

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-831

PHARMACOLOGY REVIEW(S)

APR 27 2000

**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Division Of Pulmonary and Allergy Drug Products (HFD-570)**

REVIEW INFORMATION:

Review No.: 5
Reviewer Name: Luqi Pei, D.V.M., Ph.D.
Key Words:
Review Completion Date: April 27, 2000
Information to be Conveyed to Sponsor: Yes _____ No x

APPLICATION INFORMATION:

IND or NDA Application No: NDA 20-831
Serial No., Content and Date of Submission: 10/19/98 and 11/23/99 supplements, complete responses to division approvable letter dated 6/26/98.
Sponsor: Novartis Pharmaceutical Corporation, East Hanover, NJ
Drug Name: Foradil™ Aerolizer (Formoterol fumarate DPI)
Class: Beta 2 adrenergic bronchodilator
Indication: Prevention and treatment of bronchoconstriction in patients—years and older with reversible obstructive airway disease.
Usage: 12 µg, bid, with the maximum daily dose of — µg/patient

REVIEW SUMMARY:

This review evaluates the sponsor's preclinical responses to the Division's approvable letter dated June 26, 1998. The letter listed comments that the sponsor must respond to prior to the approval of the application. The preclinical comments of the letter can be summarized as the following: 1. Clarify the discrepancies in tumor incidences between the statistical analysis and summary incidence tables for the mouse dietary study. 2. Reassess systemic exposure of formoterol in toxicology studies. 3. Provide the deposition factors used for the preclinical inhalation toxicology studies. In their submissions dated October 19, 1998 and November 23, 1999, the sponsor has sufficiently addressed the above comments. This review, from the pharmacology and toxicology viewpoint, recommends an approval of this application.

Documents Submitted and Included in This Review:

A complete response to the Approvable letter by the Division dated June 26, 1998. Submitted on 10/19/98 (vol. 1 p10-13, vol. 5, p1-15) and 11/23/99 (vol. 1, p21-25, and 88-89).

Previous Reviews

Review#	Reviewer	Review Date	Review Description
1	Tracey Zoetis	March, 1998	Review of carcinogenicity studies
2	Tracey Zoetis	May 28, 1998	Review of the original submission
3	Luqi Pei	March 13, 2000	Follow-up review of the carcinogenicity studies
4	Luqi Pei	April 25, 2000	Labeling review

INTRODUCTION

This review evaluates the sponsor's responses to the preclinical deficiencies of the application outlined in the Division's approvable letter dated June 26, 1998. Comments 8 – 10 of Section B of the letter detailed preclinical deficiencies of the application. These deficiencies can be summarized as the following (text of the deficiencies can be found in the review):

- Comment B.8. Clarify and explain discrepancies in tumor incidences between the statistical analysis and summary incidence tables for the mouse dietary study.
- Comment B.9. Provide realistic exposure information for toxicology studies.
- Comment B.10. Report the estimated deposition factor used for the preclinical inhalation toxicology studies.

The sponsor has responded to the above comments in the submissions of October 19, 1998 and November 23, 1999. This review evaluates the sponsor's responses to the above comments.

REVIEW

This review is based on data in the most recent submission (November 23, 1999) because the submission of October 19, 1998 contained essentially the same information.

1. Response to comment B.8

Divisional Comment B.8 states: "The incidence of some findings in the statistical analysis of the dietary studies does not match that reported in the summary incidence tables. For example, in the mouse dietary study, the incidence of benign hepatomas in the incidence table (vol. 49, p176) differs from that presented in the statistical analysis (vol. 49, p428), as illustrated in the following table. Clarify and explain these discrepancies."

Incidence of Benign Hepatomas in the Incidence Table and Statistical Analysis

Group	[Incidence Table] NDA vol. 49, page 176)	[Statistical Analysis] NDA vol. 49, page 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

In their response, the sponsor stated that numbers in the above table were correct. Differences were due to the way in which the tables of incidence and statistical analysis were compiled. The statistical analysis table showed incidence of all affected animals, while the "Summary of

Microscopic Findings" table showed only the number of animals with the "main" diagnosis, carcinoma. Main diagnosis was defined as an animal that had both hepatocellular carcinoma and benign hepatoma. The explanation is satisfactory.

2. Response to Comment B.9

Divisional Comment B.9 states: "Plasma exposure (AUC) data from preclinical studies play a critical role in the evaluation of the safety of formoterol-fumarate. You have noted in your submission that there were difficulties with the method(s) used to evaluate plasma formoterol levels in animal studies. The values provided are much higher than would be expected given 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 (C_{max} = 1100 nmol/L and AUC = 4300 nmol.h/L at a 60 mg/kg/day dose level) that was used for comparison to humans. The AUC values from the dietary study seem more realistic based on the administered dose and, thus, we are concerned that the claimed large dose multiples between humans and animals are inaccurate. Specifically, we are concerned with the reported exposure data (AUC, C_{max} etc.) associated with the carcinogenicity studies, reproductive and development studies, and the chronic toxicity studies.

Provide realistic exposure information for these studies, or provide an explanation of why such data are not accurate. We note that in humans levels as low as an AUC of 1.33 nmol.h/L based on an inhaled dose of 120 mcg, are measurable."

The sponsor explained in two areas: analytic method to measure formoterol levels and models used to estimate the plasma levels.

1. Analytic method.

The sponsor stated that "A variety of analytical methods¹ were used to measure formoterol in biological fluids" and "The[se] methods ... varied in sensitivity, and there were early difficulties in achieving the sensitivity necessary to measure formoterol in the plasma of all dose groups." However, the sponsor argued that the validity of each method was established. They further argued that these studies did not overestimate the drug levels, and dismissed any contribution of analytical method to the variability of reported exposure levels.

This explanation is unsatisfactory. Dr. Luqi Pei has reviewed the relationship between analytic method and plasma formoterol levels (see pharmacology and toxicology review by L. Pei dated March 13, 2000). He concluded that detection sensitivity improved over time and significantly impacted the estimation of formoterol levels in the plasma.

1. Methods used to measure formoterol include

~~_____~~ They varied in sensitivity in measuring formoterol. The ~~_____~~ the most sensitive method, was developed only in the ~~_____~~ and was used to measure plasma levels of formoterol in a recent pivotal PK study in humans, but not in animals.

2. Models used to estimate plasma levels of formoterol in animals

The sponsor stated that previously reported plasma levels and animal to human AUC ratios were derived from ADME and pharmacokinetic studies rather than toxicokinetic studies, and that these data provided a more accurate and realistic assessment of systemic exposure. They further argued that toxicokinetic data underestimated the exposure because these data were often limited to single time-point monitoring.

