

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 20831/000** Priority: **1S** Org Code: **570**
 Stamp: **26-JUN-1997** Regulatory Due: **18-FEB-2001** Action Goal: District Goal: **24-FEB-1998**
 Applicant: **NOVARTIS PHARMS** Brand Name: **FORADIL (FORMOTEROL FUMARATE)12MCG CAPS**
59 RT 10 Established Name:
EAST HANOVER, NJ 079361080 Generic Name: **FORMOTEROL FUMARATE**
 Dosage Form: **PDR (POWDER)**
 Strength: **12 MICROGRAMS**

FDA Contacts: **P. JANI (HFD-570) 301-827-1050** , Project Manager
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation:

ACCEPTABLE on 27-OCT-2000 by M. GARCIA (HFD-322) 301-594-0095
ACCEPTABLE on 12-MAY-2000 by M. GARCIA (HFD-322) 301-594-0095
ACCEPTABLE on 25-JUN-1998 by M. GARCIA (HFD-322) 301-594-0095
WITHHOLD on 27-APR-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: _____ DMF No: _____
 _____ AADA No:

Profile: **CHG** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE PACKAGER**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **05-SEP-2000**
 Decision: **ACCEPTABLE**
 Reason: **BASED ON PROFILE**

Establishment: _____ DMF No:
 _____ AADA No:

Profile: **CHG** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE PACKAGER**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **05-SEP-2000**
 Decision: **ACCEPTABLE**
 Reason: **DISTRICT RECOMMENDATION**

Establishment: **2416082** DMF No:
NOVARTIS PHARMA INC (CIBA) AADA No:
OLD MILL RD
SUFFERN, NY 10901

Profile: **ADM** OAI Status: **NONE**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
 Milestone Date **05-SEP-2000**
 Decision: **ACCEPTABLE**
 Reason: **BASED ON PROFILE**
 Profile: **CTL** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date **05-SEP-2000**
 Decision: **ACCEPTABLE**
 Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE RELEASE
 TESTER
 FINISHED DOSAGE STABILITY
 TESTER**

Establishment: **9692043**
NOVARTIS PHARMA INC (CIBA)
SCHAFFHAUSERSTRASSE
CH-4332 STEIN, , SZ

DMF No: **_____**
 AADA No:

Profile: **CHG** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date **05-SEP-2000**
 Decision: **ACCEPTABLE**
 Reason: **DISTRICT RECOMMENDATION**
 Profile: **CRU** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date **05-SEP-2000**
 Decision: **ACCEPTABLE**
 Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MICRONIZER
 FINISHED DOSAGE
 MANUFACTURER
 FINISHED DOSAGE STABILITY
 TESTER**

Establishment: **9612715**
NOVARTIS PHARMA INC (SANDOZ)
RINGASKIDDY/CORK, RINGASKIDD

DMF No:
 AADA No:

Profile: **CTL** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date **05-SEP-2000**
 Decision: **ACCEPTABLE**
 Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE
 TESTER**

Establishment: **9614433**
NOVARTIS PHARMANALYTICA SA
LOCARNO, , SZ

DMF No:
 AADA No:

Profile: **CTL** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE STABILITY
 TESTER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Milestone Date **26-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: _____
DMF No: _____
AADA No: _____

Profile: **CHG** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE PACKAGER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-SEP-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: _____
DMF No: _____
AADA No: _____

Profile: **RSP** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE STERILIZER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-SEP-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: _____
DMF No: _____
AADA No: _____

Profile: **CSN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-SEP-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: _____
DMF No: _____
AADA No: _____

Profile: **CSN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

MANUFACTURER

Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-SEP-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

**APPEARS THIS WAY
ON ORIGINAL**

CDER Establishment Evaluation Report
for June 08, 1998

Application: NDA 20831/000
Stamp: 26-JUN-1997 Regulatory Due: 26-JUN-1998
Applicant: NOVARTIS PHARMS
59 RT 10
EAST HANOVER, NJ 079361080

Priority: 1S
Action Goal:
Brand Name: FORADIL (FORMOTEROL
FUMARATE)12MCG CAPS
Established Name:
Generic Name: FORMOTEROL FUMARATE
Dosage Form: PDR (POWDER)
Strength: 12 MICROGRAMS

FDA Contacts: P. JANI (HFD-570) 301-827-1050 , Project Manager
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation:

WITHHOLD on 27-APR-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: _____ DMF No: _____
_____ AADA No: _____

Profile: POW OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 22-DEC-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment: 2416082
NOVARTIS PHARMA INC (CIBA)
OLD MILL RD
SUFFERN, NY 10901

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 02-SEP-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY
TESTER

Establishment: 9692043
NOVARTIS PHARMA INC (CIBA)
SCHAFFHAUSERSTRASSE
CH-4332 STEIN, , SZ

DMF No: _____
AADA No.

