Relevant Microscopic Findings in the Liver - Incidence (p value)

	Males					Females				
Dose (mg/kg/day):	0	2	5	20	50	0	2	5	20	50
N	*85*	*83*	*85*	*84*	*85*	*85*	*84*	*85*	*85*	*85*
Hypertrophy	19	43 (.000)	38 (.013)	38 (.004)	27 (.133)	12	27 (.002)	26 (.004)	18 (.162)	14 (.359)
Benign Hepatoma	24	24 (.748)	24 (.388)	31 (.106)	25 (.646)	11	12 (.516)	17 (.176)	19 (.073)	14 (.168)
Hepatocarcinoma	10	12 (.568)	19 (.201)	18 (.134)	26 (.001)	2	5 (.268)	3 (.577)	11 (.006)	7 (.023)
All Liver Tumors[1]	28	31 (.671)	40 (.181)	40 (.045)	41 (.072)	11	14 (.420)	19 (.087)	26 (.002)	19 (.019)

[1]Note: tumor types and criteria for combining these tumors were not specified in the Sponsor's report.

A table of the incidence of all primary neoplasms in the mouse dietary carcinogenicity study is provided in Attachment 2.

MOUSE STUDY COMMENTS

This study was adequately designed and with sufficient survival to ascertain the carcinogenic potential of CGP 25827A when administered to mice at levels of 0, 2, 5, 20, and 50 mg/kg/day for two years. The selected doses provided an acceptable margin (>25 fold) of plasma AUC rodent to human ratios. The NOEL for the liver neoplasia was 5 mg/kg/day for males (all liver tumors) and females (carcinoma and all liver tumors). The NOEL for the neoplastic findings in female reproductive organs was not identified in this study.

Findings in the female genital tract (leiomyoma and leiomyosarcoma) are a known response to this class of drug in mice (Gibson et. al. 1987, Sells and Gibson, 1987). The incidence of these findings in the treated groups indicates that adequate doses and bioavailability of CGP 25827A were present in the mice of this study to ascertain the carcinogenic potential of the test compound.

OVERALL CONCLUSION

Two of the four carcinogenicity studies with Formoterol fumarate are considered to have been adequately designed and with sufficient survival to ascertain the carcinogenic potential of Formoterol fumarate in the species and strains tested, based on two criteria. The first criteria is consistent with the ICH Guideline on Dose Selection for Carcinogenicity Studies of Pharmaceuticals, in that doses achieved or exceeded the minimum exposure of a 25 fold ratio of rodent to human plasma AUC. The second criteria is the demonstration of tumor types known to be reliable markers of the carcinogenic potential of β agonists.

Using the criteria described in the ICH Guideline, dose selection was acceptable based on plasma AUC drug levels. The AUC values for humans were determined to be 1.3 after a 200 µg oral dose and 1.3 after a 120 µg inhalation dose. The following table illustrates the rodent to human plasma AUC ratios relevant to dose setting for these studies. —

Species	Sex	Dose mg/kg/day	AUC µmol·h/L	Multiple of maximum daily dose
Rat	♂	2.0	17	32
	♂	5.0	46.9	88
	♂	10.0	219.1	412
	♂	12.5	267.6	503
	♀	12.5	317.3	596
	♂	25	560.3	1060
	♀	25	814.1	1530
	♂	50	1420.4	2670
	♀	50	4856.6	9129
Mouse	♂	6	130	244
	♂	60	1100	2068

The presence of female reproductive organ tumors (leiomyomas and/or leiomyosarcomas) is a reliable marker of the carcinogenic response to β agonists (Sells and Gibson, 1987); only the dietary studies in rats and mice yielded this result. The incidence of this rare tumor was 0/70, 0/70, 1/70, 1/70, and 3/70 for Groups 1 - 5 female rats, respectively and the incidence of leiomyoma + leiomyosarcomas was 4/85, 16/84, 16/85, 16/85 and 22/85 for Groups 1 - 5 female mice, respectively. The response was detected only in the high dose (20 mg/kg/day) for rats but was present for all treated groups (as low as 2 mg/kg/day) of mice.

QUESTION FOR DISCUSSION

What tumors should be included in the labeling?

Should tumors from studies where the MTD was clearly exceeded be included in the label?