Dr. Luqi Pei recently reviewed the appropriateness of different animal models for estimating plasma formoterol levels in the carcinogenicity studies (see pharmacology and toxicology review by L. Pei dated March 13, 2000). He found that AUC ratios for the 2-year drinking water carcinogenicity study in mice could vary by thousands of fold, depending upon the animal studies used to derive the ratio. He also found that using data from the oral gavage pharmacokinetic study overestimated systemic exposure. This is contrary to the sponsor's argument that the pharmacokinetic, rather than toxicokinetic, data provides a more realistic assessment of systemic exposure to formoterol in animals. Dr. Pei concluded that toxicokinetic data from dietary administration, not pharmacokinetic data from oral gavage administration, were more indicative of plasma drug levels achieved in the drinking water carcinogenicity study in mice.

For the dietary carcinogenicity study in mice, AUC ratios have varied significantly between submissions. Table 1 lists AUC ratios in previous reviews or submissions for a dietary formoterol dose of 50 mg/kg/day in mice. The June 26, 1997 submission estimated the ratio to be 2,440. This ratio was later revised to 5,660, and recently revised again to 300. The newly revised calculation relies on plasma level data from the dietary study that likely provides a more realistic estimate of exposure than data from pharmacokinetic studies using other modes of administration.

Table 1. Variance in AUC Ratios among Submissions¹

Submission	Date of Submission	AUC Ratio	Reference
Original	6/26/97	2,440 ²	Draft CAC minutes by T. Zoetis dated 4/27/98. See Review 3.
Supplement		5,640 ²	Draft revised CAC minutes by T. Zoetis dated 2/16/00. See Review 3.
Supplement	10/19/98 11/23/99	300	Review by Pei dated 3/13/00

1. AUC Ratios between mice receiving 50 mg/kg/day formoterol in diet and humans.
2. Estimated by linear extrapolation in which a dose of 5 mg/kg/day corresponds to an AUC ratio of 244 and 564 respectively.

Although the sponsor still argues the validity of the pharmacokinetic data for estimating plasma formoterol levels, they did recalculate exposure levels in animals based on dietary toxicokinetic

data. Table 2 summarizes the newly calculated AUC ratios between animals and humans. The listed dose levels of 20 and 50 mg/kg/day for rats and mice were the high doses in the respective 2-year dietary carcinogenicity studies. Table 2 shows that exposure to formoterol in these animals reaches at least 300 times that in humans. These data seem to provide a more realistic assessment of AUC ratios between animals and humans than pharmacokinetic data. Pharmacokinetic studies were generally gavage studies in which the metabolic capacity for the drug could be overwhelmed by the bolus nature of the administration.

Table 2. Comparison of Systemic Formoterol Exposure between Animals and Humans¹

Species	Sex	Dose (mg/kg)	Route	AUC (nmol.h/L)	Multiple of Human Exposure	
					By sex	Mean (M & F)
Rat	M	20	P.O. diet	547	1028	900
	F	20	P.O. diet	518	786	
	M	0.38	Inhalation	78	147	138
	F	0.54	Inhalation	68.5	129	
Mouse	M	50	P.O. diet	113	212	300
	F	50	P.O. diet	202	380	
Dog	M	0.025	Inhalation	19.8	37	169
	F	0.025	Inhalation	160	301	

1. Extracted from Table 2, vol. 22.1, page 89 (submission of 11/23/99).
2. Based on a human maximum daily dose of 48 µg/day.

The re-evaluation of the AUC data in mice and rats indicates that mice and rats in the carcinogenicity studies have been sufficiently exposed to formoterol. The above discussion shows that animals in the dietary carcinogenicity studies have been exposed to the formoterol at levels approximately 300 times the humans, even with the rather conservative estimates that are based on AUCs derived from single time point. In his review dated March 13, 2000, Dr. Luqi Pei previously concluded that mice and rats in the drinking water studies had been exposed to the drug at similar or higher levels. These data show that mice and rats in the carcinogenicity studies have apparently achieved systemic exposure in excess of 25 fold human exposure, one of the acceptable endpoints for dose selection for carcinogenicity studies for a non-genotoxic compound.

Because of the sufficiently large exposure ratios in these studies in mice and rats, dose selections for formoterol in these studies should be considered as acceptable. The unavailability of precise dose ratios should not affect the overall validity and evaluation of these carcinogenicity studies. Thus, this issue is not worth further pursuing although the sponsor's explanation to comment B.9 is unsatisfactory.

3. Response to Comment B.10

Comment B.10 requests the sponsor to report the estimated deposition factor used for preclinical inhalation toxicology studies. Table 3 summarizes deposition factors that were reported in these submissions and were used previously in estimating doses.

Table 3. Deposition Factors Used in Calculating Formoterol Exposure in Animals*

Deposition Factor	Study No.	Contract Labs
1	936077, 936116	—
	906154, 906155, 926074,	—
	926109, 926111,	—
0.82 - 0.88	906224	—
0.65	936115	—

Source: Vol. 22.1, page 10, submission of November 23, 1999.

The November 23, 1999 submission contained two reports from contract laboratories — report dated August 10, 1998 and — 700233 report dated July 29, 1998 (vol. 22.11)] to support the above summary data. A detailed review of these individual reports is not necessary because they do not contain significant, additional information.

Conclusion

The sponsor has adequately responded to all preclinical deficiencies in the approvable letter dated June 26, 1998. These responses included a clarification of the discrepancies in tumor incidences between the statistical analysis and summary incidence tables for the mouse dietary study, recalculations of systemic exposure in toxicology studies, and the estimated deposition factors used for the preclinical inhalation toxicology studies. These responses are reasonably sufficient.

The safety of formoterol fumarate for the proposed indication has been established preclinically. The previous review team has concluded that this application contained sufficient data to support the safety of the proposed indication (see Pharmacology and Toxicology Review by Tracey Zoetis dated May 28, 1998). The review team, however, also found several deficiencies in the application. These deficiencies were conveyed to the Sponsor in the letter dated June 26, 1998. The sponsor has reasonably and sufficiently responded to all deficiencies raised by the pharmacology and toxicology discipline. Also, a labeling review for this application has been completed recently (Dr. Luqi Pei's review dated April 25, 2000). From the pharmacology and toxicology viewpoint, approval of this application is recommended.

