prior to sample collection.

11 Three month drinking water study followed by a single gavage dose prior to sample collection.

Mean Pharmacokinetics of Formoterol fumarate

Species n/sex/group	N/sex/ group	Duration (days)	Dose (mg/kg)	Route	Timepoint (h)	AUC	Cmax	t _{1/2} (h)	Reference (vol:page)
Dog	3/♂	1	0.02	IV	0 - 10	13.9 ng·h/L		2.9	F-1-4-5 (64:80)
		1	0.02	Oral	0 - 10	6.26 ng·h/L	2.92	2.3	
		1	0.05	Oral	0 - 10	13.75 ng·h/L	4.43	3.5	
		1	0.10	Oral	0 - 10	42.72 ng·h/L	12.09	3.4	
Dog	4/sex	~365	.006	Inhalation	0 - 24	3.5 - 65.9 nmol·h/L	0.6 - 7.1		F) 1995/004 (67:184)
			.018		0 - 24	10.2 - 365 nmol·h/L	1.2 - 48.9		

The results of one early study suggested differences in pharmacokinetic parameters between male and females rats. However the study is invalid due to unreliable analytical methods, low sample size (n=2), excessive within-group variability, and lack of confirmation of results upon repeat analysis (B4/1991, DM 2/1991, 1009/05, 1994/063).

Absorption

AUC values for radioactive indicators of unchanged Formoterol fumarate in the mouse were 33.48 and 315.5 $\mu\text{mol}\cdot\text{l}^{-1}\cdot\text{hr}$ after a single oral dose of 6 and 60 mg/kg, respectively. The corresponding direct O-glucuronide levels were 28.6 and 266.3 $\mu\text{mol/l}$, for these groups of mice, respectively (DM 1/1991).

In the rat, oral absorption was measured using radio-labeled Formoterol fumarate after a single dose of 50 $\mu\text{g/kg}$ (F-1-4-1). ^3H -Formoterol fumarate was primarily absorbed from the small intestine. Enterohepatic circulation was also demonstrated in this study by administering bile collected from animals dosed with ^3H -Formoterol fumarate to naïve animals. In this case, 69% of the administered dose was absorbed.

Evidence of Absorption in Pivotal Toxicity Studies

Low concentrations of Formoterol fumarate in plasma often could not be detected or measured from animals used in pivotal toxicity studies. The following table summarizes the available information regarding plasma levels of Formoterol fumarate in at the termination of pivotal toxicity studies.

Plasma Concentrations of Formoterol fumarate in Pivotal Toxicity Studies					
Study	Species	Dosage Form	Dose mg/kg	Concentration (range or mean)	Reference
3-month Rangefinding	Mouse	Dietary	140	2.2 - 3.8 pmol/L	B 106/1990
			400	4.6 - 8.6 pmol/L	
			1400	7.2 - 39.3 pmol/L	

Plasma Concentrations of Formoterol fumarate in Pivotal Toxicity Studies					
Study	Species	Dosage Form	Dose mg/kg	Concentration (range or mean)	Reference
24-month Carcinogenicity	Mouse	Dietary	2	Not detected	43/1993
			5	Below limits	
			20	3.2 nmol/L	
			50	6.3 nmol/L ¹²	
3-month Rangefinding	Mouse	Drinking Water	65	15.8 nmol/L	B 23/1992
			120	29.6 nmol/L	
			180	9.0 nmol/L	
28-day Palatability	Rat	Dietary	0.4	Not detected	B 84/1990
			1.8	1.1 pmol/g	
			4.5	1.2 pmol/g	
			18	5.6 pmol/g	
3-month Rangefinding	Rat	Drinking Water	8.5	1.8 nmol/L	B 8/1991
			18.6	4.5 nmol/L	
			36.1	11.8 nmol/L	
3-month Rangefinding	Rat	Dietary	0.5	Not measured	B 68/1991
			2	Not measured	
			5	Not measured	
			20	6.1 nmol/L	
24-month Carcinogenicity	Rat	Dietary	0.5	Not measured	B 14/1992
			2	7.4 nmol/L	
			5	11.2 nmol/L	
			20	19.9 nmol/L	
Acute Inhalation	Rat	Dry Powder	.84	Not measured	49/1993
			1.6	Not measured	
			1.8	78 nmol/L	
28-day Inhalation	Rat	Dry Powder	0.16	Not measured	20/1993
			0.5	Not measured	
			1.15	26.9 nmol/L	
13-week Inhalation	Dog	Dry Powder	.003	Not measured	B 65/1991
			.014	Not measured	
			.055	3.5 nmol/L	

Distribution

The distribution of radio-labeled Formoterol fumarate was studied using both _____ techniques in mice (DM 1/1991) and rats (F-1-4-1). These studies indicate the accumulation of Formoterol fumarate does not occur at a level or a rate that would pose a safety concern.

