CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-279

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Labeling comments

NDA	21-279 (000)
Drug Substance	Formoterol fumarate
Drug Product(s)	Foradil (formoterol fumarate inhalation powder)
Sponsor	Norvatis Pharmaceutical Corporation
Type of submission	Proposed labeling changes for NDA 21-279 Foradil Aerolizer COPD patients
Date of submission	9/12/2001, and 9/18/2001 (Fax)
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D. OCPB/DPE-2

Synopsis
On 9/12/2001, the sponsor submitted the revised package insert that reflects the mutual agreement on the label for NDA 21-279 Foradil Aerolizer for COPD patients during the teleconference held on 9/10/2001.

However, the sponsor found that there was an accidental omission of a sentence in the pharmacodynamic section of the label. In addition the sponsor proposed that the technical term of "purse rate" be used in place of " heart rate" in the second and third paragraph of pharmacodynamic section. These corrections and proposal have been faxed on 9/18/2001 (See attachment on this review).

Based on the discussion with the reviewing medical officer (Dr. Eugene Sullivan), the use of the term " purse rate" in place of "heart rate" is acceptable.

Recommendation
The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the labeling proposal under the sections of "Pharmacokinetics" and "Pharmacodynamics" submitted on 9/12/2001and 9/18/2001, and found that the sponsor's proposal is acceptable.

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

Emmanuel Fadiran, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

cc NDA 21-279/N-000, Division File
HFD-870: Emmanuel Fadiran, John Hunt, Henry Malinowski
HFD-570: Craig Ostroff, Eugene Sullivan

C:\dmautop\temp\labelingcomment2.doc

Attachment #1. The sposnor' fax on 9/18/2001 that includes corrections

APPEARS THIS WAY
ON ORIGINAL

Dr. Kathleen Sammellas
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
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NOVARTIS

Fax

Attention: Ms. Sandra Barnes
Supervisory Product Manager
Division of Pulmonary and Allergy Drug Products

Date: September 18, 2001
1 page including cover
Facsimile #: 301-827-1271

Re: NDA 21-279 Foradil Aerolizer COPD label negotiation proposed edits

Dear Sandy:

As per my recent voicemail to you, I would like to confirm that I have received the FDA comments on the clinical trials sectionof the Foradil Aerolizer label from my colleague, Sharon Olmstead.

Novartis finds the FDA edits acceptable. In addition we would like to bring to your attention an accidental omission of a sentence in the pharmacodynamics section of the label and two technical corrections in the same section (see below in bold).

Please let me know when all FDA comment have been noted, so that I can submit a fully agreed package insert officially to the file. Please call me to confirm fax receipt and edit status: 973-781-3666.

Best regards,
Kathy

Second and third paragraph of pharmacodynamic section lines 149-165 :

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-279 (000)
Drug Substance	Formoterol fumarate
Drug Product(s)	Foradil (formoterol fumarate inhalation powder)
Sponsor	Norvatis Pharmaceutical Corporation.
Type of submission	Original NDA
Date of submission	9/22/2000
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D. OCPB/DPE-2

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1. EXCECUTIVE SUMMARY

On 9/22/2000, the sponsor submitted NDA 21-279 for Foradil ™, a capsule for inhalation of formoterol fumarate powder (12 µg) via Aeorlizer ™. Formoterol is a β-adrenergic agonist. The proposed indication is for the — bronchoconstriction in patients with → chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis. Foradil has been approved on 2/16/2001 for asthma (NDA 20-831). The present submission is to expand the indication to COPD. The proposed dose is 1 capsule inhaled twice daily.

The sponsor conducted 2 clinical trials (studies 056 and 058) for safety and efficacy in COPD patients.

In Section 6 of the NDA, the sponsor submitted
(1) pharmacokinetic (PK) study (n=21) in COPD patients as a subset of clinical trial,
(2) the results of genotype analysis for 2C19 and 2D6 from the two clinical trial (n=239) in COPD patients, and
(3) the results of analysis of age effect on systemic exposure in asthmatic and COPD patients.

Based on the urinary excretion data, formoterol appeared to be less exposed systemically in COPD patients than in asthmatic patients after inhalation of Foradil 12 or 24 µg.

Formoterol accumulated in the body to some extent in COPD patients (accumulation index of 1.19 -1.38) after 12 weeks administration of 12 or 24 µg formoterol dry powder b.i.d. The degree of the accumulation in COPD patients is less than in asthmatic patients (accumulation index of 1.67 – 2.08).