/S/

Tracey Zoetis, M.S.
Pharmacology/Toxicology Reviewer

/S/

Hilary Sheevers, Ph.D.
Team Leader

ATTACHMENT 1

Incidence of Neoplastic Lesions Observed in the
Dietary Carcinogenicty Study with Formoterol fumarate in Rats

Organ	Finding	Incidence									
		Males					Females				
	Dose:	0	.05	2	5	20	0	.05	2	5	20
Adenohypophysis											
	cholesterol granuloma	1	1	0	0	0					
	adenoma	33	31	31	28	29					
	leukemic infiltration	0	0	0	1	0					
Adrenal											
	malignant lymphoma infiltration	0	0	0	1	1					
	leukemic infiltration	0	1	0	1	1					
Adrenal cortex											
	carcinoma	1	0	1	0	0					
	adenoma	2	5	5	3	6					
	myelolipoma	0	0	0	1	0					
Adrenal medulla											
	benign tumor	5	3	2	3	3					
	malignant tumor	0	2	0	2	0					
Bone											
	osteogenic sarcoma	1	1	1	1	0					
Bone Marrow											
	malignant lymphoma	0	1	1	1	2	1	0	0	2	0
	leukemic infiltration	0	1	0	1	1	1	0	1	0	0
Brain											
	malignant astrocytic glioma	0	1	0	1	1					
	oligodenroglioma	1	0	0	0	0					
Cerebral Meninges											
	hemangioma	0	0	1	0	0					
Ear											
	granuloma	4	0	3	8	4					
Epididymis											
	spermatic granuloma	1	0	0	0	1					
	leukemic infiltration	0	1	0	0	0					
Heart											
	angiosarcoma metastasis	0	1	0	0	0					
	malignant lymphoma infiltration	0	0	0	0	1					
	leukemic infiltration	0	0	0	1	0					
Hematopoietic tissue											
	myeloid leukemia	0	1	0	1	1	1	0	1	0	0
Kidney											
	adenoma	0	1	0	0	0					
	carcinoma						1	0	0	0	0
	lipoma	0	0	1	0	0					

Organ	Finding	Incidence									
		Males					Females				
	Dose:	0	.05	2	5	20	0	.05	2	5	20
	malignant lymphoma	0	0	1	1	2	0	0	0	2	0
	leukemic infiltration	0	1	0	1	1	1	0	1	0	0
Large intestine											
	leiomyoma						1	0	0	0	0
	malignant lymphoma infiltration						1	0	0	0	0
Liver											
	benign hepatoma	0	0	0	2	1	1	1	0	0	1
	fibrosarcoma infiltration	0	0	0	0	1					
	leukemic infiltration	0	1	0	1	1	1	0	0	2	0
	malignant lymphoma infiltration	1	0	0	2	0					
Lung											
	granuloma	0	0	0	2	0	1	0	2	1	2
	foreign body granuloma	2	2	1	0	1	0	0	0	0	1
	carcinoma metastasis	0	0	1	1	0	2	1	1	1	2
	squamous cell carcinoma	1	0	0	0	0					
	squamous cell carcinoma metastasis	0	1	0	0	0					
	angiosarcoma metastasis	0	1	0	0	0					
	ostiogenic sarcoma metastasis	1	0	0	1	0					
	malignant lymphoma infiltration	0	0	0	1	1	1	0	0	0	0
	leukemic infiltration	0	1	0	1	1	1	0	1	0	0
Lymph node											
	hemangioma	1	0	0	0	0	0	1	1	0	0
	angiosarcoma	0	0	0	1	0					
	malignant lymphoma infiltration	0	0	1	1	2	1	0	0	1	0
	leukemic infiltration	0	1	0	1	1	1	0	1	0	0
Lymphoreticular tissue											
	malignant lymphoma	0	1	1	1	2	1	0	0	2	0
Mediastinum											
	benign mesothelioma	1	0	0	0	0					
	angiosarcoma metastasis	0	1	0	0	0					
Mouth											
	foreign body granuloma	0	1	0	0	0					
	squamous cell carcinoma	0	0	1	1	0	0	0	1	1	1
	leukemic infiltration						1	0	1	0	0
Mammary											
	adenoma						4	1	4	4	3
	carcinoma	0	0	0	1	0	9	14	17	10	10
	fibroadenoma	3	1	1	0	3	29	30	24	32	22
	papilloma						1	0	0	0	0
	fibroma						1	0	3	1	1
	malignant lymphoma infiltration						1	0	0	0	0