Profile: CHG OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 24-APR-1998
Decision: ACCEPTABLE

Responsibilities: FINISHED DOSAGE
MANUFACTURER

Reason: **DISTRICT RECOMMENDATION**

Establishment: _____
DMF No: _____
AADA No: _____

Profile: _____ OAI Status: **NONE** Responsibilities: _____
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **20-JAN-1998**
Decision: **WITHHOLD**
Reason: **FIRM NOT READY**

Establishment: _____
DMF No: _____
AADA No: _____

Profile: **RSP** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE STERILIZER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-MAR-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: _____
DMF No: _____
AADA No: _____

Profile: **CSN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-SEP-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: _____
DMF No: _____
AADA No: _____

Profile: **CSN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE**

CDER Establishment Evaluation Report
for June 08, 1998

Page 3 of 3

MANUFACTURER

Last Milestone: **OC RECOMMENDATION**
Milestone Date **08-SEP-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

APPEARS THIS WAY
ON ORIGINAL

Executive CAC
April 11, 2000

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Chuck Resnick, Ph.D., HFD-110, Alternate Member
Luqi Pei, Ph.D., HFD-570, Presenting Reviewer
Robin Huff, Ph.D., HFD-570, Team Leader

Authors of Draft: Tracey Zoetis and Luqi Pei, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #: 20-831
Drug Name: Formoterol fumarate
Sponsor: Novartis

Background information

This meeting is a follow-up meeting to the Executive CAC held on April 14, 1998 to evaluate the carcinogenicity of formoterol fumarate. Formoterol is a long acting beta 2 adrenergic bronchodilator. The proposed indication for formoterol is prevention and maintenance treatment of bronchoconstriction in patients with reversible obstructive airway disease. The drug is administered by inhalation via a metered dose dry powder inhaler.

Carcinogenicity of formoterol fumarate was evaluated in two studies each in rats and mice. The routes of administration were dietary and drinking water for each species. All four studies were reviewed at the previous Executive CAC meeting, in which additional information was requested so as to better evaluate these studies. The review team in HFD-570 collected the requested information and the current meeting re-evaluated these four studies in light of all available information.

Evaluation

Mouse Carcinogenicity Studies

Two 2-year carcinogenicity studies were conducted in mice to evaluate carcinogenicity of formoterol fumarate. In the first study, mice (Tif:MAGf [SPF], 50/sex/dose) were exposed to formoterol in diet at daily doses of 0, 2, 5, 20 and 50 mg/kg. The high dose (50 mg/kg/day) corresponds with an AUC value that is approximately 300 times the anticipated human daily exposure. There were no statistically significant differences in survival rate between treated and control groups. Statistically significant increases in the incidence of leiomyomas and leiomyocarcinomas were observed in female reproductive organs of animals in all treated groups. Statistically significant increases in the incidence of

hepatocellular carcinoma were observed in the 50 mg/kg/day males and in the 20 and 50 mg/kg/day females.—

In the second study, mice (B6C6F1/crl Br, 50/sex/dose) were exposed to formoterol in drinking water at daily doses of 0, 69, 137 and 267 mg/kg. Plasma drug levels were not determined during the study, but data from other studies suggested that the low dose (69 mg/kg/day) corresponds with an AUC value that is approximately 410 times the anticipated human daily exposure. There were no statistically significant differences in survival rate between treated and control groups. The incidence of adrenal subcapsular adenomas and carcinomas was increased in treated animals (0/46, 3/41, 1/50 and 5/50 in controls, LD, MD and HD, respectively) and was statistically significant at the HD of 267 mg/kg/day. Significance was achieved at all doses if tumor incidence was combined with the incidence of moderately severe to severe hyperplasia, and the historical control for these tumor types is zero for all studies (13) conducted at the test facility. Uterine leiomyomas, a tumor type known to be associated with beta agonists, were not observed in the study, but this strain of mice has been reported to be resistant to this tumor.

Rat Carcinogenicity Studies

Two 2-year carcinogenicity studies were conducted in rats to evaluate carcinogenicity of formoterol fumarate. In the first study, rats (Tif:RAIf[SPF], 50/sex/dose) were administered formoterol in diet at daily doses of 0, 0.5, 2, 5, and 20 mg/kg. The high dose (20 mg/kg/day) corresponds with an AUC value that is 900 times the anticipated human daily exposure. There were no statistically significant differences in survival between treated and control groups. Tumors observed in this study were limited to the reproductive system in females. Dose-related but statistically non-significant increases in the incidence of ovarian leiomyomas were observed (0/70-C, 0/70-LLD, 1/69-MLD, 1/69-MHD and 3/69-HD). Dose-related increases in the incidence of benign granulosa/theca cell tumors (1/70-C, 5/70-LLD, 6/69-MLD, 6/69-MHD and 8/69-HD) were also observed in the ovaries.