Among 239 COPD patients, 7 and 11patients were poor metabolizers (PMs) for CYP 2C19 and for CYP 2D6, respectively. However, it should be noted that none of subjects for PK study was characterized as a PM. Therefore, it was impossible to compare the systemic exposures in PMs vs. in extensive metabolizers (EMs).

While a correlation has been clearly observed between plasma concentration and QTc increase in healthy volunteers in the earlier submission (NDA 20-831), such an analysis could not be made in COPD patients since the QTc was measured only before the dosing.

It appeared that the age effect on pharmacokinetics of formoterol is not conclusive, although there was a trend of increased systemic exposure with age.

While only limited pharmacokinetic information was obtained in COPD patients, the majority of pharmacokinetic information in asthmatic patients as well as in healthy volunteers has been collected in the earlier submission (NDA 20-831) and it was possible to compare systemic exposures in COPD and asthmatic patients. Therefore, this reviewer is of the opinion that the present submission is acceptable from a pharmacokinetic perspective. Based on the submitted pharmacokinetic data, the Clinical Pharmacology section (Absorption and Excretion) needs to be revised as recommended in Labeling Comments of the present review.

2. LABELING COMMENT

(Underlined portion is the Agency's recommendation)

2-1. The paragraph beginning with Line 89 should be read as follows:

e.

This suggests some extent of accumulation of formoterol in plasma with multiple dosing. The excreted amounts of formoterol at steady state were close to those predicted based on single dose kinetics. As....."

2-2. Line 129: Include number of patients with COPD. The sentence beginning in Line 128 should be read as " Following inhalation of 12 mcg or 24 mcg dose by patients with COPD the

2-3. Line 119 ; Add following sentence:

3. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II has reviewed the Human Pharmacokinetics and Bioavailability section of NDA 21-282/N-000 and found that the provided data are acceptable from a pharmacokinetic perspective. The labeling comments need to be communicated to the sponsor as appropriate.

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

Emmanuel Fadiran, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

cc NDA 21-279/N-000, Division File
HFD-870: Emmanuel Fadiran, John Hunt, Henry Malinowski
HFD-570: Craig Ostroff, Eugene Sullivan

4. Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings
(Question Based Review)

Is the pharmacokinetics of formoterol in chronic obstructive pulmonary disease (COPD) patients different from that in asthmatics?

The urinary excretion of either unchanged or total formoterol was determined in a subset of patients with asthma or with COPD investigated in clinical safety and efficacy studies. The sponsor considered the urinary excretion data as a measure of the systemic availability. This reviewer is of the opinion that this approach is acceptable from a pharmacokinetic perspective, since it has been shown in the earlier submission (NDA 20-831) that the urinary excretion parallels plasma formoterol disposition, and the elimination half-lives estimated from urine and plasma data are similar.

For the purpose of the comparison, the urinary data after 12 weeks of administration (12 or 24 µg b.i.d.) to asthmatic patients was extracted from the earlier data and compared to that in COPD patients (Table 1).

Table 1. Comparison of urinary excretion (% of dose) of unchanged formoterol in COPD patients and that in asthmatics after 12 weeks of dosing (12 or 24 µg b.i.d.)

Dose (b.i.d.)	**12 µg**		**24µg**	
Patients	**Asthmatics**	**COPD**	**Asthmatics**	**COPD**
N	7	9	9	9
Arithmetic mean	9.89	6.88	10.40	6.46
SD	3.64	2.72	2.46	1.69
Min				
Max				
Geometric mean	9.29	6.41	10.13	6.27
Lower 95 % CI	6.52	4.79	8.51	5.16
Upper 95 % CI	13.25	8.98	12.29	7.76

Table 2. Comparison of urinary excretion (% of dose) of total formoterol (i.e., unchanged and glucuronized form) in COPD patients and that in asthmatics after 12 weeks of dosing (12 or 24 µg b.i.d.)

Dose (b.i.d.)	**12 µg**		**24µg**	
Patients	**Asthmatics**	**COPD**	**Asthmatics**	**COPD**
N	7	9	9	9
Arithmetic mean	27.47	15.57	25.76	12.69
SD	4.67	5.25	9.93	5.10
Min				
Max				
Geometric mean	27.16	14.81	24.12	11.91
Lower 95 % CI	23.15	11.53	18.12	8.76
Upper 95 % CI	31.79	19.60	33.39	16.61

Formoterol appeared to be less exposed systemically in COPD patients than in asthmatic patients after inhalation of Foradil ™ 12 or 24 µg.