¹² Excludes an outlier of 77.2 nmol/L.

Following a *single oral dose* of 0.5 or 5 mg ³H-Formoterol fumarate/kg in 3 rats/group, concentrations of the test material were found in various tissues and organs within 30 minutes of dosing (— F-1-4-1). Concentrations were highest in the kidney, liver, lung, plasma, and whole blood. Concentrations of ³H-Formoterol fumarate increased in various tissues for the first 6 hours and decreased dramatically by the sample collection at 24 hours.

Following *repeated oral administration* of 0.05 mg ³H-Formoterol fumarate/kg/day for 21 days in rats, the concentrations of radioactivity in tissues gradually increased until Day 14 and remained constant thereafter (Sasaki, et al. 1983).

Protein Binding

The binding of Formoterol fumarate to plasma protein was assessed *in vitro* using rat, dog, and human plasma (— F-1-1-6), and *in vivo* in dogs after oral dosing with 0.1 mg Formoterol fumarate/kg. *In vitro* binding was 50 to 65% for all species and independent of the concentration tested (0.1 - 100 ng/ml). *In vivo* binding in the dog ranged from 44 to 60% and was constant over the 10-hour post-dose sample collection period. Formoterol fumarate primarily bound to albumin with only negligible amounts bound to α -1-acid glycoprotein or γ -globulin (— R 41/1991).

Metabolism

Data from rat and dog studies demonstrate that Formoterol fumarate is metabolized extensively after oral administration before reaching systemic circulation (Sasaki et al. 1983). The primary metabolite is a direct phenolic O-glucuronide (Ia) and can be found in mice, rats, dogs, and humans. Other metabolites also occur via glucuronidation. The following diagram illustrates the biotransformation pathway of Formoterol fumarate. A table comparing the metabolic profiles of several species is also presented.



Species Comparison of the Metabolic Profiles of Formoterol fumarate			
Test Model	Major Metabolite (% of dose)	Other Metabolites	Reference
<i>In vitro Hepatocytes</i>			
Rat	Ia ¹³	IIa and IIb ¹⁴	DM(EU) 28/1996
Guinea Pig	Ia		DM(EU) 28/1996
Dog	Ia		DM(EU) 28/1996
Marmoset	Ia	Ib ¹⁵	DM(EU) 28/1996
<i>In vivo Models</i>			
Mouse (oral)	Ia (~70% in urine)		DM 1/1991
Rat (oral)	Ia (95% in bile) I ¹⁶ (5% in urine)		Sasaki et al. 1982
Dog (oral)	Ia (~80% in bile) I (~20% in urine)		Sasaki et al. 1982
Human (oral)	I (6% in urine) Ia (24% in urine) Ib (5% in urine) II (<1% in urine) IIa + IIb (15% in urine)		B 46/87

Transpulmonary transport and metabolism

In vitro models using perfused rat lung and radio-labeled Formoterol fumarate indicate that the drug is rapidly transported to the blood from the airway and is not metabolized by the lung (93/02/C/2R).

Elimination

Elimination of Formoterol fumarate and its metabolites is rapid and complete. It occurs to a great extent within the first 24 hours following dosing and is complete within 4 to 5 days (Sasaki et al. 1982, — F-1-4-5, — F-1-4-3, DM 1/1991, DM 2/1991). In rats and dogs, excretion occurs through hepatic metabolism and most of the radio-labeled Formoterol fumarate is recovered from the bile and/or feces (DM 2/1991, — F-1-4-3). In mice, renal excretion is evidenced by a relatively high percentage of radio-labeled Formoterol fumarate recovered in urine (DM 1/1991). With repeated dosing in dogs, plasma levels of Formoterol fumarate and urinary excretion concentrations increase during the first 2 days after the initiation of dosing and remain constant thereafter — F-1-4-7). Results of excretion studies in rats, dogs, and mice are summarized in the following table.

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- 13 Direct phenolic O-glucuronide.
14 Phenolic glucuronides of the O-desmethyl metabolite.
15 Direct aliphatic O-glucuronide.
16 Unchanged Formoterol fumarate.