APPEARS THIS WAY
ON ORIGINAL

Recommendation

From the pharmacology and toxicology viewpoint, an approval of this application (NDA 20-831, formoterol fumarate as a bronchodilator) is recommended.

LSI 4/27/00

Luqi Pei, Ph.D.
Pharmacologist and Toxicologist

LSI 4-27-00

Robin Huff, Ph.D.
Team Leader

CC: /NDA 20831
/ HDF-570 Divisional File
/Pei
/Huff
/Jani

APPEARS THIS WAY
ON ORIGINAL

APR 25 2000

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Division Of Pulmonary and Allergy Drug Products (HFD-570)

REVIEW INFORMATION:

Review No.: 4
Reviewer Name: Luqi Pei, D.V.M., Ph.D.
Key Words: Labeling review
Review Completion Date: April 25, 2000
Information to be Conveyed to Sponsor: Yes No

APPLICATION INFORMATION:

IND or NDA Application No: NDA 20-831
Serial No., Content and Date of Submission: 10/19/98 and 11/23/99 supplements, complete response to division approvable letter dated 6/26/98
Sponsor: Novartis Pharmaceutical Corp., East Hanover, NJ
Drug Name: Foradil™ Aerolizer (Formoterol fumarate DPI)
Class: Beta 2 adrenergic bronchodilator
Indication: Prevention and treatment of bronchoconstriction in patients - years and older with reversible obstructive airway disease
Usage: 12 µg, bid, with the maximum daily dose of — µg/patient

Review Summary: This document reviews preclinical sections of the labeling for formoterol fumarate. The review also drafts the suggested text of the labeling to be conveyed to the sponsor.

INTRODUCTION

This application is currently in the second review cycle. Its original application was filed on June 27, 1997 and was considered approvable by the Division on June 26, 1998. Subsequent submissions were filed on October 19, 1998 and November 23, 1999. Internal due date for the latest submission is May 2000.

This application proposes to use formoterol fumarate, a long acting beta 2 adrenergic bronchodilator, for the prevention and treatment of bronchoconstriction in patients with reversible airway disease. The drug is administered by inhalation via a metered dose dry powder inhaler.

The preclinical section of the application was reviewed previously and it was concluded that "data submitted supports the safety of formoterol fumarate under the proposed conditions of use" (see Tracey Zoetis' review dated May 28, 1998). The Division determined that the

application was approvable (Division letter dated June 26, 1998). The Executive Carcinogenicity Assessment Committee of the Center recently reviewed the carcinogenic potential of the drug (See Exec. CAC meeting minutes dated April 11, 2000). Labeling for this application, however, has not been reviewed. This labeling review is generated in light of all available data.

REVIEW

This section reviews preclinical portions of the labeling for the formoterol fumarate DPI. Specifically, it reviews labeling sections for carcinogenesis, mutagenesis, impairment of fertility; pregnancy/ teratogenic effects; and overdose. The review proceeds with a summary of data relevant to the labeling. The suggested text for the labeling can be found at the end of the review.

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenic potential of formoterol fumarate has been evaluated in two studies each in rats and mice. The routes of administration were dietary and drinking water in each species. These four studies generally showed increases in incidences of leiomyomas of the ovary and uterus in the female (Mrs. Tracey Zoetis' reviews dated March and May 28, 1998). Leiomyoma is known to be associated with beta agonists in rodents. Depending upon the specific study, other tumors such as those in adrenal glands, liver and ovaries were also observed. These findings, however, lacked not only trans-species and trans-sex effects, but also reproducibility. For example, adrenal subcapsular adenomas and carcinomas were observed in male mice in the drinking water study only, but not in female mice in the same study, nor in the mouse dietary study and rat studies. Significance of these tumors, therefore, is unknown at present. Nonetheless, they should be noted in the preclinical labeling of this drug.

To facilitate the labeling review process, Table 1 summarizes significant tumor findings in relationship to dose in these four studies. The table does not include the incidence of tumors in the mammary and thyroid glands because the Executive Carcinogenicity Assessment Committee of the Center concluded that they were not treatment-related. Exposure ratios in the table (multiple of human AUC) were based on the November 23, 1999 submission in which oral (dietary) doses of 20 and 50 mg/kg/day in rats and mice, respectively, correspond to mean AUC ratios of 900 and 300 between animals and humans. A more detailed examination of the AUC and systemic exposure to formoterol in rats and mice can be found in Dr. Luqi Pei's review dated March 13, 2000.

APPEARS THIS WAY
ON ORIGINAL

Table 1. Incidences of Significant Tumors in the Formoterol Carcinogenicity Studies

Species/ Strain	Route	Dose (mg/kg /day)	Multiple ¹ of human AUC	Tumors		
				Uterine/ ovary Leiomyomas, ♀		Others
Rat						
Tiff	Diet	0	-	0/70	1/70	(Benign granulosa/ Theca cell Tumors, ♀)
		0.5	23	0/70	5/70	
		2	90	1/69	6/69	
		5	225	1/69	6/69*	
		20	900	3/69	8/69*	
SD	Drinking water	0		1/48		
		15	675	14/50*		
		32	1,440	14/50*		
		64	2,880	16/50*		
Mouse						
Tiff	Diet	0	-	4/85	10/85, 2/85 ²	(Hepato- carcinoma ♂, ♀)
		2	12	13/84*	12/83, 5/84	
		5	30	13/85*	19/85, 3/85	
		20	120	14/85*	17/84, 11/85*	
		50	300	17/85*	26/85*, 7/85*	
B6C3F1 ³	Drinking water	0	0	-	0/46	(Adrenal subcapsular adenoma, ♂)
		69	410	-	3/41	
		137	820	-	1/50	
		267	1,600	-	5/50*	

1. Based on exposure ratios of 300 at 50 mg/kg/day in mice and 900 at 20 mg/kg/day in rats, respectively, and assuming proportionality of the plasma AUC to oral dose.
 2. Figures represent incidences in males and females respectively.
 3. Mrs. Zoetis' review dated March 1998 and the Exec. CAC minutes dated April 11, 2000 incorrectly listed the mouse strain in the drinking water study as B6C6F1. The correct strain should be B6C3F1.
- *. Statistically significantly different from the control (P < 0.05).

Note:

There are some differences between the sponsor-proposed labeling and the suggested labeling. The suggested labeling omits the mammary and thyroid C-cell tumor findings because the Executive CAC has concluded that these tumors may not be treatment-related. The suggested labeling also omits additional explanation for the granulosa/Theca cell tumors. The sponsor argued that "the formation of benign granulosa/Theca cell tumor is a typical pathologic change in aging rats subject to hormonal stimulation". This argument would be more believable if both rat studies had shown the same tumor type. The observation of granulosa/Theca tumors only in the rat dietary study, not in the rat drinking water study, did not support their statement.