In the second study, Sprague-Dawley rats were exposed to formoterol in drinking water at doses of 0, 15, 32 and 64 mg/kg/day. Plasma drug levels were not monitored during the study. Survival rate was decreased in all treated groups. The respective incidences of survival for control, low mid and high dose groups were 64, 38 (p=.013), 46 (p=.042), and 46 (p=.088) % in the males, and 56, 36 (p=.043), 30 (p=.006), and 32 (p=.003) % in the females. Increased incidences of ovarian leiomyomas were observed in all treated female groups and were considered a treatment-related effect. Other tumors such as observed in thyroid and mammary gland may not be treatment-related effects. Compared with the concurrent control, a slight but statistically significant increase in incidences of thyroid c-cell adenomas and carcinomas was observed in high dose males. Slight but statistically significant increases in incidences of mammary adenocarcinomas were observed in the mid and high dose females. The observed incidences of the thyroid and mammary tumors in the treated groups, however, were within the historic data range for the control animals in the laboratory. Thus, these thyroid and mammary tumors may not be treatment-related.

Executive CAC Recommendations and Conclusions:

The following recommendations were made regarding the biological significance of the tumor findings and the reporting of the results in the product label. Salient information has been captured in the table below, with details provided in the preceding text of the minutes.

Significant Neoplastic Findings in Mice Considered for Inclusion in Labeling					
Tumor Type	Dosing Method	Lowest Dose at Which Tumor was Observed (mg/kg/day)/sex	Inclusion in the labeling		Rationale
			Yes	No	
Adrenal Subcapsular adenoma + carcinoma	Water	69/♂	x		This tumor type appears to be an endpoint of a hyperplastic response to the drug that occurred at all doses.
Uterine leiomyomas + leiomyosarcomas	Diet	2/♀	x		This finding is known to be associated with this class drug in the given species.
Hepatocellular carcinoma	Diet	50/♂, 20/♀	x		The incidence of this finding is significantly different from control values in the testing facility.

Significant Neoplastic Findings in Rats Considered for Inclusion in Labeling					
Tumor Type	Dosing Method	Lowest Dose at Which Tumor was Observed (mg/kg/day)/sex	Inclusion in the labeling		Rationale
			Yes	No	
Ovarian leiomyoma	Water Diet	15/♀ 20/♀	x		The finding is known to be associated with this class of drugs in this species.
Ovary: benign granulosa/theca cell tumors	Diet	0.5/♀	x		The incidence of this tumor was increased at all doses and was viewed as biologically significant when considered with the increased incidence of hyperplasia.
Thyroid c-cell adenoma and carcinoma	Water	64 /♂		x	The incidence of this tumor in the current study was within historical control ranges of the performing laboratory. Also, it was noted only in treated group with significantly low survival rate.
Mammary adeno-carcinoma	Water	32/♀		x	Tumor incidence in the current study was within historical control ranges of the performing laboratory.

1 10 1
/S/

~~Joseph DeGeorge, Ph.D.
Chair, Executive CAC~~

04/14/00

cc:\

- Trout/Division File, HFD 570
- Jani/Program Manager, HFD-570
- Huff/Team Leader, HFD-570
- Pei/Reviewer, HFD-570
- Seifried /HFD-024

APPEARS THIS WAY
ON ORIGINAL

TROUT
JANI

To: Joseph DeGoerge, Ph.D.
Chair of the Carcinogenicity Assessment Committee

From: Luqi Pei, Ph.D. /S/ 3/13/00
Pharmacology and Toxicology Reviewer, HFD-570

Through: Robin Huff, Ph.D. /S/ 3-13-00
Pharmacology and Toxicology Team Leader, HFD-570

Subject: CAC minutes for formoterol fumarate, NDA 20-831

The purpose of this memo is to provide the Carcinogenicity Assessment Committee (CAC) requested information to evaluate the carcinogenic potential of formoterol fumarate (NDA 20-831, Novartis) so that the Committee can close the minutes of the Executive CAC Meeting held on April 14, 1998. Mrs. Tracey Zoetis, the previous pharmacology and toxicology reviewer for the application, drafted the minutes and sent them to Mrs. Adele Seifried on April 27, 1998. Appendix 1 is a copy of the draft minutes.

According to the draft minutes, the Exec. CAC requested six action items in the evaluation of carcinogenicity studies of formoterol in mice and rats. Table 1 summarizes these action items.