Mean Cumulative Excretion of Radio-labeled Formoterol fumarate					
Dose	% in Bile	% in Urine	% in Feces	% Total	Reference
Rats					
5 mg/kg	72.11	21.12	6.37	99.60	DM 2/1991
20 mg/kg	75.22	21.08	3.57	99.87	
50 mg/kg	70.76	19.96	5.00	94.45	
Dogs					
10 µg/kg	-	36.8	52.1	88.9	F-1-4-3
100 µg/kg	-	36.9	52.0	88.9	
Mice					
6 mg/kg	-	64.22	33.6	97.82	DM 1/1991
60 mg/kg	-	75.88	23.80	99.68	

Conclusions Regarding Pharmacokinetics and Toxicokinetics

Formoterol fumarate is absorbed after first pass glucuronidation. Oral absorption and bioavailability vary between species as a result of the extent of first pass metabolism and enterohepatic circulation. In rats, glucuronide metabolites are excreted in bile and Formoterol fumarate is then re-absorbed in the small intestine. Plasma or urine levels of accumulated Formoterol fumarate do not occur at concentrations or rates that would pose a safety concern during prolonged exposure. Plasma protein binding was similar between rat, dog, and human plasma and ranged from 50 to 65%. Biotransformation products occur as a result of O-glucuronidation, with direct phenolic glucuronide as a primary metabolite in mice, rats, dogs, and humans. Elimination of Formoterol fumarate appears to be rapid and complete within 4 to 5 days of dosing. In rats, most radio-labeled Formoterol fumarate is recovered in the bile and feces. In mice, renal excretion is evidenced by relatively high levels of radio-labeled Formoterol fumarate recovered in urine.

The low concentration of Formoterol fumarate tested presented technical difficulties in the analytical methodology. Nevertheless, exposure to and disposition of Formoterol fumarate was demonstrated in animal studies. The Sponsor reported that exposure to Formoterol fumarate in animal studies, based on plasma AUC levels, was 28 to 9100 times higher than that predicted for humans following a maximum daily dose of 48 µg/day.

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REVIEW AND EVALUATION OF PAHRAMCOLOGY/TOXICOLGY DATA
DIVISION OF PULMONARY DRUG PRODUCTS

BACKGROUND INFORMATION:

Reviewer Name: Tracey Zoetis, M.S.
Division Name: Division of Pulmonary Drug Products
HFD No. HFD-570
Review Completion Date: June 1, 1998
NDA No. 20-831
Related INDs: _____
Serial Number: 000
Submission Date: June 26, 1997
Information to Communicate to Sponsor: See Recommendations
Sponsor or Agent: Novartis Pharmaceuticals Corporation
59 Route 10
Hanover, NJ 07936
Manufacturer: DMF # _____

DMF# _____

DRUG

Code Name: Formoterol fumarate
Generic Name: Not applicable
Trade Name: Foradil®
Chemical Name: \pm 2-hydroxy-5-[(1RS)-1-hydroxy-2-[[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate
CAS Registry No.: 45229-80-7
Molecular Formula: $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$
Molecular Weight: 840.9
Chemical Structural Formula: 

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Drug Class: beta-2-andrenoceptor agonist

The cardiotoxicity of beta agonists appears to be a consequence of their pharmacologic activity. The effect on the heart is first seen as an increased heart rate, which could be a consequence of a direct interaction with beta receptors in the heart, but is most probably the result of reflex tachycardia, secondary to beta-2-mediated vasodilation and hypotension. Once this effect reaches excessive levels, ischemic changes occur since the oxygen supply can no longer be maintained. This results in focal necrosis and subsequent fibrosis in the anaerobic regions. The papillary muscle of the left ventricle appears to be particularly sensitive. If the effects on the heart result from pharmacologic activity of the agents it follows that their potency as cardiotoxins will be related to their potency as beta agonists. This was confirmed in a direct experimental comparison in dogs in which formoterol was found to be 10 times more active than _____ at inducing increased heart rate and cardiac lesions, which is keeping with the potency of these two compounds as beta agonist. If excessive tachycardia is a prerequisite for cardiotoxicity, no effects are to be expected at doses which do not increase the heart rate. Clinical experience in humans shows that doses below 72 $\mu\text{g}/\text{day}$ do not effect heart rate. Thus, the proposed _____ $\mu\text{g}/\text{day}$ maximum human dose appears to be within an acceptable safety margin for cardiotoxicity.

Other Clinically Relevant Issues

No other clinically relevant issues were identified for Formoterol fumarate. Toxicity manifests as exaggerated pharmacodynamic effects of beta agonists. The effects observed with Formoterol fumarate were consistent with those described in the literature for other beta agonists.

Conclusions

Taken together, the data submitted supports the safety of Formoterol fumarate under the proposed conditions of use. Adequate safety margins appear to exist for inhalation exposure, although additional data is being sought to make valid plasma level comparisons between animals and humans.

Formoterol fumarate was not genotoxic or mutagenic in any of the assays submitted. The following table summarizes major findings and the dose levels at which they occur.