Pregnancy/ teratogenic effects

The sponsor proposes category B for formoterol pregnancy labeling. The following discussion, however, suggests the C category.

Table 2 summarizes reproductive toxicity studies performed with formoterol fumarate. The summary was extracted from Mrs. Zoetis' review dated May 28, 1998. The route of administration was oral for all studies. Table 2 shows that formoterol fumarate does not have any teratogenic effect, but the drug may cause stillbirth and increased neonatal mortality when given at the late stages of pregnancy in rats and rabbits. This contrasts the sponsor's claim that "Formoterol fumarate... have revealed no evidence of ... harm to the fetus...."

Table 2. Summary of Reproductive Toxicity Study Findings of Formoterol Fumarate

Study #	Species	Description	Dosing		Significant findings
			mg/kg/day	Time (GD)	
D-4-1	Rat	Fertility	0.2, 30, 60	-(14-60) - 7	No effect on fertility parameters
820741	rat	Fertility	0.3, 1, 3	-(14-60) - 21	No effect on fertility parameters
D-4-2	Rat	Embryo-fetal	0.2, 6, 60	7 - 17	Delayed ossification of minor bones at all doses, ↓ heart weight and ↓ fetal weights in the MD and HD groups
D-4-3	Rabbit	Embryo-fetal	0.2, 60, 500	6 - 18	↓ Neonatal survival at HD ¹
D-4-4	Rat	Peri & post-natal	0.2, 6, 30	17 - 21	↑ Stillborn and neonatal death rats at MD & HD
D-4-5	Rat	Foster & nursing	6	17 - 21	↑ Stillbirth, ↑ neonatal death rate

1. Mrs. Zoetis' review dated May 28, 1998 concludes: "A decrease in neonatal survival was noted within 24 hours postpartum at the 500 mg/kg[day] dose level when compared to controls." However, the review also states: "Neonatal mortality was noted in the F₁ generation (75.4% survival compared to 97.6% survival in the control group) and is believed to be the result of a lower number of implantation sites (mean = 9.0, 8.9, 8.9 and 7.3 for Groups 1 - 4, respectively) and fewer live fetuses (mean 8.7, 7.8, 8.3 and 6.1 for groups 1 - 4, respectively) in this high dose group."

Overdosage

The median and minimal lethal dose levels were not available from the previous reviews. However, Mrs. Zoetis collected the following information:

"The minimum acute lethal inhalation dose of Formoterol fumarate in laboratory animals is 156 mg/kg in rats, at least 26,000 times the maximum recommended daily inhalation dose on a mg/m² basis. The oral median lethal dose of Formoterol fumarate in laboratory animals was 322 mg/kg in the Chinese hamster (36,000 times the maximum recommended human dose on a mg/m² basis); 1120 and 1260 mg/kg in juvenile male and female rats, respectively (189,000 and 106,000 times the maximum recommended human dose on a mg/m² basis, respectively); 3125 and 5583 mg/kg in adult male and female rats, respectively (528,000 and 943,000 times the maximum recommended human dose on a mg/m² basis, respectively); and 6696 and 8308 mg/kg in male and female mice, respectively (566,000 and 702,000 times the maximum recommended human dose on a mg/m² basis, respectively)."

— Extracted from Mrs. Zoetis' email message to Dr.
Luqi Pei on February 16, 2000

For clarity, the above information is summarized into a table in the suggested labeling. The mean lethal oral doses in animals were the average of males and females. The maximum recommended human daily inhalation dose is assumed to be 0.037 mg/m² (0.048 mg ÷ 50 kg × 37 [km] = 0.037). The table uses conversion factors of 3, 4 and 6 for mice, hamsters and rats, respectively.

SUGGESTED LABELING FOR THIS NDA

Carcinogenesis/Mutagenesis/Impairment of Fertility

The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately — times human exposure at the maximum recommended daily dose). In the dietary study, the incidence of benign ovarian theca cell tumors was increased at doses of 0.5 mg/kg and above (AUC exposure at the low dose of 0.5 mg/kg was approximately — times human exposure at the maximum recommended daily dose). This finding was not produced in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately — times human exposure at the maximum recommended daily dose) in the dietary study. The incidence of hepatocarcinoma was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females (AUC exposure approximately — times human exposure at the maximum recommended daily dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg

and above (AUC exposure at the low dose of 2 mg/kg was approximately — times human exposure at the maximum recommended daily dose). Increases in leiomyomas of the female genital tract have been similarly demonstrated with other beta agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts, and micronucleus tests in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg, approximately — times the maximum recommended daily inhalation dose in humans on a mg/m² basis.

Pregnancy/Teratogenic Effects

PREGNANCY CATEGORY C: Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately — times the maximum recommended daily inhalation dose in humans on a mg/m² basis) and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately — times the maximum recommended daily inhalation dose in humans on a mg/m² basis). When given to rats throughout organogenesis, oral doses of 0.2 mg/kg and above delayed ossification of the fetus, and doses of 6 mg/kg and above decreased fetal weight.

Use in Labor and Delivery

Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately — times the maximum recommended daily inhalation dose in humans on a mg/m² basis) and above in rats receiving the drug for several days at the end of pregnancy. These effects were not produced at a dose of 0.2 mg/kg (approximately — times the maximum recommended daily inhalation dose in humans on a mg/m² basis). There are no adequate and well-controlled human studies that have investigated the effects of formoterol during labor and delivery. Because beta agonists may potentially interfere with uterine contractility, formoterol should be used during labor only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised — formoterol is administered to nursing women. There are no well-controlled human studies of the use of formoterol in nursing mothers.