Table 1. The Action Items Requested by the Exec. CAC on Formoterol¹

Species/Study	Action Item
Mouse studies	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	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 1).

The following actions have been taken since the Exec. CAC meeting:

A. Mouse Studies

- a. *Examine historical control data for adrenal subcapsular adenoma and carcinoma in male mice.*

Historical control data for adrenal subcapsular adenoma and carcinoma in male mice were examined. It was found that the reported incidence for adrenal subcapsular adenoma and carcinoma in high dose males does not fall within historical control values of the test facility.

b. *Re-examine AUC levels for mice.*

AUC levels for mice were re-examined. It was found that mice in both studies have been sufficiently exposed to formoterol. Plasma formoterol levels in the high dose groups in the two carcinogenicity studies in mice were likely to be more than 300 times the expected human plasma levels.

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. AUC ratios reported in the previous reviews were extrapolated from other studies with different modes of administration. These ratios may have overestimated the systemic exposure.

The AUC ratios have been recalculated. This re-examination found that plasma drug levels were available in the dietary carcinogenicity study and its high dose (50 mg/kg/day) corresponds with an AUC value of approximately 300 times the anticipated human daily exposure.

The AUC ratios for the drinking water study have been recalculated—relying on data from dietary route of administration. Actual systemic exposure in the drinking water carcinogenicity study in mice is unknown because plasma drug levels were not monitored in the study. Although a precise AUC ratio cannot be obtained for the drinking water study, the 2-year dietary carcinogenicity study appears to provide a reasonable estimate of the systemic exposure in the drinking water carcinogenicity study (a dose of 65 mg/kg/day in a 3-month drinking water study resulted in plasma drug levels comparable to those achieved with a 50 mg/kg/day dietary dose). Extrapolation from the dietary toxicokinetic data indicates that the low dose group (69 mg/kg/day) in the drinking water carcinogenicity study may have been exposed to formoterol at 410 times the anticipated human daily exposure. Thus, mice receiving 69, 137 and 267 mg/kg/day of formoterol in the drinking water study have achieved sufficient systemic exposure.

- c. *Examine criteria used by the Sponsor in combining liver tumors in the dietary study.***
Criteria used by the Sponsor in combining liver tumors in the dietary study were examined. It was 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). This combination was consistent with that recommended by the National Toxicology Program.

B. Rat studies

a. *Re-examine AUC levels in comparison with tumor data.*

AUC levels in comparison with tumor data were re-examined. It was found that a direct comparison of AUCs in relation to tumor incidences in the two rat studies was

not possible because of the lack of relevant data. Plasma drug level was monitored in the dietary study (0.5, 2, 5 and 20 mg/kg/day), but not in the drinking water study (15, 32 and 64 mg/kg/day). Similar to the mouse studies, AUC data for the drinking water study in previous reviews were extrapolated from other studies with different modes of administration. Those data may not provide the best estimate of systemic exposure in rats.

Despite the lack of direct AUC comparison, toxicologic evaluation indicates that the increased tumor incidence in the drinking water study could be related to an increase in systemic exposure. Previous toxicological evaluation has concluded that all doses (15 - 64 mg/kg/day) in the drinking water study exceeded the maximum tolerated dose (MTD). In comparison, none of the doses (\leq 20 mg/kg/day) in the dietary study reached the MTD. Because higher tumor incidences were observed in the drinking water study than in the dietary study, the increase in tumor incidences in the drinking water study appears to be related to increased systemic exposure. Other factors may have also contributed to the observation. For example, the difference in animal strain could also play a role. Rat strains were Sprague-Dawley in the drinking water study and Tif:RAIf(SPF) in the dietary study.

b. Evaluate mammary tumors using time-weighted adjustments for survival.

Mammary tumors using time-weighted adjustments for survival were evaluated. There were no statistically significant differences from control or significant trends in mammary tumors using this analysis.

c. Evaluate historical control data for mammary tumors.

Historical control data for mammary tumors were evaluated. The increases in the study were within historical ranges of the testing facility.

The above discussion summarizes actions that were requested by the Exec. CAC and have been taken by reviewers for the evaluation of formoterol carcinogenicity. Hopefully, this memo provides sufficient information for the Committee to close the minutes. The Division will conduct a labeling review as soon as the minutes are closed. The internal action date for this application is April 2000.

The draft minutes (original draft date of April 27, 1998) have been revised to reflect the above actions and are provided for signature (Appendix 2).