Summary of Notable Findings and Dose Ratios to Adult Humans on a mg/m^2 Basis

Assay	Species	Route	Dose (mg/kg)	Dose (mg/m^2)	Dose Ratio for Adults	Effect
1-Year Chronic	Dog	Oral	.01	0.2	6	Myocardial fibrosis
1-Year Chronic	Dog	Inhale	0.015	0.3	8	NOAEL
1-Year Chronic	Rat	Inhale	0.030	0.18	5	NOAEL
1-Year Chronic	Rat	Inhale	0.120	0.72	20	Degeneration of seminiferous tubules
10Year Chronic	Rat	Inhale	0.4	2.4	70	Myocardial fibrosis
Reproduction and	Rat	Oral	6	36	1000	Stillbirth and neonatal death

Assay	Species	Route	Dose (mg/kg)	Dose (mg/m ²)	Dose Ratio for Adults	Effect
Developmental Toxicology						
Carcinogenicity	Rat	Water	15	90	2500	Ovarian leiomyoma
Carcinogenicity	Rat	Diet	20	60	3400	Ovarian leiomyoma
Carcinogenicity	Mouse	Diet	2	6	170	Ovarian leiomyoma - leiomyosarcoma
Carcinogenicity	Mouse	Diet	20	60	1700	Hepatocellular carcinoma
Carcinogenicity	Mouse	Diet	50	150	4200	Testicular tubular atrophy
Carcinogenicity	Mouse	Water	267	801	22,000	Adrenal subcapsular adenoma - carcinoma

Language to be used in Letter to Sponsor

The language reported under the Recommendations section below can be used in communication with the Sponsor.

RECOMMENDATIONS

1. It was noted during the course of the review of the dietary carcinogenicity studies that the incidence of some findings in the statistical analysis does not exactly match that reported in the summary incidence tables. For example, in the mouse dietary study, the incidence of benign hepatoma reported in the incidence table (v.49 p. 176) differs from that presented in the statistical analysis (v.49, p. 428), as illustrated in the following table.

Incidence of Benign Hepatoma in the
Incidence Table and Statistical Analysis

Group	Reference	
	v.49 p.176	v.49 p. 428
0	18/85	24/85
2	19/85	24/85
5	21/85	31/85
20	24/84	33/84
50	15/85	25/85

The Sponsor should recheck their submission and clarify the discrepancies.

2. The AUC data play a critical role in the evaluation of the safety of Formoterol fumarate. The Sponsor noted in their submission that there were difficulties with the method(s) used to evaluate plasma levels in animals studies. The values provided are

much higher than would reasonably be expected in a drug of this type and class. In addition, we note that the C_{max} identified in the mouse dietary carcinogenicity study is 6.3 nmol/l for a 50 mg/kg/day dose, far below the number provided in the mouse drinking water study (AUC = 4300 nmol/ml) and used for comparison to humans.

The values from the dietary study seem more realistic based on the dose and thus we are concerned with the claimed exceeding large dose multiples between humans and animals. Specifically, we are concerned with reported exposure data (AUC, C_{max}, etc.) associated with the carcinogenicity studies, reproductive and development studies, and the chronic toxicity studies. The Sponsor should provide realistic exposure information for these studies, or provide an explanation of why such data are not attainable. We note that in humans levels as low as an AUC of 1.33 nmol·h/l based on an inhaled dose of 120 µg, is measurable.

3. The Sponsor should report the assumed deposition factor for the inhalation studies included in this submission.

Tracey Zoetis, M.S.
Pharmacology/Toxicology Reviewer

Hilary Sheevers, Ph.D.
Team Leader

Original NDA 20,831

cc HFD-570/Division File
HFD-570/H. Sheevers
HFD-570/P. Jani
HFD-570/T. Zoetis

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guinea-pig tracheae: comparison of relaxation with receptor binding. *Lung* 170(3):163-80.

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APPEARS THIS WAY
ON ORIGINAL

REVIEW AND EVALUATION OF PAHRAMCOLOGY/TOXICOLGY DATA
DIVISION OF PULMONARY DRUG PRODUCTS

2

BACKGROUND INFORMATION:

Reviewer Name: Tracey Zoetis, M.S.
Division Name: Division of Pulmonary Drug Products
HFD No. HFD-570
Review Completion Date: May 28, 1998
NDA No. 20-831
Related INDs: _____
Serial Number: 000
Submission Date: June 26, 1997
Information to Communicate to Sponsor: See Recommendations
Sponsor or Agent: Novartis Pharmaceuticals Corporation
59 Route 10
Hanover, NJ 07936

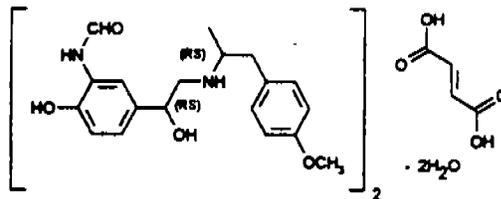
Manufacturer:

