CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-831

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR 25 2000

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-831
Formoterol fumarate 12 μg/capsule

SUBMISSION DATE:
11/23/99 (Serial No. BZ)

BRAND NAME: Foradil Aerolizer-Dry Powder for Inhalation

SPONSOR: Novartis

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Original Amendment (Responses to the Approvable Letter)

TITLE: "Review of Sponsor's Responses To The Agency's Approvable Letter"

BACKGROUND:

Novartis' NDA 20-831 for Foradil (formoterol fumarate 12 μg/capsule) Aerolizer-Dry Powder for Inhalation was submitted to the Agency for review on 06/24/97. Foradil contains formoterol fumarate, a relative long acting chiral, β-adrenergic agonist. It is formulated as a dry powder capsule for oral inhalation. Foradil is indicated for the prevention and maintenance treatment of asthma and bronchoconstriction in patients 5 years of age and older with reversible obstructive airway diseases, including patients with symptoms of nocturnal asthma. The human Pharmacokinetics/Bioavailability (PK/Bio) section (Item 6) of the above NDA was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) on 06/05/98. An approvable letter was received by the sponsor on 06/26/98 with deficiencies that needed to be addressed. Deficiency Nos. 11, 12 and 13 were related to OCPB.

SYNOPSIS:

On 11/23/99, the sponsor resubmitted complete responses and the revised package insert (PI) to NDA 20-831 (Serial No. BZ). The sponsor's responses and the revised PI are therefore reviewed here.

OCPB Comment No. 11 related to Study # ——— (US) 1996/048:

a. *Submit blank and the representative ——————— to demonstrate assay specificity.*

Response:

The sponsor indicated that the requested ——————— were contained in original volume 1.75 p. 072-073.

Reviewer's Comment:

The information provided in the original NDA indicates that the assay is specific for formoterol. Therefore, the sponsor's response is acceptable.

b. *Clarify whether the two lots of 12 and 24 mcg capsules used in this trial were the to-be-marketed formulation/device with regard to composition, drug microcrystalline size distribution, method of manufacture, production size/scale, and site of manufacture.*

Response:

The sponsor indicated that only one batch (E-1549) and formulation (H-3831) of 12 µg formoterol fumarate capsules were used in this trial which is the to-be-marketed formulation with regard to composition, drug microcrystalline size distribution, method of manufacture, production size/scale, and site of manufacture (Stein, Switzerland). The production size/scale was ——— capsules which represented —— of commercial production batch ——— capsules).

Reviewer's Comment:

The sponsor's response is acceptable.

c. *Submit complete single-dose urinary excretion data.*

Response:

For Study # —— (US) 1996/048 (multiple-dose study, 12 and 24 µg given BID), the timed urine fractions were not collected after the first dose. All urine excreted between 0-12 hr was collected as a single fraction. The kinetics of formoterol excretion after single inhaled dose [Study # ——(US) 1996/054, single-dose PK of 120 µg] was evaluated in detail previously. Further analyses on urinary (R,R)- and (S,S)-formoterol data obtained from the multiple-dose Study # —— (US) 1996/048 were conducted. The results are summarized below:

Table 1. Additional Analysis of Urinary Data (0-12 hr) Obtained From Study —— (US) 1996/048

0- 12 hr Urinary Data	% of Dose (R,R)- + (S,S)-Racemate	% of Dose (S,S)-Formoterol	% of Dose (R,R)-Formoterol	Ratio of (R,R)- to Racemate
WK 0, 12 µg, (1st dose)	5.90 ± 1.06[a]	3.15 ± 0.78	2.47 ± 0.49	0.40
WK 0, 24 µg, (1st dose)	6.02 ± 1.72	3.66 ± 1.00	2.40 ± 0.71	0.39
WK 4, 12 µg BID (Steady State)	11.5 ± 4.3	6.70 ± 1.96	4.67 ± 2.45	0.39
WK 4, 24 µg BID (Steady State)	10.1 ± 2.40	5.76 ± 1.47	4.38 ± 1.04	0.43

[a]. Mean ± standard deviation (SD).