APPEARS THIS WAY
ON ORIGINAL

11 PAGE(S) REDACTED

Draft

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**CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT
AND
FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET**

DRUG IDENTIFICATION

NDA: 20-831
IND: _____
Drug Code #: CGP 25827A
CAS#: 43229-80-7
DIVISION(s): Pulmonary Drug Products, HFD-570
DRUG NAME(s): Foradil (Formoterol fumarate)
SPONSOR: Novartis Pharmaceuticals Corporation
P/T REVIEWER: Tracey Zoetis
P/T REVIEW DATE: March 1998
THERAPEUTIC CATEGORY: Bronchodilator
PHARMACOLOGICAL/
CHEMICAL CLASSIFICATION: Selective β_2 -adrennergic receptor
PRIOR FDA DOSE
CONCURRENCE (Div./CAC)? : No
MUTAGENIC/GENOTOXIC
(y/n/equivocal/na; assay): Negative in full battery including *in-vitro* assays

- mutagenicity in microorganisms
- reversion in bacteria
- *salmonella*/mammalian-microsome mutagenicity
- V79 Chinese hamster point mutation test
- unscheduled DNA synthesis repair in rat hepatocytes
- unscheduled DNA synthesis repair in human fibroblasts
- transformation assay in mammalian fibroblasts
- chromosome analysis of CHO cells

and *in vivo* assays

- mouse micronucleus test
- rat micronucleus test
- chromosome analysis in somatic cells of Chinese hamsters.

BACKGROUND INFORMATION

Index of Studies
Included in this
Review:

Study No. 1 – Rat Drinking Water Study
Study No. 2 – Rat Dietary Study
Study No. 3 – Mouse Drinking Water Study
Study No. 4 – Mouse Dietary Study

Chronology of Events: Dose rangefinding studies for carcinogenicity testing began in 1979. Carcinogenicity studies were conducted in rats and mice via drinking water in 1980 - 1982. Interpretation of the rat study was confounded by low survival. Additional histopathology was performed over the years to elucidate findings in the rat study, with a final amendment to the report dated 1989. Also in 1989, dietary rangefinding studies began in rats and mice. The rat dietary study was conducted from 1989 - 1991 and the mouse dietary study was conducted from 1990 - 1992.

Metabolism: The primary metabolite of Formoterol fumarate is a direct phenolic O-glucuronide and is common to mice, rats, dogs, and humans. No major metabolites are unique to any species tested. Protein binding was similar between rat, dog, and human plasma and ranged from 50 to 65%.

Pharmacokinetics: Formoterol fumarate is present at low or undetectable levels in human plasma at anticipated human doses. Interspecies comparison of plasma concentrations of the drug is confounded by unreliable analytical methods for quantifying the drug in plasma at low doses. Plasma levels were, however, quantified at high doses and are useful for dose setting in the subject carcinogenicity studies.

STUDY NO. 1 -- RAT DRINKING WATER CARCINOGENICITY STUDY

RAT STUDY DURATION (weeks): 104
STUDY STARTING DATE: August 21, 1980
STUDY ENDING DATE: August 18, 1982
REPORT DATE: September 3, 1983 with Amendments to July 12, 1989
LABORATORY: _____
RAT STRAIN: Sprague-Dawley
ROUTE: Oral (Drinking Water)
DOSING COMMENTS: The *MTD* was exceeded in all groups as evidenced by low survival. The interpretation of carcinogenic findings is confounded by the low survival.

APPEARS THIS WAY
ON ORIGINAL

BASIS FOR DOSE SELECTION:
(MTD; AUC; ratio; saturation;
maximum feasible)

The rationale for dose selection was not discussed. The MTD was exceeded in the 2-year study, however the 3-month dose range finding study did not yield results that were predictive of an effect on long term survival. Findings in the 3-month study using doses identical to those of the 2-year study included: myocardial fibrosis in 0/10, 1/10, 2/10, and 0/10 males in Groups 1 - 4, respectively and thigh muscle hypertrophy was noted in all treated and no control rats. Weights of male reproductive organs (epididymides, seminal vesicles, and prostate) were lower in treated than control groups. Uterine weights were slightly increased for all treated groups when compared to controls. Body weight and food consumption values were higher for all treated groups when compared to controls. A no observable effect level (NOEL) was not identified for these findings.

Prior FDA Concurrence:

None

Dosing Information

Group	No./Sex/Group	Dose Level (mg/ml)	Actual Compound Consumed (mg/kg/day)
1	50	0	0
2	50	.125	15
3	50	.25	32
4	50	.50	64

Exposure to CGP-25827A in drinking water was measured in a later study in rats (B8 1991). Rats designated as Groups 1, 2, and 3 were dosed for 3 months at levels of 12.5, 25, and 50 mg/kg/day, respectively, followed by a single gavage dose just prior to sample collection. Results indicated AUC values of 687.9, 1658.2, and 2659.4 nmol·h/L for Groups 1 - 3, respectively.