Organ	Finding	Incidence									
		Males					Females				
	Dose:	0	.05	2	5	20	0	.05	2	5	20
Nasal mucosa											
	malignant lymphoma infiltration						1	0	0	1	0
	squamous cell carcinoma infiltration						0	0	1	0	0
Ovary											
	benign granulosa/theca cell						**1**	**5**	**6**	**6***	**8**
	leiomyoma						**0**	**0**	**1**	**1**	**3**
Pancreas											
	sarcoma infiltration	0	0	0	0	1					
	malignant lymphoma infiltration	0	1	0	1	0	1	0	0	0	0
	leukemic infiltration	0	1	0	0	0	0	0	1	0	0
Pancreatic Islet											
	carcinoma	3	1	2	1	2					
	adenoma	6	3	2	6	0					
Peripheral Nerve											
	neuroma	0	0	0	1	0					
Peritoneum											
	benign mesothelioma	1	0	0	0	0					
Pituitary											
	malignant lymphoma infiltration	0	1	0	0	0					
Prostate											
	carcinoma	0	0	1	2	0					
	adenoma	1	2	2	2	3					
	leukemic infiltration	0	1	0	0	0					
Salivary gland											
	carcinoma	1	0	0	0	0					
	fibroma	1	0	0	0	0					
	neurinoma	0	0	0	1	0					
	malignant lymphoma infiltration						1	0	0	1	0
	leukemic infiltration						0	0	1	0	0
Seminal vesicle											
	leukemic infiltration	0	1	0	0	0					
Skeletal muscle											
	hemangioma	0	0	0	0	1					
	leukemic infiltration	0	1	0	1	0					
	malignant lymphoma						1	0	0	0	0
Skin											
	kerathocanthoma	2	0	3	2	4	0	0	1	0	0
	squamous cell papilloma	1	1	0	0	3					
	squamous cell carcinoma	0	1	1	1	1	0	0	1	0	0
	basal cell carcinoma	0	1	1	1	0	0	0	1	0	0
	basosquamous carcinoma	0	0	0	1	0					
	granuloma						0	0	0	0	1
Spleen											

Organ	Finding	Incidence									
		Males					Females				
	Dose:	0	.05	2	5	20	0	.05	2	5	20
	hamartoma	1	0	0	0	0					
	hemangioma	1	0	0	1	0	1	0	0	0	0
	angiosarcoma metastasis	0	1	0	0	0					
	malignant lymphoma infiltration	0	1	1	1	2	1	0	0	2	0
	leukemic infiltration	0	1	0	1	1	1	0	1	0	0
Stomach											
	malignant lymphoma infiltration						1	0	0	1	0
	leukemic infiltration						1	0	0	0	0
	foreign body granuloma						0	0	1	0	0
Subcutaneous tissue											
	foreign body granuloma	0	1	0	0	1	0	1	0	0	0
	fibroma	20	21	14	9	15	2	6	2	4	5
	fibrosarcoma	2	2	3	0	1					
	histiocytoma	1	1	0	1	1	0	3	0	0	0
	lipoma	3	3	3	4	1	1	3	2	0	2
	hemangioma	0	0	0	0	1					
	angiosarcoma	0	1	0	0	0					
	malignant neurinoma	1	0	0	0	0					
	malignant lymphoma	0	0	0	0	1	1	0	0	0	0
	undifferentiated sarcoma						0	0	0	0	1
	histiocytic sarcoma						0	0	0	1	0
Testis											
	spermatic granuloma	0	1	0	1	0					
	unclassified malignant tumor	0	0	0	1	0					
	benign interstitial cell tumor	1	1	0	0	1					
	malignant interstitial cell tumor	0	0	1	0	0					
Thyroid											
	carcinoma	1	0	0	1	0					
	adenoma	0	0	3	1	1					
	gangliocytoma	0	0	1	0	0					
	malignant lymphoma	0	0	0	0	1					
	c-cell adenoma	**7**	**3**	**7**	**6**	**11**					
	c-cell carcinoma	1	0	0	1	0					
	c-cell ad + carc + gangliocytoma	**8**	**3**	**8**	**7**	**11**					
	leukemic infiltration	0	1	0	0	0					
Thymus											
	benign thymoma	1	0	0	1	0					
	malignant lymphoma infiltration	0	0	0	0	1					
	leukemic infiltration	0	1	0	1	0					
Trachea											
	c-cell carcinoma infiltration						0	1	0	0	1
Uncertain Site											