The modified urinary assay method employed is similar to that used previously for Study # —— (US) 1996/054. The validation data are shown below:

Quality Control:

1. **R,R- enantiomer**:

QC: ———— nmol/L (n=5)
Recovery: ———
Precision (CV%): ——

2. **S,S- enantiomer**:

QC: ———— nmol/L (n=5)
Recovery: ———
Precision (CV%): ——

The sponsor concluded that:

1. The sum of the enantiomers showed similar mean excretion values as measured using non-specific assay method for unchanged formoterol previously. The mean ratios of sum of enantiomers/formoterol levels (previous data) ranged from 96.3 to 102.6%.

2. The mean excreted amounts of the enantiomers at steady state show some accumulation, the accumulation indices being 1.95 and 1.68 for 12 and 24 μg, respectively. They are close to the mean values, 2.08 and 1.67, respectively, obtained from the total unchanged formoterol levels and to that (1.60) predicted from the single-dose plasma PK data [Study # — (US) 1996/054].

3. The ratios of (R,R)- to racemate level (around 0.40) are consistent between two dosing rates (12 and 24 μg BID) and between single- and multiple- dose PK studies.

4. ———— of metabolizing cytochrome P-450 enzymes in patients or *in vivo* interconversion between R,R- and S,S- formoterol at therapeutic dose range are seemingly unlikely which is consistent with previous *in vitro* data.

Reviewer's Comment:

The above data show that based on urinary data, the absorption of inhaled formoterol appeared to be linear in single-dose (12 up to 120 μg) and multiple-dose (12 and 24 μg BID) studies. The sponsor's additional analysis and the response are acceptable. However, the statement that ————————————————————

————————————————————

therefore, it may not be included in the PI.

d. *The accounting of study dropouts is not clear from the report submitted. Provide an accounting of all subjects enrolled.*

Response:

There were errors in the original table. A new table with correct numbers is provided.

Reviewer's Comment:

For the correct table, please see the 11/23/99 submission for details. The sponsor's response is acceptable.

OCPB Comment No. 12 related to Study # —— (US) 1996/054:

a. *Conduct a subset analysis, more fully investigating the effect of gender on formoterol disposition, e.g., clearance.*

Response:

The analyses of gender effects on formoterol PK are shown below:

Table 2. Reanalyses of Gender Effects on the PK of Formoterol [Study # —— (US) 1996/054]

Least Squares Means			
PK Parameter\Gender	**Male (n=8)**	**Female (n=4)**	**p-Value**
Total Cl (ml/min)	4056	3573	0.5779
Total CL (ml/kg/min)	51.3	47.2	0.6337
C_{max} (pmol/L)	270.	256	0.8515
$T_{1/2}$ (hr)	10.4	9.2	0.2935
Renal CL (ml/min)	341	273	0.0992
Renal CL (ml/kg/min)	4.24	3.52	0.3095

The sponsor concluded that the apparent difference in formoterol disposition is partially due to body weight difference between males and females. The difference after adjusting for body weight does not warrant special labeling for the gender difference.

Reviewer's Comment:

The sponsor's response is acceptable.

b. *With regard to the plasma and urine assay performance validation, only summary data are reported. Submit data to fully demonstrate linearity, accuracy, precision, and specificity of the method. Include complete standard curve data, independent quality control results, and representative* ——— *For further details on currently accepted assay validation, refer to Shah VP et al., Pharm. Res. Vol. 9, No. 4 (1992).*

Response:

The detailed assay validation data were provided and are summarized below:

A. Plasma:

QC: ——— pmol/L (n=5)
Recovery: ———
Accuracy: ———
Inter-day Precision (CV%): ———

B. Urine:

1. **R,R- enantiomer**:

QC: ——— nmol/L (n=4)
Recovery: ———
Accuracy: ———
Intra-day Precision (CV%): ———

2. **S,S- enantiomer**:

QC: ——— nmol/L (n=4)
Recovery: ———
Accuracy: ———
Intra-day Precision (CV%): ———

Reviewer's Comment:

The sponsor has provided detailed assay method validation data, therefore, their response is acceptable. Please see their 11/23/99 submission for details.