Overdosage



 / S / 4/25/00

Luqi Pei, Ph.D.
Pharmacology/Toxicology Reviewer

 / S / 4-25-00

Robin Huff, Ph.D.
Team Leader

Original NDA 20,831
Cc: NDA 20831/ HFD-570/Division File
HFD-570/ Huff / Jani / Pei

**APPEARS THIS WAY
ON ORIGINAL**

Jan
MAR 13 2000

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Division Of Pulmonary and Allergy Drug Products (HFD-570)

REVIEW INFORMATION:

Review No.: 3
Reviewer Name: Luqi Pei, D.V.M., Ph.D.
Key Words: Carcinogenicity studies, pharmacokinetics, draft CAC minutes
Review Completion Date: March 13, 2000
Information to be Conveyed to Sponsor: Yes _____ No x

APPLICATION INFORMATION:

IND or NDA Application No: NDA 20-831
Serial No., Content and Date of Submission: 11/23/99 supplement, complete response to division approvable letter dated 6/26/97.
Sponsor: Novartis Pharmaceutical Corporation, East Hanover, NJ
Drug Name: Foradil™ Aerolizer (Formoterol fumarate DPI)
Class: Beta 2 adrenergic bronchodilator
Indication: Prevention and treatment of bronchoconstriction in patients — years and older with reversible obstructive airway disease.
Usage: 12 µg, bid, with the maximum daily dose of — µg/patient

REVIEW SUMMARY:

This review examines outstanding issues in the evaluation of four carcinogenicity studies of formoterol. It specifically reevaluates reported AUC values and tumor incidence data in these studies in mice and rats. The review finds that no reliable AUC data are available in any of the four studies, but plasma levels of reasonable quality are available in the two dietary studies. Neither AUC or plasma level of formoterol is available in the two drinking water studies. Previously reported AUC data for these carcinogenicity studies were extrapolated from either single time-point samples or other studies with different modes of administration, durations and doses. Because the calculated AUC values vary significantly depending upon the pharmacokinetic parameters used in calculations, the previously reported AUCs may have overestimated the actual systemic exposure in mice and rats. This review derives new AUC ratios between animals and humans, when possible. It also examines the available AUC data in relation to tumor incidence. It concludes that mice and rats in these four studies have been sufficiently exposed to the drug.

TABLE OF CONTENTS

INTRODUCTION	2
REVIEW	4
Reexamination of AUCs in Mouse	4
AUCs and Their Relationship to Tumor Data in Rat	9
OVERALL SUMMARY	12
APPENDICES	13
Appendix 1	13
Appendix 2	17
Appendix 3	21

Documents Submitted and Included in This Review:

A complete response to the Approvable letter by the Division dated June 26, 1998. Submitted on 10/19/98 (vol. 1 p10-13, vol. 5, p1-15) and 11/23/99 (vol. 1, p21-25, and 88-89).

Previous Reviews

Review #	Reviewer	Review Date	Review Description
1	Tracey Zoetis	March, 1998	Review of carcinogenicity studies
2	Tracey Zoetis	May 28, 1998	Review of the original submission

INTRODUCTION

This review provides a follow-up to the Executive Carcinogenicity Assessment Committee (Exec. CAC) Meeting held on April 14, 1998 to evaluate the carcinogenic potential of formoterol fumarate (NDA 20-831, Novartis). Its purpose is to reexamine a few outstanding issues so that the Committee can close the minutes. The review specifically examines AUC data in mice and rats and tumor incidence data in rats.

On April 14, 1998, the Exec. CAC reviewed four carcinogenicity studies of formoterol in mice and rats in NDA 20-831. Table 1 summarizes the designs of these studies. Various tumors were found (Appendix 1).

Table 1. Summary of the 2-Year Carcinogenicity Studies of Formoterol in NDA-20831¹

Study No.	Species	Strain	Route of administration	Formoterol Dose (mg/kg/day)	Animals/sex/dose	Testing Laboratory
1	Rat	SD	Drinking water	15, 32, 64	50	—
2	Rat	Tif:RAIf(SPF)	Dietary	0.5, 2, 5, 20	50	Ciba-Geigy
3	Mouse	B6C6F1/Crl Br	Drinking water	69, 137, 267	50	—
4	Mouse	TIF:MAGf (SPF)	Dietary	2, 5, 20, 50	50	Ciba-Geigy

1. Extracted from Pharmacology and Toxicology Review by T. Zoetis dated March, 1998.

The Committee concluded that additional information was needed for proper evaluation of these studies. Table 2 summarizes the Committee's information request. The summary is based on draft meeting minutes authored by Mrs. Tracey Zoetis, the previous pharmacology and toxicology reviewer, on April 27, 1998. These minutes have not been finalized. Because the new internal action date for this application is April 2000, the Division needs to conduct the labeling review as soon as possible. It is necessary to close the Exec. CAC minutes so that the Division can conduct a proper labeling review.

Table 2. The Action Items Recommended by the Exec. CAC on Formoterol¹

Species/Study	Action Item
Mouse studies	<ul style="list-style-type: none"> a. Examine historical control data for adrenal subcapsular adenoma and carcinoma in male mice. b. Re-examine AUC levels for mice. c. Find out what criteria was used by the Sponsor in combining liver tumors in the dietary study.
Rat Studies	<ul style="list-style-type: none"> a. Re-examine AUC levels in comparison with tumor data. b. Evaluate mammary tumors using time-weighted adjustments for survival. c. Evaluate historical control data for mammary tumors.

1. Source: Draft Exec. CAC minutes drafted by Tracey Zoetis on April 27, 1998 (Appendix 2) and updated on February 16, 2000 (Appendix 1).

Since the Executive CAC meeting, the previous pharmacology review team, which consisted of Mrs. Tracey Zoetis and Dr. Hilary Sheevers, has taken considerable actions on this application. Table 3 summarizes these actions.

Table 3. The Action Items Taken by the Previous Review Team on Formoterol¹

Species/Study	Action Item
Mouse studies	<ul style="list-style-type: none"> a. Examined historical control data for adrenal subcapsular adenoma and carcinoma in male mice and found that the reported incidence for high dose males does not fall within historical control values of the test facility. b. Examined criteria used by the Sponsor in combining liver tumors in the dietary study and found that the combination of liver tumors originally reported as "hepatocellular tumors" represents a combination of hepatocellular carcinoma and benign hepatoma (also referred to as hepatocellular adenoma). The team also found that this combination was consistent with that recommended by the National Toxicology Program.
Rat Studies	<ul style="list-style-type: none"> a. Evaluated mammary tumors using time-weighted adjustments for survival and found that no statistically significant differences from control or significant trends were revealed. b. Evaluated historical control data for mammary tumors and found that the increases in the study were within historical ranges of the testing facility.

1. Source: Draft Exec. CAC minutes by Tracey Zoetis dated February 16, 2000 (Appendix 1).

However, two issues remain outstanding. They are: 1) re-examine AUC levels in mice, and 2) re-examine AUC levels in comparison with tumor data in rats. This review examines these two issues.