Formoterol accumulated in the body to some extent in COPD patients (accumulation index of 1.19 -1.38 based on the urinary excretion of the unchanged formoterol) after 12 weeks administration of 12 or 24 µg formoterol dry powder b.i.d. The degree of the accumulation in COPD patients is less than in asthmatic patients (accumulation index of 1.67 – 2.08; from the present labeling). The degree of accumulation of formoterol after multiple doses for 12 weeks (steady state) was close to that predicted based on single dose kinetics

What is the formoterol pharmacokinetics/pharmacodynamics in the poor metabolizers for 2C19 and 2D6?

Among 239 COPD patients, 7 (among them, 2 were given 12μg and 5 were given 24 μg) and 11 patients (among them 4 were given 12μg and 7 were given 24 μg) were poor metabolizers of CYP 2C19 and for CYP 2D6, respectively. However, none of subjects for PK study was characterized as a PM. Therefore, it was impossible to compare the systemic exposures in poor metabolizers vs. in extensive metabolizers.

The medical officer was asked to review for formoterol related adverse effects that are specific for PMs of 2C19 or 2D6.

The heart rate was not increased in the 11 PMs of 2D6. However, in the 4 out of 5 PMs of 2C19, the heart rate increased when higher dose (24 μg b.i.d.) was given. The increased heart rate was not shown every visit in some patients. The two individuals treated with low dose (12 μg b.i.d.) did not show increased heart rate. Overall it was difficult to make definitive conclusion that the PMs of 2C19 are more susceptible to heart rate increase by formoterol than EMs of 2C19.

It should be noted that a correlation has been observed between plasma concentration and heart rate and QTc prolongation in healthy volunteers in the earlier submission (NDA 20-831; refer to the Tables 3 and 4). However, such an analysis could not be done in COPD patients since the QTc was measured only before the dosing.

Table 3. The correlation of heart rate increase vs. urinary excretion in healthy volunteers

Dose (μg)	Urinary excretion (ng)	Estimated heart rate increase	Standard error	95% confidence interval
Placebo	0	7.43	1.66	(4.07, 10.80)
12	375	8.73	1.55	(5.61, 11.86)
24	762	10.08	1.47	(7.11, 13.05)
48	1484	12.59	1.47	(9.62, 15.56)
96	3000	17.86	1.99	(13.83, 21.89)

Table 4. The correlation of QTc increase vs. urinary excretion in healthy volunteers

Dose (μg)	Urinary excretion (ng)	Estimated QTc increase	Standard error	95% confidence interval
Placebo	0	13.43	2.36	(8.65, 18.20)
12	375	13.73	2.34	(9.00, 18.45)
24	762	14.67	2.27	(10.07, 19.26)
48	1484	18.14	2.15	(13.80, 22.48)
96	3000	32.70	3.41	(25.80, 39.60)

After the combined [intravenous & oral] administration, over 80 % of the total radioactivity is recovered, and the 20% of the total radioactivity is demethylated form. Therefore, assuming that the demethylation of formoterol involves only 2C19 and the demethylation pathway is completely blocked in PMs of 2C19, it is estimated that the systemic exposure of formoterol will be increased less than 2 times.

In this context, this reviewer recommends that the following sentence be included in the labeling under the section of "Clinical Pharmacology":

> " Patients who are deficient in CYP2D6 or CYP2C19 (poor metabolizers) may have higher plasma concentrations of formoterol and therefore, may experience greater incidence of cardiovascular or other systemic adverse effects of formoterol (See Precautions)"

Is there any age effect on pharmacokinetics of formoterol?

It appeared that the age effect on pharmacokinetics of formoterol is not conclusive, although there was a trend of increased systemic exposure by age after 12 µg dose (Refer to the following Figures 1-4). This reviewer does not recommend any change of labeling due to the age effect on pharmacokinetics of formoterol.

Figure 1. Correlation of plasma AUC $_{0\text{-}6\ hours}$ vs. age. Left panel represents after the 12 µg of single dose and right panel is after multiple dose for 12 weeks b.i.d.