OCPB Comment No. 13 related to Package Insert:

The draft package insert and carton and container labels should be modified to reflect the above comments submitted. Further labeling comments are being reserved at this time pending resolution of the aforementioned deficiencies.

Response:

We have incorporated the information provided in your comments and our replies into the proposed draft package insert and carton and container labels. We have also updated all references in the annotated package insert, and provide where applicable full literature references to replace abstracts, which only were available previously.

Reviewer's Comment:

Sponsor's proposed package insert is revised and comments are provided. Please see the following Agency's labeling comments for details (in Attachment 1). The sponsor's proposed annotated PI is in Attachment 2.

RECOMMENDATION:

Novartis submitted their responses on 11/23/99 to NDA 20-831(Serial No. BZ) for Foradil (formoterol fumarate 12 µg/capsule) Aerolizer-Dry Powder for Inhalation. The responses were submitted to address the deficiencies listed in the approvable letter dated 06/26/98. The above responses are reviewed by OCPB/DPE II. The sponsor's responses to OCPB comments are found acceptable. The following Labeling Comment (in Attachment 1) needs to be conveyed to the sponsor. It is recommended that the Agency's comments on formoterol PK be incorporated in the proposed PI.

LABELING COMMENT: (Needs to be sent to the sponsor)

The Agency's version of proposed labeling for formoterol PK subsection under the Clinical Pharmacology section is provided in Attachment 1.

/S/ 04/24/2000

04/17/2000
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Ramana Uppoor, Ph.D. RU 04/24/2000

FT initialed by Ramana Uppoor, Ph.D. /S/ 04/25/2000

cc: NDA 20-831, HFD-570 (Anthracite, Jani), HFD-870 (S.M. Huang, R. Uppoor, T.M. Chen), CDR (B. Murphy).

NDA 20-831 (Serial No. BZ) for Foradil (formoterol fumarate 12 µg/capsule) Dry Powder for Inhalation

Attachment 1

Agency's Proposed Formoterol PK Subsection

3 PAGE(S) REDACTED

NDA 20-831 (Serial No. BZ) for
Foradil (formoterol fumarate 12 μg/capsule)
Dry Powder for Inhalation

Attachment 2

Sponsor's Proposed Annotated PI (10/98 version)

JUN – 5 1998

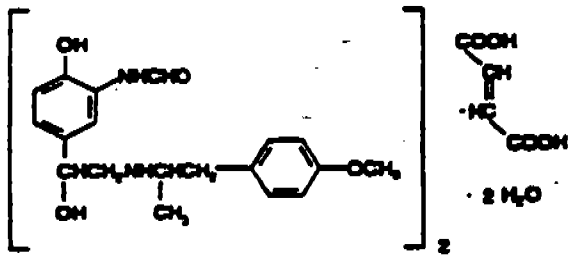
Clinical Pharmacology & Biopharmaceutics Review

NDA 20-831
Foradil™ (formoterol fumarate)
Capsules for Inhalation

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Type of Submission:
New NDA, NME, 1S
Submission Date:
6/24/97