DMF # _____

DMF# _____

DRUG

Code Name: Formoterol fumarate
Generic Name: Not applicable
Trade Name: Foradil®
Chemical Name: \pm 2-hydroxy-5-[(1RS)-1-hydroxy-2-
[[[(1RS)-2-(4-methoxyphenyl)-1-
methylethyl]amino]ethyl]formanilide
fumarate dihydrate
CAS Registry No.: 45229-80-7
Molecular Formula: $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$
Molecular Weight: 840.9
Chemical Structural Formula:



Drug Class:

beta-2-andrenoceptor agonist

- Indication:** Prevention and maintenance treatment of bronchoconstriction in patients _____ years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma, and for the prevention of exercise-induced bronchospasm.
- Clinical formulation (and components):** Micronized Formoterol fumarate _____ mg/capsule) _____ with lactose (to 25 mg/capsule), placed in hard gelatin capsules.
- Route of Administration:** Inhalation
- Proposed clinical protocol or use:** Formoterol fumarate will be administered twice daily via an _____ oral inhalation device. The maximum daily dose is _____ mcg.
- Previous clinical experience:** This drug is marketed in two forms in several countries. The earliest approval for the aerosol solution was in September 1990 in Switzerland. The earliest approval for the Dry Powder Capsules was January 1993 in New Zealand. The aerosol solution form is currently marketed in Austria, Denmark, Dubai, Greece, Holland, Hong Kong, Israel, Italy, South Africa, Spain, Switzerland and Turkey. The Dry Powder Inhalation form is marketed in Austria, Denmark, Egypt, Finland, Holland, Ireland, Israel, Sweden, Switzerland, and the United Kingdom. It available free of charge in New Zealand, in the absence of reimbursement.
- Disclaimer:** Some of the information contained in this review may have been obtained directly from the Sponsor's submission.

INTRODUCTION AND DRUG HISTORY

Information regarding this drug was originally submitted to the FDA when it was being developed in the form of an _____ by Ciba-Geigy _____ (IND _____). Development of the drug shifted to a dry powder inhalation form and this application was submitted to the agency by Novartis Pharmaceutical Corporation in February 1995 (IND _____). Several preclinical studies were reviewed during the

course of drug development and those reviews were considered along with the current NDA submission.

STUDIES REVIEWED WITHIN THIS SUBMISSION

A comprehensive battery of studies were submitted to support the safety of Formoterol fumarate. The types of studies reviewed within this submission include:

- Pharmacokinetics/Toxicokinetics
- Toxicology
- Carcinogenicity
- Reproductive Toxicology
- Genetic Toxicology
- Special Toxicology (e.g., dermal sensitization and irritation studies).

In addition, safety pharmacology studies were considered and an overall summary is provided in this review.

Individual studies included in this submission and reviewed include the following.

Pharmacokinetics and Toxicokinetics

INDEX OF ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION STUDIES INCLUDED IN THIS REVIEW

No.	Study Title	Study No.
1.	(Fomoterol fumarate): Disposition and metabolism of Fomoterol fumarate, a new bronchodilator, in rats and dogs	Sasaki et al. 1982
2.	Absorption, distribution, metabolism and excretion of formoterol fumarate (BD 40A): 1. Pharmacokinetics in the rat and dog	Kamimura et al. 1984
3.	Absorption and excretion of BD 40A in dogs	Hasegawa et al. 1983
4.	(Fomoterol fumarate): Pharmacokinetics in male and female rats; determination of formoterol in plasma of rats after a single peroral dose of Fomoterol fumarate, 12.5, 25, and 50 mg/kg body weight	Ackermann et al. 1991
5.	(Fomoterol fumarate): 2-week inhalation toxicity study in rats; determination of Fomoterol in urine of rats after pulsed inhalation exposure to Fomoterol fumarate	Ackermann et al. 1986
6.	(Fomoterol fumarate): 3-month inhalation toxicity study in dogs; determination of Fomoterol in urine of dogs after daily inhalation of Fomoterol fumarate using metered dose aerosol packs	Ackermann et al. 1987
7.	(Fomoterol fumarate): 3 month inhalation toxicity study in dogs	— R 6/1991 supplement to 806161
8.	(Fomoterol fumarate): Absorption and disposition studies in mice	DM 1/1991
9.	Absorption and distribution of Fomoterol fumarate in rats	— F-1-4-1
10.	Determination of Fomoterol in plasma of rats during administration of Fomoterol fumarate via drinking water for 3 months and after a single peroral dose (Dose levels 12.5, 25, and 50 mg/kg body weight at the end of the treatment	906174