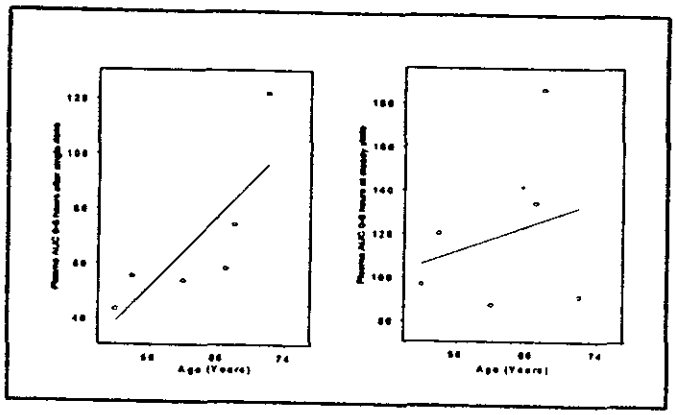


Figure 2. Correlation of plasma AUC $_{0\text{-}6\ hours}$ vs. age. Left panel represents after the 24 µg of single dose and right panel is after multiple dose for 12 weeks b.i.d.

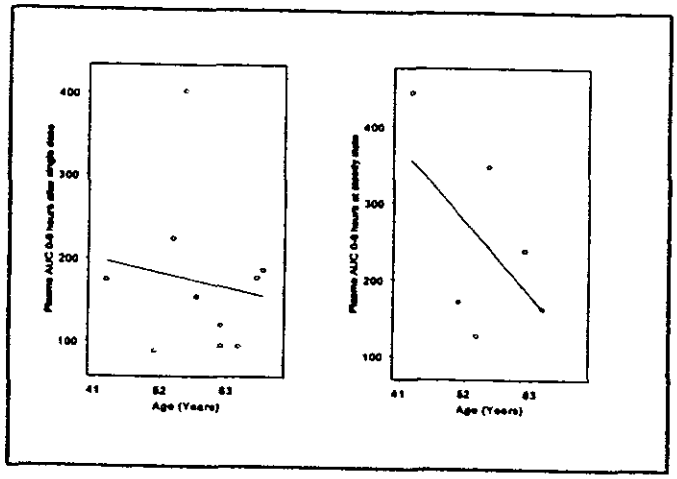


Figure 3. Correlation of urinary excretion of unchanged formoterol vs. age. Left panel represents after the 12 µg of single dose and right panel is after multiple dose for 12 weeks b.i.d.

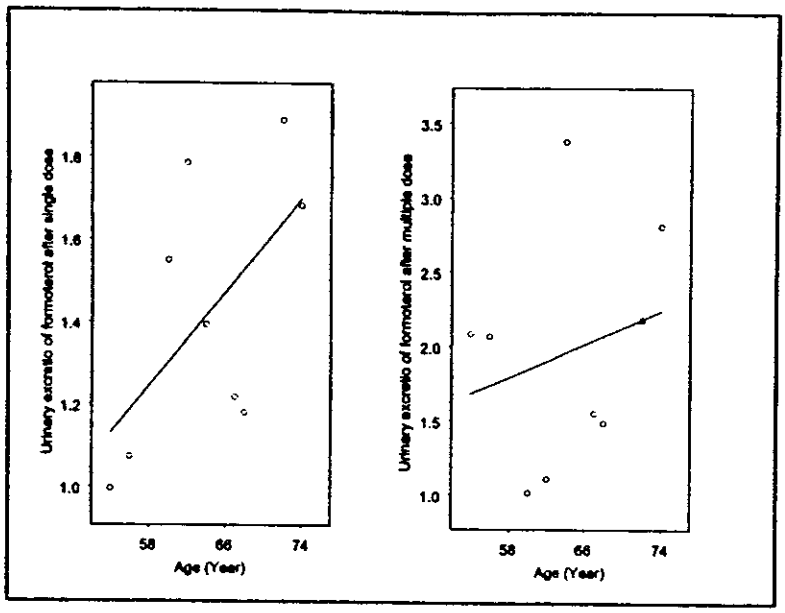
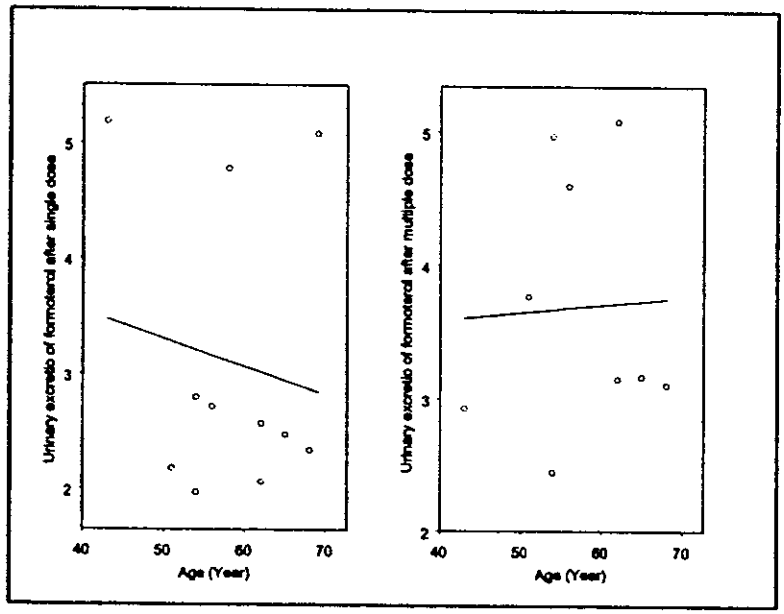