REVIEW

A. Re-examination of AUCs in Mouse

There were two 2-year mouse carcinogenicity studies of formoterol in mice, one dietary study and one drinking water study. Respective formoterol dose levels were 2, 5, 20 and 50 mg/kg/day in the dietary study and 69, 137 and 267 mg/kg/day in the drinking water study. Plasma formoterol levels in these studies are discussed below:

1. *The 2-year Dietary Carcinogenicity Study*

Plasma formoterol levels were determined at weeks 5, 26, 53, 78 and 105, using _____ (Zoetis' review dated May 28, 1998). The limit of quantitation was _____ Plasma formoterol levels in the 2 and 5 mg/kg/day groups were below the limit of quantitation. The 20 and 50 mg/kg/day groups showed mean plasma levels of 3.2 and 6.3 nmol/L, respectively. Mean AUC in the 50 mg/kg/day group is estimated to be 158 nmol.h/L (estimated from a single time point of 6.3 nmol/L, vol. 22.1, page 88)¹. This level of systemic exposure is approximately 300 times the human exposure (0.53 nmol.h/L at 48 µg/day, Vol. 22.1, p 89). The human exposure is extrapolated from the plasma AUC of 1.33 nmol.h/L for people receiving 120 µg inhaled formoterol [(1.33 nmol.h/L ÷ 120 µg) x 48 µg = 0.53 nmol.h/L].

2. *The 2-year Drinking Water Study*

Plasma drug levels were not monitored during the mouse drinking water study. Previously reported AUC ratios in the draft Exec. CAC minutes were mathematically derived from a single dose (gavage) pharmacokinetic study. These values vary among the drafts and reviews. The draft minutes dated April 27, 1998 (Appendix 2) state that the low dose (69 mg/kg/day) animals had an AUC value approximately _____ times that achieved at the maximum recommended human dose. The draft dated February 16, 2000 revised this value to 8083 (Appendix 1). Detailed calculations are not clear from either these draft minutes or previous reviews, but the reviews indicate that the plasma drug levels were calculated from pharmacokinetic parameters obtained in an oral gavage study (DM 1/1991). A reevaluation of the plasma formoterol levels and AUC ratios is necessary.

1. AUCs are usually calculated from data collected from several time-points post dosing, not a single time-point. However, the sponsor has shown that their calculated AUCs based on data from a single time-point are lower than those based on data from several time-points (Vol. 22.1, p 12). Apparently, this would result in lower AUC ratios between animals and humans. This approach seems to be more conservative and, thus, acceptable.

a. Estimate of Plasma Formoterol Levels in the Drinking Water Carcinogenicity Study

The estimated plasma formoterol levels (or AUCs) in the drinking water carcinogenicity study in mice can vary tremendously, depending upon the pharmacokinetic parameters used to obtain these numbers. Pharmacokinetic data for formoterol in mice are available with oral gavage, dietary, and drinking water administration. The duration of treatment ranged from single bolus dose to 24 months. Table 4 summarizes C_{max} and AUC values (when available) of these studies. Surprisingly, plasma formoterol levels vary by several orders of magnitude. For example, at similar doses of the drug, the respective C_{max}s are 1100 for oral gavage (60 mg/kg), 15.8 for drinking water (65 mg/kg), and only 0.004 nmol/L for dietary administration (140 mg/kg/day).

Table 4. Summary of Plasma Formoterol Levels in Mouse

Study #	Route	Dose	Duration	Measurement (h)	AUC nmol.h/L	C _{max} nmol/L		
DM 1/1991 ¹	Oral gavage	6	Single dose	0 - 4	300 ²	150		
		60		0 - 6	4300 ²	1100		
DM B29/ ¹ 1992	Drinking Water	65	3 months		-	15.8		
		120			-	29.6		
		180			-	9.6		
B106/1990 ¹	Dietary	140	3 months			0.004		
		400				0.009		
		1400				0.040		
Carc. study	Drinking Water	69	2 yr	ND	ND	ND		
		137						
		267						
Carc. study	Dietary	2, 5	2 year	0 - 24	-	BLQ		
		20			-	3.2		
		50			158 ³	6.3		

1. Extracted from draft review of formoterol pharmacokinetics and toxicokinetics by Tracey Zoetis dated February 16, 2000 (Appendix 3).
2. Fax from the sponsor to Mrs. P. Jani and T. Zoetis dated May 12, 1998.
3. Mean of 113 (male) and 222 (female). Source: vol. 21.1, p 88 of submission dated 11/23/99.
4. ND = Not determined, BLQ = Below limit of quantitation.

The use of pharmacokinetic data collected in various studies to derive AUC ratios for the 2-year drinking water study is discussed below.

1) The Oral Gavage Study

Predicted exposure ratios between mice and humans would be approximately 7,900, 16,000 and 30,000 for mice receiving 69, 137 and 267 mg/kg/day of the drug in drinking water, using pharmacokinetic data generated in the oral gavage study. These ratios probably over estimate the actual exposure in mice.

The above prediction uses pharmacokinetic parameters from single oral gavage doses of 6 and 60 mg/kg of formoterol in mice in which the respective AUCs are 300 and 4300 nmol.h/L. Data suggest that the plasma formoterol level might be proportional to the administered dose. Assuming a mean AUC of approximately 60.8 nmol.h/L per mg formoterol, doses of 69, 137 and 267 mg/kg/day would produce the predicted plasma AUC values of 4,200, 8,300, 16,000 nmol.h/L for formoterol, respectively. These AUCs correspond to AUC ratios of approximately 7,900, 16,000 and 30,000 for the low, mid and high dose groups, respectively, based on a human AUC of 0.53 nmol.h/L.

2) The 3-Month Drinking Water Study

Although this study used the same route and mode of administration as the 2-year drinking water carcinogenicity study, this is not an ideal study to use to predict systemic exposure because plasma levels lacked a dose-concentration relationship. In the 3-month study, mice received formoterol at doses of 65, 120 and 180 mg/kg/day in drinking water. Plasma drug levels were 15.8, 28.6 and 9.6 for the low, mid and high dose groups, respectively. Reasons for the lack of a dose-concentration relationship are not clear. No AUC ratios can be obtained based on the limited plasma level data.

Despite its shortcomings, this study provides hints of the overestimate of systemic exposure in the 2-year carcinogenicity study if the oral gavage data are used. This is because the plasma drug levels in the 3-month drinking water study were only a fraction of those in the single dose gavage study. For example, respective plasma drug levels were 15.8 nmol/L for a dose of 65 mg/kg/day in the 3-month drinking water study and 1,100 nmol/L for a dose of only 60 mg/kg in the oral gavage study. Because the plasma drug level in the oral gavage study is seventy-fold higher than that in the drinking water study, estimated AUC ratios for the drinking water carcinogenicity study would be significantly higher if calculated using the oral gavage data. For a dose of 69 mg/kg/day, the AUC ratio estimate would be 7,900 using the oral gavage study, but 800² using the drinking water study. Apparently, the oral gavage study would result in an overestimate of systemic exposure in the drinking water carcinogenicity study.