No.	Study Title	Study No.
11.	Absorption and disposition studies in male and female rats after doses of 5 to 50 mg/kg [¹⁴ C]CGP 25827A	DM 2/1991
12.	Pharmacokinetics of the enantiomers of Fomoterol in plasma of male and female rats after single 10 mg/kg peroral administration of the enantiomers	1994/015
13.	3-month oral (via drinking water); phramacokinetic study in rats; Determination of Fomoterol in plasma of rats after a single peroral dose (dose level: 12.5, 25, and 50 mg/kg body weight), following administration via drinking water for 3 months	916052
14.	Plasma concentrations of the unchanged drug following intravenous administration of BD 40B and BD 40A in dogs	F-1-4-16
15.	Absorption, distribution, metabolism and excretion of Fomoterol fumarate (BD40A): 3. Plasma concentrations and urinary excretion of unchanged drug after continuous administration in dogs	F-1-4-7
16.	Pharmacokinetics of the enantiomers of formoterol in male dogs after single 0.3 mg/kg peroral administration of the enantiomers	1994/063
17.	Absorption, distribution, metabolism and excretion of Fomoterol fumarate (BD 40A): 4. Plasma Fomoterol and cAMP concentrations	F-1-4-8
18.	Fomoterol fumarate: metabolic fate after repeated oral administration of Fomoterol fumarate in rats	Sasaki et al 1983
19.	Absorption, distribution, metabolism and excretion of Fomoterol fumarate (BD 40A): 2. Binding of unchanged drug to plasma protein	F-1-4-6
20.	(Fomoterol fumarate): In vitro binding of formoterol to serum proteins	41/1991
21.	The transpulmonary transport and metabolism of ³ H-CGP 25827A (Fomoterol fumarate) following intra-tracheal instillation to the isolated rat perfused lung	#93/02/C/2R
22.	Biotransformation of Fomoterol fumarate: Isolation and structure elucidation of metabolites formed in vitro in hepatocytes of rat, guinea pig, marmoset and dog identification of metabolites in human ex vivo biological samples	DM(EU)28/1996
23.	Evaluation of a new chemical entity, CGP 25827, as an inhibitor of human P450 enzymes	XT-0424496-25827, U) 96-7804
24.	Plasma concentration of Fomoterol in mice from a 24-month carcinogenicity study with oral administration of CGP 25827A in the diet	43/1993 supplement to 907172
25.	Three-month oral (via drinking water) toxicity study in mice; determination of Fomoterol in plasma of mice during 3-month administration of Fomoterol fumarate via drinking water at concentrations of 0.25, 0.5 and 1 mg/ml water	B23/1992 supplement to 906303
26.	Three-month range finding toxicity study in mice; determination of fomoterol in plasma of mice after 1- and 3-month administration of Fomoterol fumarate in the diet at nominal dose levels of 0, 40, 140, 400 and 1400 ppm	B106/1990 supplement to 906171
27.	28-day palatability study in rats; determination of Fomoterol in plasma of rats after 28 day administration of Fomoterol fumarate in the diet at daily doses of 0, 0.4, 1.8, 4.5, and 18 mg/kg body weight	B 84/1990 supplement to 896027
28.	3-month range finding study in rats (administration in food). Determination of Fomoterol in urine and plasma of rats during 3 month administration of CGP 25827A in the diet at nominal daily doses of 0, 0.5, 2, 5, and 20 mg/kg body weight	B 68/1991 supplement to 906205
29.	24-month carcinogenicity study in rats; determination of Fomoterol in plasma and urine of rats during 24 month administration of CGP 25827A in the diet at nominal daily doses of 0, 0.5, 2, 5, and 20 mg/kg body-weight	B14/1992 supplement to 886178