Organ	Finding	Incidence									
		Males					Females				
	Dose:	0	.05	2	5	20	0	.05	2	5	20
	carcinoma						1	0	0	0	1
	malignant neuronoma	0	0	0	1	0					
	histiocytic sarcoma	1	0	0	0	0					
Urinary bladder											
	granuloma	0	0	1	0	0					
	transitional cell papilloma	1	0	0	3	1	0	1	0	0	0
	leukemic infiltration	0	1	0	1	0	0	0	1	0	0
Uterus											
	hemangioma										
	malignant lymphoma										
	infiltration										
Zymbal gland	leukemic infiltration										
	squamous cell carcinoma	0	0	1	0	0					
	infiltration										
	sebaceous squamous cell	0	1	0	0	0					
	carcinoma										

ATTACHMENT 2

Incidence of Neoplastic Lesions Observed in the
Dietary Carcinogenicty Study with Formoterol fumarate in Mice

Organ	Finding	Incidence									
		Males					Females				
	Dose:	0	.05	2	5	20	0	.05	2	5	20
Adenohypophysis	adenoma						5	9	8	4	5
Adrenal cortex	adenoma	3	4	1	3	1					
Adrenal medulla	benign medullary tumor	0	0	0	1	0	1	0	0	0	0
	malignant medullary tumor	0	1	0	0	0	1	0	0	0	0
Bone	osteoma						0	0	0	1	0
Bone Marrow											
Brain	malignant lymphoma	0	0	0	1	0					
	malignant neurinoma	1	0	0	0	0					
Fallopian tube	leiomyoma						0	1	0	0	0
Harderian gland	carcinoma	2	4	3	0	4	0	1	0	0	0
	adenoma	18	13	22	19	21	14	4	6	10	3
Kidney	carcinoma	0	0	1	0	0					
	adenoma	0	1	0	0	0					
	nephroblastoma	0	1	0	0	0					
Large intestine	mucinous carcinoma	5	1	4	1	3	0	1	1	0	0
	leiomyoma	0	0	1	0	0					
Liver	benign hepatoma	18	19	21	24	15	9	8	16	17	12
	hepatocellular carcinoma	10	12	19	17	26	1	5	3	10	7
	hepatoblastoma	1	2	0	0	0	0	1	0	0	0
	hemangioma	0	0	0	0	1	0	0	0	1	0
	angiosarcoma	2	1	1	1	0	2	0	1	0	2
	lipoma						0	1	0	0	0
Lung	carcinoma	11	12	6	8	9	6	4	4	6	4
	adenoma	13	13	20	14	17	10	11	10	7	8
Lymphoreticular tissue	malignant lymphoma	13	13	17	21	17	35	32	36	31	29
Mediastinum	hibernoma	0	0	0	0	1					
Mammary	carcinoma						3	1	2	1	4
	adenocarcinoma						6	7	8	5	6
	benign mixed tumor						0	0	0	0	1

Organ	Finding	Incidence									
		Males					Females				
	Dose:	0	.05	2	5	20	0	.05	2	5	20
Ovary	malignant mixed tumor						0	0	1	1	0
	benign granulosa/theca cell tumor						0	2	1	0	0
Pancreatic Islet	lymphangioma						0	0	1	0	0
Prostate	adenoma	1	1	0	0	0	1	0	1	0	0
	carcinoma	2	1	0	1	0					
Seminal vesicle	adenoma	0	2	0	0	0					
	carcinoma	0	1	0	0	0					
Skin	leiomyosarcoma	1	0	0	0	0					
	keratoacanthoma	0	0	1	0	0					
	squamous cell carcinoma	0	0	1	0	0	0	0	0	1	0
	squamous cell papilloma						0	0	0	0	1
Spleen	basal cell carcinoma						0	0	0	1	0
	unspecified sarcoma	1	0	0	0	0					
	malignant lymphoma	0	0	0	1	0					
Small intestine											
Stomach	leiomyosarcoma	0	0	1	0	0					
Subcutaneous tissue	squamous cell carcinoma	1	0	0	0	0					
	lipoma	1	2	5	5	5					
	angiosarcoma	0	0	1	0	0					
	lymphangioma	2	1	0	0	0					
	mast cell tumor	0	0	1	0	0					
Testis	hibernoma						0	0	0	0	1
	benign interstitial cell tumor	0	0	1	0	0					
Thyroid	histiocytic sarcoma	0	0	1	0	0					
	adenoma	0	0	0	1	0	0	1	0	0	0
Thymus	C-cell adenoma	0	0	0	1	1	0	0	0	0	1
Trachea	benign thymoma						0	0	1	0	0
Uncertain Site											
	carcinoma	0	0	1	0	0	0	0	0	0	1
	mucinous carcinoma						0	0	0	0	1
	unspecified sarcoma	0	1	0	0	0					
Uterus	histocytic sarcoma	1	1	0	0	1	0	0	0	0	1