Figure 4. Correlation of urinary excretion of unchanged formoterol vs. age. Left panel represents after the 24 µg of single dose and right panel is after multiple dose for 12 weeks b.i.d.



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Young-Moon Choi
7/17/01 12:40:26 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
7/17/01 01:09:53 PM
BIOPHARMACEUTICS
I concur

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing Memorandum

NDA:	21-279	**Sponsor:**	**Norvatis Pharmaceutical Co.**
IND:			
Brand Name:	Foradil	**Priority Classification:**	3S
Generic Name:	Formoterol fumarate	**Indication(s):**	bronchoconstriction in patients with chronic obstructivee pulmonary disease (COPD), including emphysema and chronic bronchoitis
Drug Class:	β2 agonist	**Date of Submission:**	9/25/00
Dosage Form:	Inhalation powder (using Aerolizer inhaler device)	**Route of Admin.:**	Oral
Dosing Regimen:	One 12 µg Foradil capsule every 12 hours using Aeolizer inhaler.	**Due Date of Review:**	7/25/01
Division:	DPE-2 (HFD-870)	**Medical Division:**	HFD-570
Reviewer:	Young Moon Choi, Ph.D.	**Team Leader:**	Young Moon Choi, Ph.D. (Acting)

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	✔		
Tabular Listing of All Human Studies	✔		
HPK Summary	✔		
Labeling	✔		
Reference Bioanalytical and Analytical Methods	✔		
Bioavailability and Bioequivalence Studies		✔	
Mass Balance Study		✔	
BA Studies		✔	
Absolute BA		✔	
Relative BA		✔	
BE Studies		✔	
Average BE		✔	
Population BE		✔	
Individual BE		✔	
Food-Drug Interaction		✔	
Dissolution Tests (In Vitro-In Vivo Comparison Studies)		✔	
Studies Using Human Biomaterials		✔	

Plasma Protein Binding Studies		✔	
Blood/Plasma Ratio		✔	
Metabolism Studies Using Hepatocytes, Microsomes,etc		✔	
In Vitro Drug Interaction Studies		✔	
Human Pharmacokinetics Studies		✔	
PK, and Initial Safety and Tolerability in Healthy Volunteers		✔	
Single Dose		✔	
Multiple Dose		✔	
PK, and Initial Safety and Tolerability in Patient Volunteers		✔	
Single Dose	✔		
Multiple Dose	✔		
Dose Proportionality	✔		
Single Dose		✔	
Multiple Dose		✔	
PK in Population Subsets to Evaluate Effects of Intrinsic Factors			
Ethnicity		✔	
Gender		✔	
Pediatrics	✔		
Geriatrics	✔		
Renal Impairment		✔	
Hepatic Impairment		✔	
PK to Evaluate Effects of Extrinsic Factors			
Drug-Drug Interaction: Effects on Primary Drug		✔	
Drug-Drug Interaction: Effects of Primary Drug		✔	
Population PK studies		✔	
Summary Table of PK/PD Studies		✔	
PK/PD studies in Volunteers		✔	
PK/PD studies in patients		✔	
Individual Datasets for all PK and PK/PD studies in electronic format	✔		As a review aid
Other	✔		
Genotype/Phenotype Studies	✔		
Chronopharmacokinetics		✔	

Reviewer's comment:

The sponsor submitted the present NDA (NDA 21-279) for Foradil (formoterol fumarate inhalation powder) for [redacted] bronchoconstriction in patients with [redacted] chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis.

Before submitting NDA 21-279, the sponsor submitted NDA 20-831 on 6/24/97, which is currently under review. NDA 20-831 is for the same formulation of formoterol but indicated for asthma.