RAT CARCINOGENICITY (negative; positive; MF; M; F)

**Carcinogenicity: Positive (+) or Negative (-)
for Specified Tumor Type and Lowest Dose Observed**

Tumor Type	Males	Females
Thyroid C cell tumors	+ (15 mg/kg/day)	
Ovarian Leiomyomas		+ (15 mg/kg/day)
Mammary Adenocarcinoma		+ (32 mg/kg/day)

RAT TUMOR FINDINGS

Statistically significant neoplastic findings were noted in thyroid C cells in the high dose males, ovarian leiomyomas in all treated groups of females, and mammary adenocarcinomas in mid and high dose females. The incidence of these lesions is presented in the following tables.

Dose (mg/kg/day):	0	15	32	64	Trend
N	50	50	50	49	
Hyperplasia	31 (62%)	43* (86%)	31 (62%)	40* (62%)	
Adenoma	7 (14%)	0* (0%)	10 (20%)	11 (22%)	*
Carcinoma	1 (2%)	3 (6%)	2 (4%)	5 (10%)	
Combined Adenoma + Carcinoma	8 (16%)	3 (6%)	12 (24%)	16* (33%)	
Combined Hyperplasia + Adenoma + Carcinoma	34 (68%)	46* (92%)	43* (86%)	44* (90%)	

*Statistically significant ($p \leq 0.05$).

Dose (mg/kg/day):	0	15	32	64	Trend
N	48	50	49	50	
Leiomyoma	1 (2%)	14* (28%)	14* (28%)	16* (32%)	*

*Statistically significant ($p \leq 0.05$).

Dose (mg/kg/day):	0	15	32	64
N	50	49	50	50
Adenocarcinoma	4 (8%)	7 (14%)	12* (24%)	12* (24%)
Fibroadenoma	21 (42%)	12 (24%)	14 (28%)	16 (32%)
Combined	23 (46%)	17 (35%)	24 (48%)	22 (44%)

*Statistically significant ($p \leq 0.05$).

RAT STUDY COMMENTS

Interpretation of the findings of carcinogenicity in this study is confounded by low survival rates in all treated groups. The MTD was clearly exceeded in this study as survival was less than 50% in all treated groups. The cause of death was not determined. Survival rates are indicated in the following table.

Number and Percent of Animals Surviving to Termination

Dose (mg/kg/day):	Males				Females			
	0	15	32	64	0	15	32	64
Number	32	19	22	22	28	17	15	13
%	64	38	46	46	56	36	30	32
P values		.013	.042	.088		.043	.006	.003

The number of animals surviving to termination is less than those recommended by various authorities on carcinogenicity testing (FDA Redbook II 1993; Robens et. al. in Hayes 1994). Trend analysis revealed statistical significance for females ($p = .0042$) but not for males ($p = 0.319$). Based on the significantly low survival in all treated groups, it appears that the doses used in this study were not adequate for characterization of the carcinogenic potential of Formoterol fumarate.

STUDY NO. 2 - RAT DIETARY CARCINOGENICITY STUDY

RAT STUDY DURATION (weeks): 104
 STUDY STARTING DATE: August 28, 1989
 STUDY ENDING DATE: September 5, 1991
 REPORT DATE: March 26, 1992
 LABORATORY: CIBA-GEIGY Ltd., Basle, Switzerland
 RAT STRAIN: Albino, Tif:RAIf(SPF), RII/1 x RII/2 hybrid
 ROUTE: Diet
 DOSING COMMENTS: None
 BASIS FOR DOSE SELECTION: The low-mid dose (2 mg/kg/day) yields a rodent to human plasma AUC ratio that is 32 times the (MTD; AUC; ratio; saturation; maximum feasible) anticipated human daily exposure. A previous carcinogenicity study (reported above) and a 28-day palatability study at doses of 0.4, 1.7, 4, and 18 mg/kg/day in which the drug was demonstrated to be palatable in the diet were also considered.

Prior FDA Concurrence: None

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ON ORIGINAL

Dosing Information

Group	Carcinogenicity Only	Carcinogenicity and Hematology	Carcinogenicity and Drug Level Determinations in Blood and Urine	Target Dose (mg/kg/day)
	No. Animals/sex	No. Animals/sex	No. Animals/sex	
1	50	10	10	0
2	50	10	10	0.5
3	50	10	10	2
4	50	10	10	5
5	50	10	10	20

Exposure to CGP 25827A via oral gavage was measured in a later study in rats (B4/1991 2/1991). 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(σ) and 317.3(♀); 560.3(σ) and 814.6(♀); and 1420.4(σ) and 4856.6(♀) $\mu\text{mol}\cdot\text{h}/\text{L}$ for Groups 1 - 3, respectively. Plasma AUC values for the 2 and 5 mg/kg/day dose groups were determined in a separate study (F-1-4-5) and were 17.4 and 46.9 $\mu\text{mol}\cdot\text{h}/\text{L}$, respectively.