Organ	Finding	Incidence									
		Males					Females				
	Dose:	0	.05	2	5	20	0	.05	2	5	20
	leiomyoma						**4**	**10**	**13**	**14**	**16**
	leiomyosarcoma						**0**	**3**	**2**	**3**	**5**
	carcinosarcoma						0	0	0	0	1
	hemangioma						1	0	0	0	0
	benign granular cell tumor						1	0	0	0	0
Uterus											
endometrium											
	unspecified sarcoma						1	0	0	0	1
Vagina											
	leiomyoma						0	2	0	0	1
	leiomyosarcoma						0	0	1	0	0

ABBREVIATIONS FOR TUMOR SITE IDENTIFICATION*

Aden=adenoma
AG = adrenal gland
B = brain
BD = bile duct
Carc=carcinoma
CG = clitoral gland
CS = circulatory system (e.g. hemangioepithelioma/sarcoma)
HG = harderian gland
HS = hematopoietic system (e.g. leukemia; lymphoma)
I = intestine
IS = integumentary system (e.g. connective tissue)
K = kidney
L = liver
LU = lung
MG = mammary gland
MT = mesothelial tissue
N = nose
O = ovary
OC = oral cavity
OST= osteosarcoma in bone
PG = preputial gland
PTG= pituitary gland
S = stomach
SB = subcutaneous tissue
SK = skin
SP = spleen
TG = thyroid gland
TV = tunica vaginalis
U = uterus
ZG = zymbals gland
* R. W. Tennant and J. Ashby, Mutation Research, 257 (1991), 209-227.

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3 PAGE(S) REDACTED

Draft

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 31 1998

George W. Bensch, M.D.
Immunology & Asthma Medical Group, Inc.
4628 Georgetown Place
Stockton, California 95207

Dear Dr. Bensch:

On March 9-24, 1998, Ms. Cynthia L. Evitt, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (Protocol No. 40) of the investigational drug Foradil™ (formoterol fumarate) dry powder capsules for inhalation, performed for Novartis Pharmaceuticals Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and of the documents submitted with that report, we found some deviations from the pertinent federal regulations and/or good clinical investigational practices. The inspectional observations were listed on the Form FDA 483 and discussed with you at the close of the inspection. We acknowledge the explanations you provided in your letter dated May 20, 1998. Your letter will be included as a permanent part of the inspection records.

We appreciate the cooperation shown Ms. Evitt during the inspection.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

CFN: 2953107
Field classification: VAI

Headquarters classification:
___1) NAI
_x_2) VAI-no response required
___3) VAI-response requested

Deficiencies noted:
_x_ failure to report all AE
_x_ failure to use the current approved consent form
If the Field and Headquarters classifications are different, explain why: The CI explained satisfactory in his letter dated May 20, 1998

cc:
HFA-224
HFD-570 Doc. Rm. NDA #20-831
HFD-570 Review Div. Dir.
HFD-570 MO (ANTHRACITE)
HFD-570 PM (JANI)
HFD-340 Reading File
HFD-344 Chron File
HFD-344 CIB File 9602
HFD-344 CIB REVIEWER (JU)
HFR-PA150 DIB (MOSS)
HFR-PA150 BIMO MONITOR (MCGIRL)
HFR-PA1535 FIELD INSPECTOR (EVITT)

* The result of Foradil audit sheet was FAXED to Dr. Anthracite on July 21, 1998

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

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: (301) 594-0093
FAX: (301) 594-2202

AUG 21 1998

Dr. Alex Krauer
Chairman, Board of Directors
Novartis Pharma AG
CH-4332 Schaffhauserstrasse
Stein, Switzerland

Dear Dr. Kraeur:

Thank you for the May 14, 1998 correspondence responding to our April 23, 1998 letter regarding CGMP issues raised during an inspection of the Stein, Switzerland facility (in February of this year). In addition, representatives of your firm met with our office on July 10, 1998.