3) The 3-month Dietary Study

This is not an ideal study to use to predict the systemic exposure in the 2-year drinking water carcinogenicity study because plasma levels in this study were extremely low. Formoterol doses in this study were 140, 400 and 1,400 mg/kg/day. Similar to the 3-month drinking water study, only plasma levels were available (3.8 pmol/L or lower for a dose of 140 mg/kg/day). These values, however, were thousands of folds lower than those in the 3-month drinking water study. Exposure ratios, even for the high dose group, would be less than one. These values are probably meaningless, but reasons for such low plasma levels are not clear. One possible reason may be a

2. This AUC ratio is derived from an AUC ratio in the 3-month drinking water study in which a dose of 65 mg/kg/day yielded an AUC ratio of 750 $[(750 + 65) \times 69]$. The AUC ratio of 750 was calculated from a plasma drug level of 15.8 nmol/L $[15.8 \text{ nmol/L} + 6.3 \text{ nmol/L}] \times 300$, where a plasma level of 6.3 nmol/L corresponds to an AUC ratio of 300.

less sensitive analytic method as discussed later in the review.

4) The 2-year Dietary Carcinogenicity Study

This study would yield estimated AUC ratios, between mice and humans, of approximately 410, 820 and 1,600 for oral doses of 69, 137 and 267 mg/kg/day. In the dietary study, mice received formoterol at doses of 2, 5, 20 and 50 mg/kg/day for 2 years. As discussed earlier, the 50 mg/kg/day dose yields an AUC ratio of 300. Using an AUC ratio of 6 per mg of the drug (300/50), the predicted AUC ratios would be approximately 410; 820 and 1,600 for oral formoterol doses of 69, 137 and 267 mg/kg/day, respectively.

b. Evaluation of the Appropriateness of the Animal Models

Previous discussions have shown that the predicted AUC ratios between mice and humans vary dramatically depending upon the mathematical modeling. Table 4 has shown the variability of the mouse PK data in this application. For easy interpretation of the data, Figure 1 is a graphic presentation of plasma formoterol levels as a function of dose. Such variation is rather striking. Depending on the study used to derive the AUC ratios, such variations in pharmacokinetic data would yield strikingly different predicted AUC ratios.

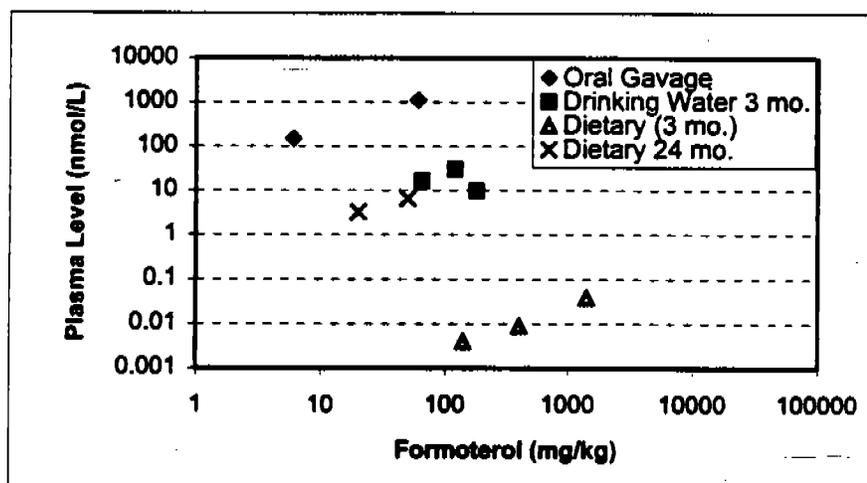


Figure 1. Plasma formoterol levels as a function of dose in mice.

Reasons for such a variation in plasma drug levels are not known at present. One possible explanation is the sensitivity of the analytic method, but the sponsor argued this might not be the case:

"... A variety of analytical methods were used to measure formoterol in biological fluid... The methods used to measure formoterol varied in sensitivity, and there were early difficulties in achieving the sensitivity necessary to measure plasma formoterol in the plasma of all dose groups. However, the report of each study includes a validation of the method used therein. Accuracy and precision can be determined across the range of

these concentrations measured..."

– Supplement of November 23, 1999, vol. 22.1, p 23

Despite the sponsor's dismissal of the contribution of the analytical method to the variability, Figure 2 shows a trend in the improvement of the analytic method over time (note: data in Figure 2 is from rat, not mouse, studies). At doses of approximately 20 mg/kg/day in rats, hardly any drug was detected in 1990, approximately 6 nmol/L was detected in 1991, while 20 nmol/L was detected in 1992. It seems that the 1992 method is probably the most sensitive one and the 1990 method is the least sensitive (the 3-month mouse dietary study discussed earlier was conducted in 1990). However, the specific method for each year was not clear from the previous reviews and recent submissions.

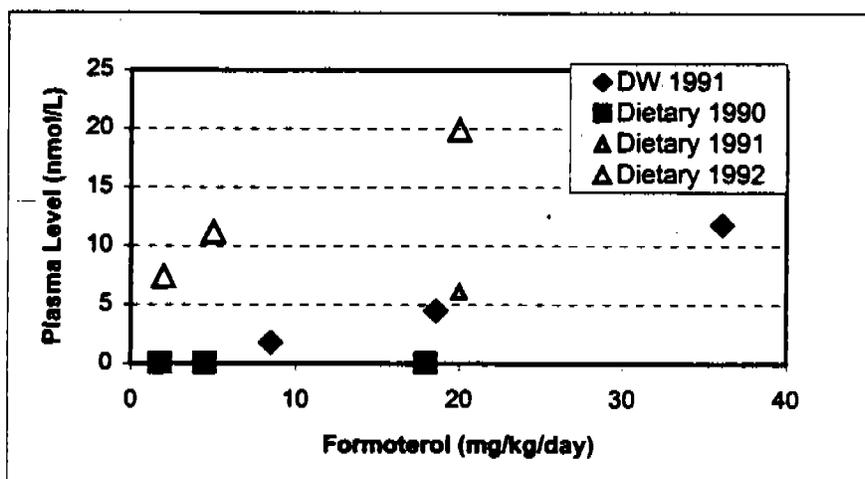


Figure 2. Plasma formoterol levels as a function of dose and time in rats. Plasma levels were extracted from the draft review of pharmacokinetic and toxicokinetic data by Mrs. Tracey Zoetis dated February 16, 2000.