RAT CARCINOGENICITY (negative; positive; MF; M; F)

Sex	+/-	Explanation
Male	-	No increase in incidence or severity of neoplasia was noted when treated groups were compared to controls.
Female	+	Tumors were limited to the female reproductive system and have been demonstrated in previous studies with drugs of this class.

RAT TUMOR FINDINGS

Treatment-related neoplastic lesions were noted in female reproductive organs and consisted of benign granulosa/theca cell tumors of the ovaries and mesovarian leiomyoma.

Although not statistically significant, mesovarian leiomyoma is a known response to this class of drug (Kelly et. al. 1993, Jack et. al. 1983). Other investigators have reported that early studies of several β_2 agonist failed to demonstrate mesovarian leiomyomas but later studies revealed "...that any β_2 adrenergic agonist would be expected to produce [this lesion] in rats if properly studied (adequate potency and bioavailability)..." (Sells and Gibson, 1987). The incidence of this lesion in the high dose group indicates that adequate doses and bioavailability of CGP 25827A were present in the rats of this study to ascertain the carcinogenic potential of the test compound (Kelly et. al., 1993; Jack et. al., 1983).

The increased incidence of benign granulosa/theca cell tumors is considered to be the endpoint of a hyperplastic response as it did not progress to malignancy. The incidence of these tumors are presented in the table below. Relevant non-neoplastic lesions are also presented in the table to illustrate the spectrum of the continuum of tumorigenesis in the case of the granulosa/theca cell tumors.

Notable Microscopic Findings in Female Reproductive Organs - Incidence (p value)

	Dose (mg/kg/day):				
	0	.05	2	5	20
<i>Ovary N:</i>	70	70	69	69	69
Cysts	7	24 (.002)	23 (.002)	34 (<.0001)	30 (<.0001)
Granulosa/Theca cell					
Hyperplasia	17	32 (.055)	33 (.032)	31 (.010)	34 (.007)
Benign	1	5 (.122)	6 (.085)	6 (.048)	8 (.051)
Malignant	1	0 (1.00)	2 (0.629)	0 (1.00)	0 (1.00)
Benign or Malignant	2	5 (.283)	8 (.075)	6 (.127)	8 (0.142)
Total (hyperplasia, benign, or malignant)	18	36 (.019)	36 (.016)	33 (.013)	39 (.002)
Mesovarian leiomyoma	0	0 (1.00)	1 (.500)	1 (.480)	3 (.187)
<i>Uterus N:</i>	70	70	69	70	69
Polyps	2	3 (.582)	3 (.621)	3 (.510)	10 (.023)

The incidence of all primary tumors reported in the rat dietary study is presented as Attachment 1.

RAT STUDY COMMENTS

This study was adequately designed and selected doses provided an acceptable margin (> 25 fold) of the plasma AUC rodent to human ratios and yielded the neoplastic lesion that serves as a marker for adequacy in carcinogenicity testing for this class of drug (Sells and Gibson, 1987). The presence of mesovarian leiomyomas in high dose females indicates that adequate potency, bioavailability, and strain sensitivity was achieved in this study to ascertain the carcinogenic potential of CGP 25827A. Survival was not affected; thus sufficient numbers of animals were available at the end of the study to adequately characterize the carcinogenic response to the test compound.

STUDY NO. 3 - MOUSE DRINKING WATER CARCINOGENICITY STUDY

MOUSE STUDY DURATION (weeks): 104
 STUDY STARTING DATE: September 8, 1980
 STUDY ENDING DATE: September 14, 1982
 REPORT DATE: September 16, 1983
 LABORATORY:

MOUSE STRAIN: B6C6F1/Crl Br
 ROUTE: Drinking water
 DOSING COMMENTS: None
 BASIS FOR DOSE SELECTION: (MTD; AUC; ratio; saturation; maximum feasible) The rationale for dose selection was not discussed. However a 3-month study conducted at dose levels 0.25, 0.50, and 1.0 mg/ml (or 99, 190, and 424 mg/kg/day) yielded no treatment-related effects at the high dose level (D-8-3).
 PRIOR FDA CONCURRENCE: None

Dosing Information

Group	No./Sex/Group	Dose Level (mg/ml)	Compound Consumed (mg/kg/day)
1	50	0	0
2	50	.25	69
3	50	.50	137
4	50	1.0	267

Exposure to CGP 25827A via a single oral gavage dose was determined in a later study using 2 male mice (DM 1/1991). The mice received 6 and 60 mg/kg doses, respectively. Resultant AUC values were 130 and 1100 $\mu\text{mol}\cdot\text{h/L}$, respectively.