Your firm's correspondence appears to provide an adequate action plan for meeting CGMP requirements. The acceptability of the implementation of these corrections will be confirmed in our next scheduled inspection. While some corrections remain outstanding, we are classifying your firm as an acceptable supplier of aseptically processed pharmaceuticals based upon your written and verbal commitments (the latter during our meeting of July 10). Please keep our office updated on the status of promised corrections and advise us in the event that stated timelines for corrections are altered.

In addition, please continue to send us copies of microbiological and particulate environmental monitoring results outside established alert and action levels for batches for US supply manufactured in ———————— Please also provide the deviation investigation reports for any microbiological environmental data which exceeds alert or action limits.

If I can provide any further information, feel free to contact me at (301) 594-0095.

Sincerely,

/S/

Richard L. Friedman,
Consumer Safety Officer
Investigations and Pre-approval
Compliance Branch

CC:

A.N. Karabelas, Ph.D.
Executive Committee Member
Head of Healthcare Division and Pharma Sector
Novartis Pharma AG
CH-4002 Basel, Switzerland

Stuart Heir
Head of Worldwide Corporate QA
Novartis International AG
CH-4002 Basel, Switzerland

Ann Bailey
Vice President Corporate QA, North America
Novartis
59 Route 10
E. Hanover, NJ 07936-1080

Food and Drug Administration
Rockville MD 20857

MAR 9 1998

Stephen J. Pollard, M.D.
Allergy & Asthma Research Institute
9800 Shelbyville Road, Suite 220
Louisville, Kentucky 40223

Dear Dr. Pollard:

Between November 19 and 26, 1997, Inspector Dia D. Prince, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (Protocol No. 41) of the investigational drug Foradil™ (formoterol fumarate) dry powder capsules for inhalation, performed for Novartis Pharmaceuticals Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and of the documents submitted with that report, we conclude that you adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Inspector Prince during the inspection.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

CFN: NA
Field classification: NAI
Headquarters classification:
_X_ 1) NAI
___ 2) VAI-no response required
___ 3) VAI-response requested

cc:
HFA-224
HFD-344
HFD-340 r/f
HFR-MA400
HFR-MA450
HFD-Review Division Div.:570; Dir./Doc. Rm. : NDA #20-831
CSO:PJani; MO:RAnthracite IND#
r/d:HWJu:
Review Date:
Final Date:SLK

*The result of Foradil audit sheet was sent to Dr. Anthracite today.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 27 1998

Warren W. Pleskow, M.D.
317 N. El Camino Real, Stuite 506
Encinitas, California 92024

Dear Dr. Pleskow:

On December 2-11, 1997, Mr. Thomas R. Beilke, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (Protocol No. 41) of the investigational drug Foradil™ (formoterol fumarate) dry powder capsules for inhalation, performed for Novartis Pharmaceuticals Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and of the documents submitted with that report, we conclude that you did adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Mr. Beilke during the inspection.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

CFN: 2084125
Field classification: NAI
Headquarters classification:
_X_1) NAI
___2) VAI-no response required
___3) VAI-response requested

cc:
HFA-224
HFD-344
HFD-340 r/f
HFR-PA200
HFR-PA250
HFD-Review Division Div.:570; Dir./Doc. Rm. : NDA #20-831
CSO:PJani; MO:RAnthracite IND#
r/d:HWJu:1/5/98
Review Date:AEH:
Review Date:BLB:1/22/98
Final Date:SLK:1/22/98

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 3 1997

William R. Lumry, M.D.
AARA Research Center
9900 N. Central Expressway/Suite 555
Dallas, Texas 75231

Dear Dr. Lumry:

Between October 28 and November 7, Ms. Kelly J. Pegg, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (Protocol No. 40) of the investigational drug Foradil™ (formoterol fumarate) dry powder capsules for inhalation, performed for Novartis Pharmaceuticals Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and of the documents submitted with that report, we conclude that you did adhere to pertinent Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Ms. Pegg during the inspection.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

CFN: 1646875
Field classification: NAI
Headquarters classification:
_X_ 1) NAI
___ 2) VAI-no response required
___ 3) VAI-response requested

cc:
HFA-224
HFD-344
HFD-340 r/f
HFR-SW100
HFR-SW150
HFD-Review Division Div.:570; Dir./Doc. Rm. : NDA #20-831
CSO:PJani; MO:RAnthracite IND#
r/d:HWJu:12/2/97
Review Date:AEH:12/3/97
Review Date:BLB:12/3/97
Final Date:SLK:12/3/97