Reviewer:
Brad Gillespie, PharmD



Synopsis Foradil™ is formoterol fumarate, a relatively long acting chiral, β-adrenergic agonist. It is formulated as a dry powder capsule for inhalation. The proposed indication is for the prevention and maintenance treatment of bronchoconstriction in patients with reversible airway disease to include patients with symptoms of nocturnal asthma and for the prevention of exercise-induced bronchospasm. The sponsor proposes marketing Foradil as a 12 μg dry powder capsule for inhalation. The proposed dose will be 1 ——— inhaled twice daily. Foradil was shown clinically to provide an equal, to more rapid onset of action than inhaled albuterol with at least 12 hours of sustained efficacy (as measured by all pulmonary function tests). Due to the lack of an assay adequately sensitive to measure plasma formoterol concentrations, the pharmacokinetic program is limited. An *in vitro* metabolism study conducted in support of this application indicated that formoterol is O-demethylated by CYP2D6, 2C19, 2C9 and 2A6. The mass balance study demonstrated that formoterol undergoes a marked O-glucuronidation *in vivo*. An *in vitro* CYP450 inhibitor study indicated that formoterol has the potential to modestly inhibit CYP2D6-mediated catalysis at a K_i anticipated to be several orders of magnitude more than the plasma formoterol concentrations obtained clinically. *In vitro* binding studies demonstrated that formoterol is not substantially bound to human plasma proteins. An *in vivo* human study showed that formoterol fumarate, when inhaled as a dry powder is at least 25% bioavailable based on urinary excretion of unchanged and conjugated formoterol. In an oral mass balance study (n=2) radioactivity recovery in the urine and feces was approximately 60% and 33%, respectively. It is not clear what fraction of formoterol recovered in the feces is unabsorbed drug, and which portion is via biliary excretion. With regard to chirality: Formoterol has two chiral centers. Foradil is a racemic mixture of (R,R) and (S,S) formoterol. Formoterol is enantiomeric, a racemic mixture of (R,R) and (S,S) formoterol. After inhalation of a single-dose of 120 μg formoterol fumarate, the (S,S)-enantiomer was cleared more rapidly than its (R,R) counterpart.

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Background Foradil™ is formoterol fumarate formulated as a dry powder capsule for inhalation. Formoterol fumarate is a relatively long acting, chiral, β_2-adrenergic agonist. The sponsor is proposing an indication of the prevention and maintenance treatment of bronchoconstriction in patients with reversible airway disease, to include patients with symptoms of nocturnal asthma and for the prevention of exercise-induced bronchospasm. In addition to the four pivotal clinical safety and efficacy trials, the sponsor has submitted 37 studies in the Human Pharmacokinetics section of the NDA. A total of seven were reviewed in this document. These include three pharmacokinetic 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. Of the pharmacokinetic studies not selected for review, they were either redundant or used an alternative dosing form (

. It is important to note that for this inhaled product, 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. Therefore, the pharmacokinetic program is very limited.

Formulations Formoterol fumarate has a molecular weight of 840.9 and is a white to yellowish powder freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol, slightly soluble in water and practically insoluble in acetone, ethyl acetate and diethyl ether. Foradil is formulated as a — clear gelatin capsule containing —— ; micronized formoterol fumarate and 25 mg lactose. Only one of the pivotal studies reviewed for this submission used a dry powder inhalation method of administration (Study —— (US) 1996/048). Both 12 and 24 µg capsules were used. It is unclear if this is the same as the to be-marketed formulation/device with regard to composition, method of manufacture or scale. The sponsor is requested to provide this information. The balance of the studies used either an oral solution (mass balance study) or bulk drug substance (*in vitro* protein binding and metabolism studies).

Summary of Pharmacokinetics

Absorption: Study — US) 1996/048 demonstrated that formoterol fumarate, when administered as a dry powder inhalation is at least 25% absorbed based on urinary excretion of both unchanged and conjugated formoterol. In the oral radiolabel mass balance study (Study 26/1986), a urinary recovery of approximately 60% was observed. While it is possible that (an) unidentified (and unmeasured) metabolite(s) is (are) present in the urine, the unidentified metabolites described in the mass balance study accounted for only approximately 2% of the dose administered. It is unclear if the O-demethylated metabolite formed in the formoterol *in vitro* metabolism study is present *in vivo*. Study — (US) 1996/048 also showed a proportionality of formoterol urinary excretion between the 12 and 24 µg doses. This suggests that there may be a formoterol dose proportionality over this range. In protocol 054, subjects inhaled a single 120 µg dose of Foradil. A peak plasma concentration of 266 pmol/L was

observed 5 minutes after dosing. Total exposure, as measured by plasma AUC was 1330 pmol•hr/L.