Another potential contributor is metabolic capacity for the drug in mice. Formoterol undergoes extensive metabolism after oral administration. If metabolic pathways are saturated, a significant elevation of plasma drug levels could be seen. Single bolus gavage dosing could overwhelm metabolic pathways. Unfortunately, the metabolic profile of formoterol in mice is incomplete and its bioavailability is unknown.

The above discussions present a challenge in selecting an appropriate animal model for estimating the systemic exposure in the drinking water carcinogenicity study. Table 5 summarizes the predicted AUC ratios for a dose of 69 mg/kg/day formoterol, based on AUCs or plasma levels from the various studies. The oral gavage study would likely overestimate systemic exposure in mice, while the 3-month dietary study would likely underestimate the systemic exposure. Conducted most recently, the 3-month drinking water study and the 24-month dietary study were in general agreement. These two studies may probably provide the best estimate under the circumstances. They would predict AUC ratios between 410 and 800 for

a formoterol dose of 69 mg/kg/day in mice. These AUC ratios are greater than the AUC ratio of 25 currently accepted for carcinogenicity study dose selection. Thus, the dose selection for the 2-year drinking water carcinogenicity study is acceptable.

Table 5. Estimated AUC Ratios for 69 mg/kg/day of Formoterol in the 2-Year Drinking Water Study in Mice

Study #	Route	Dose (mg/kg/day)	Duration	Plasma C. nmol/L	Predicted AUC Ratio (for 69 mg/kg/day)
DM 1/1991	Oral gavage	60	1 day	1100	7,900
DM B29/1992	DW water	65	3 months	15.8	800
2-yr carc. study	Dietary	50	2 years	6.3	410
B106/1990	Dietary	140	3 months	0.002-0.004	0.06

c. Conclusion of the AUC Evaluation in the Drinking Water Study

A re-examination of pharmacokinetic data from various studies indicates that mice in the 2-year drinking water carcinogenicity study receiving formoterol doses of 69 mg/kg/day or more would likely have plasma exposure at least 410 times the expected human exposure. Thus, the dose selection for this drinking water study may be considered appropriate.

B. AUCs and Their Relationship to Tumor Data in Rat

1. AUCs

Similar to the mouse studies discussed previously, the quality of toxicokinetic data in the rat carcinogenicity studies is also variable. There were also two 2-year carcinogenicity studies in rats, one drinking water study and one dietary study. Formoterol dose levels were 0.5, 2, 5 and 20 mg/kg/day in the dietary study and 15, 32 and 64 mg/kg/day in the drinking water study, respectively. Plasma drug levels were assessed in the dietary study, but not the drinking water study.

APPEARS THIS WAY
ON ORIGINAL

a. AUCs in the Dietary Study

The re-evaluation reveals that the systemic exposure to formoterol in the high dose group (20 mg/kg/day) is at least 900 times the exposure at the maximum recommended human daily inhalation dose. AUC data for the 2-year dietary study in previous reviews are somewhat confusing³. A re-evaluation of the plasma levels revealed the following.

Plasma and urine formoterol levels were determined at weeks 12, 26, 53, 78 and 105. Mean plasma drug levels were 7.4, 11.2 and 19.9 nmol/L for doses of 2, 5, and 20 mg/kg/day, respectively. AUC ratios are not available in the report because of the nature of single time-point data. However, using their recent model to estimate AUC from single time-point data, the sponsor recently estimates that a plasma level of 19.9 nmol/L (in the 20 mg/kg group) corresponds to an AUC of 483 nmol.h/L, and approximately 900 times the exposure at the maximum recommended human inhalation dose (vol. 22.1, p 89).

a. AUCs in the 2-Year Drinking Water Carcinogenicity Study

Similar to the mouse drinking water carcinogenicity study, plasma drug levels were not monitored in the drinking water study in rats, and the reported formoterol AUC levels were extrapolated from pharmacokinetic parameters of single dose oral gavage studies. There were two oral gavage pharmacokinetic studies in rats (B4/1991 and B8/1991). Formoterol dose levels were 12.5, 25 and 50 mg/kg in both studies. Table 6 summarizes the AUCs in Study B4/1991. The estimated AUC ratio between rats and humans for the 25 mg/kg group would be 1,300, based on an AUC of 0.53 nmol.h/L in humans.

Using an AUC ratio of 52 (1300/25) per mg of formoterol as a reference, the estimated AUC ratios in the drinking water carcinogenicity study would be approximately 780, 1,700 and 3,300 for the oral doses of 15, 32 and 64 mg/kg/day. Furthermore, the estimated AUC ratio for 20 mg/kg/day would be 1,000. This ratio is comparable to the estimated ratio of 900 for the same dose in the dietary study. These data suggest that the oral gavage study may give a reasonable

3. The pharmacology and toxicology review by Tracey Zoetis dated March 1998 states the following: "... Exposure to CGP 25827A [formoterol] was measured in a later study in rats (B4/1991, B2/1991). Rats designated as Groups 1, 2 and 3 received a single dose at levels of 12.5, 25 and 50 mg/kg/day, respectively. Results indicated AUC values of 267.6 (M) and 317.3 (F); 560.3 (M) and 814.6 (F); and 1420.4 (M) and 4856.6 (F) nmol.h/L for Groups 1 - 3, respectively....". However, Study B4/1991 was an oral gavage study, which may not be directly applicable to the dietary study.

The review dated May 28, 1998 differs from the above. Its method section for the review of the 2-year dietary study indicates that the determination of the plasma formoterol levels was done at weeks 12, 26, 53, 78 and 105. This is correct, as indicated by Study Report B14/1992. Report B14/1992 is titled "24-month carcinogenicity study in rats; determination of formoterol in plasma and urine during 24 month administration of CGP 25827A in diet at the nominal daily doses of 0, 0.5, 2, 5 and 20 mg/kg body weight". The review, however, does not mention the actual plasma levels in the result section. Nonetheless, the draft review of pharmacokinetic and toxicokinetic data dated February 16, 2000 (Appendix 3) states that plasma formoterol levels in Report B14/1992 were 7.4, 11.2 and 19.9 nmol/L for doses of 2, 5, and 20 mg/kg/day in rats, respectively. Most data in this February 16, 2000 draft were not reviewed in the toxicokinetic section of the May 28, 1998 review.