MOUSE CARCINOGENICITY (negative (-); positive (+); MF; M; F)

Sex	+/-	Explanation
Male	+	Adrenal subcapsular cell hyperplasia was noted in all treated groups of males and appeared to progress to adenoma in 0, 5, 2, and 10 % of males in Groups 1 - 4, respectively, and to carcinoma in 0, 2, 0, and 2% in males in Groups 1 - 4, respectively.
Female	-	No increase in incidence or severity of neoplasia was noted when treated groups were compared to controls.

MOUSE TUMOR FINDINGS

Tumor findings were limited to the continuum of hyperplasia to carcinoma in subcapsular adrenal cells of treated male mice. The incidence of these findings is as follows:

Number of Males with Adrenal Subcapsular Lesions				
Dose (mg/kg/day):	0	69	137	267
Number examined	46	41	50	50
Hyperplasia (Severity Grade)				
Minimal (1)	29	5	9	14
Slight (2)	14	22	27	11
Moderate (3)	1	9	8	13
Moderately Severe (4)	0	2	4	8
Severe (5)	0	1	1	2
Adenoma	0	2	1	5
Carcinoma	0	1	0	1
Hyperplasia (Grade 1 - 5) + Adenoma or Carcinoma	44	39	49	50
Hyperplasia (Grade 4 - 5) + Adenoma or Carcinoma	0	6*	6*	15*
Adenoma + Carcinoma	0	3	1	5*

*Significantly different from control ($p \leq 0.05$)

MOUSE STUDY COMMENTS

Tumors in female reproductive organs (i.e., leiomyomas) have been demonstrated to be reliable indicators of the appropriate dose, bioavailability, and potency of β agonists in carcinogenicity studies (Sells and Gibson, 1987). This important finding was lacking in the current study. Therefore, it is concluded that this study does not adequately ascertain the carcinogenic potential of CGP 25827A.

STUDY NO. 4 - MOUSE DIETARY CARCINOGENICITY STUDY

MOUSE STUDY DURATION (weeks):	104
STUDY STARTING DATE:	September 24, 1990
STUDY ENDING DATE:	October 27, 1992
REPORT DATE:	May 13, 1993
LABORATORY:	CIBA-GEIGY Ltd., Basle, Switzerland
MOUSE STRAIN:	Tif:MAGf(SPF)
ROUTE:	Diet
DOSING COMMENTS:	None
BASIS FOR DOSE SELECTION: (MTD; AUC; ratio; saturation; maximum feasible)	The approximate mid dose (6 mg/kg/day) yields a rodent to human plasma AUC ratio that is 244 times the anticipated human daily exposure. A previous carcinogenicity study (reported above) and a 3-month rangefinding study with target doses of 0, 40, 140, 400, and 1400 mg/kg/day were also considered. Increased heart weight without microscopic correlate was noted at the lowest dose tested in the 3 month study.
PRIOR FDA CONCURRENCE:	None

Dosing Information

Group	Carc. only	Carc. and Hematology	Carc. and Plasma level Determinations	Target Dose
	No. Animals/sex	No. Animals/sex	No. Animals/sex	(mg/kg/day)
1	50	10	25	0
2	50	10	25	2
3	50	10	25	5
4	50	10	25	20
5	50	10	25	50

Exposure to CGP 25827A via was determined in a later study (DM 1/1991). The mice received 6 and 60 mg/kg doses, respectively. Resultant AUC values were 130 and 1100 $\mu\text{mol}\cdot\text{h/L}$, respectively.

MOUSE CARCINOGENICITY (negative; positive; MF; M; F)**Statistically Significant Differences from Control**

Sex	+/-	Explanation
Male	+	"All liver tumors" were significant in 20 and 50 mg/kg/day groups and liver carcinoma was significant in the 50 mg/kg/day group.
Female	+	"Smooth muscle tumors" of the female reproductive system was significant in all treated groups. Liver carcinoma was significant on the 20 and 50 mg/kg/day groups.

MOUSE TUMOR FINDINGS**Neoplastic Findings in the Female Genital Tract - Incidence (p value)**

	Dose (mg/kg/day):				
	0	2	5	25	50
<i>Number Observed</i>	85	84	85	85	85
Leiomyoma (1)	4	13 (.051)	13 (.030)	14 (.018)	17 (.005)
Leiomyosarcoma (2)	0	3 (.117)	3 (.125)	3 (.200)	5 (.061)
Smooth Muscle Tumor (1 + 2)	4	16 (.010)	16 (.006)	16 (.005)	22 (.001)