Distribution: In report R41/1991, the sponsor describes experiments designed to determine formoterol's degree of binding to human serum albumin, α-1-acid glycoprotein and γ-globulin. In Report —— F-1-4-6, an ultracentrifugation plasma protein binding experiment was described where plasma protein binding of formoterol was observed over a concentration range of 0.1 to 100 ng/mL. In all cases, formoterol was not highly bound (≤63%), so changes in binding due to stress or various disease states is not expected to be clinically important.

Metabolism: The sponsor has characterized the metabolism of formoterol in Protocol 96-7015 using pooled liver and recombinant human microsomes. Based on these *in vitro* findings, it appears that formoterol is O-demethylated by CYP2D6, 2C19, 2C9 and 2A6.

The mass balance study also identified a marked O-glucuronidation of formoterol. The results obtained from Protocol —— 42496 indicated that formoterol has the potential to modestly inhibit catalysis by CYP2D6. Nevertheless, expected plasma formoterol concentrations after administration at the clinical dose should be several orders of magnitude less than the observed K_i of 33 μM (in Protocol 54, after inhalation of a single 120 μg dose, peak formoterol plasma concentrations of approximately 266 pmol/L were observed).

Elimination: In the oral radiolabel mass balance study (Study 26/1986), it was evident that urine is the major route of elimination from the body for formoterol (approximately 60%). Of the approximately 30% of total radioactivity detected in the feces, it is unclear what fraction is unabsorbed drug and what portion is via biliary excretion. While the elimination half-life of unchanged formoterol is approximately 5.6 hours, the half-life of total blood radioactivity in the mass balance study was 3 - 3.5 hours, suggesting that formoterol metabolites may be excreted more rapidly than the parent. Study —— (US) 1996/048 showed similar formoterol urinary excretion rates after inhalation of 12 and 24 μg doses. With regard to chirality: Formoterol is enantiomeric, a racemic mixture of (R,R) and (S,S) formoterol. In Protocol 054, subjects inhaled a single-dose of 120 μg formoterol fumarate. The (S,S)-enantiomer was cleared more rapidly than its (R,R) counterpart (urinary elimination half-life 12.3

versus 13.9 hours). The (S,S)- enantiomer was also excreted to a larger extent ($A_{e\ 0\text{-}48}$: 4.80% versus 3.61% of the nominal dose).

Assay A variety of different assay methods were employed by the sponsor. While all assays were independently validated, a cross-method validation study was not conducted.

Comments

Comments 1 - 5 specifically refer to Study No. —— US) 1996/048

1. Assay accuracy and precision could be demonstrated more accurately if quality control samples were more evenly distributed along the quantifiable range of the assay.
2. The sponsor is requested to submit blank and representative ———— to demonstrate assay specificity.
3. In this trial, both 12 and 24 µg capsules were used. It is unclear if the two lots/batches for the two capsule strengths were the to be-marketed formulation with regard to composition, drug microcrystalline size distribution, method of manufacture, production size/scale and site of manufacture. The sponsor is requested to provide this information.
4. The sponsor is requested to submit complete single-dose urinary excretion data.
5. The sponsor accounting of study dropouts is not clear from the report submitted. They are requested to provide an accounting of all subjects enrolled.

Comments 6 - 8 specifically refer to Study Protocol 054

6. More meaningful results could have been obtained if the sponsor had measured both unchanged and the conjugated form of formoterol.
7. The sponsor is encouraged to conduct a subset analysis, more fully investigating the effect of gender on formoterol disposition, e.g., clearance.
8. With regard to the plasma and urine assay performance validation, only summary data were reported. The sponsor is requested to submit data to fully demonstrate the linearity, accuracy, precision and specificity of the method. This should include complete standard curve data, independent quality control results and representative ———— Submission of these data is necessary to support labeling claims based on this trial. For further details on currently accepted assay validation, the sponsor is referred to: Shah VP, et al. *Pharm Res* Vol 9, No. 4 (1992).