The majority of the present NDA items 2, 3, and 4 are cross-referenced to the earlier NDA 20-831, rendering the approval of NDA 21-279 contingent on the approval of NDA 20-831.

In the Item 6 of NDA 21-279, the sponsor submitted one pharmacokinetic (PK) study in COPD patients (as a subset of clinical trial), one genotype study for the particular PK study in COPD patients, and an analysis for age effect on PK of formoterol. Other PK information is cross-referenced to NDA 20-831.

In NDA 20-831, the sponsor had submitted 37 studies in the Human Pharmacokinetic and Biopharmaceutics section. Among these 37 studies, Dr. Gillespie reviewed total 7 studies. These include three PK studies (two at the proposed dose and one with a 120 μg single dose), a radiolabel mass balance study, two in vitro protein binding studies, and two in vitro metabolism studies. Dr. Gillespie noted that for Foradil, the sponsor was unable to develop an assay of adequate sensitivity to measure plasma formoterol concentrations at the clinical dose. A recent review of the literature supported this lack of an adequately sensitive assay for formoterol.

QBR questions: (Key Issues to be Considered)

- What is the dose-systemic exposure relationship for the drug substance?
- What are the dose-systemic exposure relationships to pharmacodynamics for efficacy and adverse effect?

2. Recommendation: Suitable for filing

The Human Pharmacokinetic section of the present NDA submission has been briefly reviewed by the Division of Pharmaceutical Evaluation II, Office of Clinical Pharmacology and Biopharmaceutics for the purpose of filing. It has been found that the submission is suitable for filing. The present submission is paginated and properly organized to allow a thorough review.

_____

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

_____

Hunt John
Deputy Director
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-279, HFD-850(Lee), HFD-570(Jani), HFD-870(Malinowski, Hunt), CDR (B. Murphy)

APPEARS THIS WAY ON ORIGINAL

/s/

Young-Moon Choi
11/15/00 03:45:39 PM
BIOPHARMACEUTICS

John P. Hunt
12/7/00 04:45:13 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA or IND Number	21-279	Brand Name	Foradil
OCPB Division	DPE-2	Generic Name	formoterol fumarate
Medical Division	HFD-570	Drug Class	Adrenergic receptor (β2) agonist
OCPB Reviewer	Young Moon Choi	Indication(s)	bronchoconstriction in patients with chronic obstructive pulmonary disease, including emphysema and chronic bronchitis
OCPB Team Leader	Emmanuel Fadiran	Dosage Form	Inhalation powder(12 µg) in capsule using Aerolizer inhaler device
		Dosing Regimen	Inhalation of one 12 µg capsule every 12 hours
Date of Submission	9/25/2000	Route of Administration	Oral inhalation
Estimated Due Date of OCPB Review	7/11/2001	Sponsor	Novartis Pharmaceutical Co.
PDUFA Due Date	7/25/2001	Priority Classification	3S

Clin. Pharmaco. and Biopharm. Information

	"X" if included at filing	Number of study submitted	Number of study reviewed	Comments
STUDY TYPE				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
single dose:				
multiple dose:				
Patients-				
single dose:	x			
multiple dose:	x			N=21; As a subset of clinical trial
Dose proportionality -	x			
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	x			Checked age effect; not conclusive
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, prove of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS study				
III. Other				
Genotype/phenotype studies:	x			
Chronopharmacokinetics				

	"X" if yes	***Comments***
Application filable ?	X	
Comments sent to firm ?		See the labeling comments in the review

QBR questions (key issues to be considered)	• Is the pharmacokinetics of formoterol in chronic obstructive pulmonary disease (COPD) patients different from that in asthmatics? What is the dose (systemic exposure) and response relationship? • What is the formoterol pharmacokinetics/pharmacodynamics in the poor metabolizers for 2C19 and 2D6? • Is there any age effect on pharmacokinetics of formoterol?
Other comments or information not included above	In the Item 6 of NDA 21-279, the sponsor submitted one pharmacokinetic (PK) study in COPD patients (as a subset of clinical trial), one genotype study for the particular PK study in COPD patients, and an analysis for age effect on PK of formoterol. Other PK information is cross-referenced to NDA 20-831. NDA 20-831 was approved on 2/16/2001 for asthma.
Primary reviewer Signature and Data	**Young Moon Choi**
Secondary reviewer Signature and Data	**Emmanuel Fadiran**