No.	Study Title	Study No.
30.	Determination of Fomoterol in urine, plasma and the respiratory tract of rats form an acute pulsed inhalation toxicity study with CGP.25827A dry powder formulation (1/69)	49/1993 supplement to 926108
31.	Plasma concentrations and urinary excretion of Fomoterol in rats from a 28-day, repeated dose, pulsed inhalation toxicity study with CGP 25827A dry powder formulation	20/1993 supplement to 926111
32.	Determination of Fomoterol in urine of rats during an 90 day repeated dose inhalation toxicity study with Fomoterol fumarate dry powder formulation	R 49/1991 supplement to 906154
33.	Plasma concentrations and urinary excretion of Fomoterol in rats from a 6/12 month inhalation toxicity study with a lactose powder formulation of CGP 25827A formulation, 1/73)	1996/061 supplement to 936115
34.	3-month inhalation toxicity study in rats; determination of formoterol in urine of rats after daily inhalation of Fomoterol fumarate using metered dose aerosol packs	R 33/1992 supplement to 906224
35.	Determination of Fomoterol in urine of dogs after twice daily inhalation of inhalable nebulized solution Fomoterol fumarate for 28 consecutive days	R31/1991 supplement to 906249
36.	1 month comparative inhalation toxicity in dogs; determination of Fomoterol in urine of beagle dogs during 28 day administration of CGP 25827A by the inhalation route. Comparison of tow different batches of the solution aerosol formulation of CGP 25827A	B 57/1991 supplement to 90-6158
37.	Urinary excretion and plasma concentrations of Fomoterol in dogs from a 4-week inhalation toxicity study with CGP 25827A dry powder formulation (1/69)	32/1993 supplement to 926074
38.	13 week inhalation toxicity study in dogs; determination of formoterol in urine of beagle dogs during daily inhalation of CGP 25827A, dry powder formulation	B 65/1991 supplement to 906155
39.	Plasma concentrations and urinary excretion of Fomoterol in dogs from a 6/12 month inhalation toxicity study with CGP 25827A lactose powder formulation suspension 1/73)	(F) 1995/004 supplement to 936116
40.	Plasma concentrations and urinary excretion of Fomoterol in dogs from a 13-week inhalation toxicity study with CGP 25827A as a suspension reformulation)	(F) 1995/016
41.	Urinary excretion and plasma concentrations of the (S,S) enantiomer of fomoterol in dogs from a 4-week inhalation toxicity study with CGP 29502A dry powder formulation (1/73)	1996/044 supplement to 936225
42.	Urinary excretion and plasma concentrations of the (R,R) enantiomer of Fomoterol in dogs from a 4-week inhalation toxicity study with CGP 29503A powder formulation (1/73)	1996/045 supplement to 936226
43.	Fomoterol fumarate. Absorption, distribution, metabolism and excretion of Fomoterol fumarate (BD40A): 7. Plasma concentrations and rate of urinary excretion in man	7-1-4-13
44.	Fomoterol fumarate: Pharmacokinetics study with fomoterol dry powder inhalation capsule via Aerolizer™	984008

*Toxicology***INDEX OF ACUTE TOXICOLOGY STUDIES INCLUDED IN THIS REVIEW**

No.	Study Title	Study No.
1.	Acute Oral Toxicity Study in Juvenile Rats	— D-1-3
2.	Acute Oral Toxicity Study in Chinese Hamster	825339
3.	Acute Oral Toxicity Study in Dogs	— D-1-2
4.	(Active Ingredient in Air/CFC Propellant): Acute Toxicity Study in Rats	846402
5.	(Active Ingredient in Air/CFC Propellant): Acute Inhalation Toxicity Study in Rats	841012
6.	(Active Ingredient in Air/CFC Propellant): Acute Inhalation Toxicity Study in Rats	841011
7.	(Active Ingredient in Air/CFC Propellant): Acute Inhalation Toxicity Study in Dogs	906238
8.	(Solution Aerosol): Acute Inhalation Toxicity Study in Dogs	855190
9.	(Solution Aerosol): Acute Comparative Inhalation Toxicity Study in Dogs	886174
10.	(Suspension Aerosol): Acute Inhalation Toxicity Study in Dogs	896160
11.	(Dry Powder Formulation 1:1000): Acute Pulsed Inhalation Toxicity Study in Rats	896183
12.	(Dry Powder Formulation 1:69): Acute Pulsed Inhalation Toxicity Study in Rats	926108
13.	Acute Toxicity Study in Mice and Rats (iv, ip, sc)	— D-1-1
14.	Acute Intraperitoneal Study in Mice	— D-1-1
15.	Acute Subcutaneous Study in Mice	— D-1-1
16.	Acute Intravenous Toxicity Study in Rats	— D-1-1
17.	Acute Intraperitoneal Study in Rats	— D-1-1
18.	Acute Subcutaneous Toxicity Study in Rats	— D-1-1
19.	Acute Intravenous Toxicity Study of Optical Isomers in Mice	— D-1-4
20.	Acute Intravenous Toxicity Study of Decomposition Products in Mice	— D-1-5

INDEX OF REPEATED DOSE TOXICITY STUDIES

No.	Study Title	Study No.
1.	28-Day Palatability Study in Rats	896027
2.	13-Week (Feeding) Rangefinding Study in Rats	906205
3.	13-Week Oral (Drinking Water) Toxicity Study in Rats	906174
4.	3-Month Oral (Drinking Water) Toxicity Study in Rats	916052
5.	(Suspension Aerosol): Preliminary Inhalation Tolerance Study in Rats	906223
6.	(Dry Powder Formulation 1:1000): 13-Week Inhalation Toxicity Study in Dogs	906155
7.	(Dry Powder Formulation 1:69): 4-Week Inhalation Toxicity Study in Rats	926111
8.	(Dry Powder Formulation 1:1000): 13-Week Inhalation Toxicity Study in Rats	906154
9.	13-Week Inhalation Toxicity Study in Rats	906224
✓10.	(1:73 Powder Formulation): 26/52-Week Inhalation Toxicity Study in Rats	936115
11.	13-Week Feeding Toxicity Study in Mice	906171
12.	13-Week Drinking Water Toxicity Study in Mice	— D-8-3
13.	13-Week Drinking Water Toxicity Study in Mice	906303
14.	52-Week Oral (Capsule) Toxicity Study in Dogs	850751
15.	(Dry Powder Formulation 1:69): Preliminary Inhalation Toxicity Study in Dogs	926109
16.	Inhalation Feasibility Study in Dogs	936077
17.	(Dry Powder Formulation 1:69) 4-Week Inhalation Toxicity Study in Dogs	926074
18.	(Solution Aerosol): 4-Week Comparative Inhalation Toxicity Study in Dogs	906158
19.	(1:73 Powder Formulation): 52-Week Inhalation Toxicity Study in Dogs	936116

*Carcinogenicity***INDEX OF CARCINOGENICITY STUDIES INCLUDED IN THIS REVIEW**

No.	Study Title	Study No.
20.	104-Week Oral Carcinogenicity Study in Mice	906172
21.	24-Month Oral Carcinogenicity Study in Rats	886178

*Reproductive Toxicology***INDEX OF REPRODUCTIVE TOXICOLOGY STUDIES INCLUDED IN THIS REVIEW**

No.	Study Title	Study No.
22.	Oral Segment I Study in Rats	— D-4-1
23.	Oral Segment I Study in Rats	820741
24.	Oral Segment II Study in Rats	— D-4-2
25.	Oral Segment II Study in Rabbits	— D-4-3
26.	Oral Segment III Study in Rats	— D-4-4
27.	Oral Segment III (Foster Nursing) Study in Rats	— D-4-5

*Genetic Toxicology***INDEX OF MUTAGENICITY AND GENOTOXICITY STUDIES INCLUDED IN THIS REVIEW**

No.	Study Title	Study No.
28.	Mutagenicity Tests in Microorganisms	— D-7-1
29.	Reversion Test in Bacteria	— D-7-2
30.	Salmonella/Mammalian-Microsome Mutagenicity Test	841042
31.	V79 Chinese Hamster Cells Point Mutation Test	841043
32.	Unscheduled DNA Synthesis in Rat Hepatocytes	841039
33.	Unscheduled DNA Synthesis in Human Fibroblasts	841041
34.	Test for Transformation Inducing Properties in Mammalian Fibroblasts	841044
35.	Chromosome Analysis on Chinese Hamster Somatic Cells	841040
36.	Micronucleus Test in Mice	— D-7-3
37.	Micronucleus Test in Rats	8962251
38.	Chromosome Studies on Chinese Hamster Ovary Cell Line CCL 61 <i>In Vitro</i>	896209

*Special Toxicology***INDEX OF SPECIAL TOXICOLOGY STUDIES INCLUDED IN THIS REVIEW**

No.	Study Title	Study No.
1.	Antigenicity Test in Mice	— D-6-2
2.	Skin Sensitization: Optimization: Study in Guinea Pigs	840421
3.	5-Day Intravenous Local Tolerability Study in Rabbits	855125
4.	Skin Irritation (Local Tolerability) Study in Rabbits	835278

STUDIES NOT REVIEWED WITHIN THIS SUBMISSION

Several studies had been submitted and reviewed throughout the course of the IND phase of study. These studies were not reviewed with the current submission. A list of the

studies reviewed prior to this submission is presented below. Virgil Whitehurst, Ph.D. was the reviewer for the IND submissions.

PHARMACOLOGY

Formoterol fumarate provides therapeutic benefit by relieving and preventing bronchoconstriction by relaxing airway smooth muscle via specific interaction with beta-2-adrenoceptors. The efficacy of formoterol at beta-2-adrenoceptors has been measured in both functional airway smooth muscle relaxation and biochemical second messenger assays where cAMP were determined. High levels of efficacy and potency agonism were demonstrated using conditions of induced tone or the presence of high levels of cholinergic agonists. Treatment with formoterol or other beta-2-adrenoceptor agonists is associated with reassertion relaxation, suggesting that it is functionally retained in or near the beta-2-adrenoceptor despite extensive washing of *in vitro* airway smooth muscle preparations.

The onset of action of formoterol is comparable to that of albuterol, yet the duration of action was consistently greater than that of isoproterenol or albuterol. The onset of action was reported to be 1.7 ± 0.3 minutes for formoterol, 0.8 ± 0.2 minutes for albuterol, and 17.6 ± 5.0 minutes for salmeterol when administered to guinea pig isolated trachea. (Jeppson et al., 1989). The duration of action of formoterol was in excess of 6 hours in isolated human bronchus (Advenier et al, 1991).