Comments 9 - 11 are preliminary comments referring to the proposed package insert

9. In the *Absorption* sub-section of the Pharmacokinetics section, the first sentence should be modified to read:

[ ]

Recommendation The Human Pharmacokinetics section of this NDA and the respective section of the product labeling has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II, and has been found satisfactory to support approval of the application provided that the sponsor satisfactorily addresses Comments 2 - 5 and 7 - 11. Comments 1 and 6 are for their general reference.

Please forward the above comments and recommendation to the sponsor.

/S/ 6/5/98

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

CP/B Briefing: June 2, 1998: Drs Chen, Hunt, Mehta, Selen, Uppoor

RD /S/ Ramana Uppoor, PhD., Team Leader
FP /S/ Ramana Uppoor, PhD., Team Leader
06/05/98

cc:
HFD-570 (NDA 20-831, Divisional File, Jani, Anthracite)
HFD-870 (ChenME, Hunt, Uppoor)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)

APPEARS THIS WAY
ON ORIGINAL

Urinary excretion of unchanged and total formoterol in patients with mild to moderate asthma after repeated dosing with formoterol dry powder capsules using a single-dose inhaler

Study No. — US) 1996/048 **Volume** 1.70 **Pages** 255 - 314
Investigator Multi-Center
Study Dates 5/02/95 - 5/8/96
Analytical Facility Ciba Geigy
Analysis Dates 4/18/96 - 7/19/96

OBJECTIVES Primarily to establish the clinical safety and efficacy of formoterol dry powder in mild-to-moderate asthmatics with a secondary objective of evaluating its pharmacokinetic behavior by measuring urinary excretion after multiple-dosing

FORMULATIONS (patients participating in the pharmacokinetic subset of the study received one of the following treatments)
Treatment A: 12 μg formoterol fumarate
Treatment B: 24 μg formoterol fumarate
Treatment C: 180 μg albuterol or placebo

STUDY DESIGN This was a multicenter, randomized, double-blind, double-dummy, parallel group trial comparing the safety, efficacy and tolerability of 12μg and 24μg formoterol dry powder administered twice daily compared with 180μg albuterol metered dose inhaler (MDI) administered 4 times daily. A total of 44, non-smoking mild-to-moderate adult and adolescent asthmatics enrolled in this study were selected for pharmacokinetic evaluation. Of these patients, 23 received formoterol and were included in the pharmacokinetic segment of the study (11 received 12μg, while 12 were administered 24μg). Patients were instructed to inhale the assigned formoterol dose two times daily and return to the study facility regularly for evaluation. Patients were required to abstain from the ingestion of foods and beverages containing caffeine and/or chocolate from 12 hours prior to each trial visit until the end of the trial visit. On visit 6 (Week 12) complete urine fractions were obtained 0-2, 2-4, 4-6, 6-8 and 8-12 hours after dosing. Concentrations of unchanged formoterol and conjugated formoterol were measured using an ———— method. Conjugated formoterol was hydrolyzed to free formoterol using enzyme hydrolysis.

ASSAY An ————————method was used for plasma determinations

Assay Performance

	Unchanged Formoterol	*Total Formoterol*
Linearity	**Satisfactory:** [redacted]	**Satisfactory:** [redacted]
Accuracy	**Satisfactory:** [redacted]	**Satisfactory:** [redacted]
Precision	**Satisfactory:** [redacted]	**Satisfactory:** [redacted]
Sensitivity	**LOQ:** [redacted] **nmol/L**	**LOQ:** [redacted] **nmol/L**
Specificity	**Unsatisfactory:** [redacted] **not submitted**	**Unsatisfactory:** [redacted] **not submitted**

DATA ANALYSIS

Pharmacokinetic: ~~$A_{e\,(0\text{-}12hr)}$~~, ER_{max} (highest observed urinary excretion rate: unchanged formoterol, only) and $t_{1/2}$ (unchanged formoterol, only)

Statistical: Descriptive statistics by treatment group were calculated

RESULTS A total of 16 subjects who received formoterol completed the pharmacokinetic phase of the study and were included in the analysis. Cumulative unchanged and total formoterol excretion rates are presented in Figure 1. Pharmacokinetic parameters are presented and compared in Table 1.

Figure 1. Cumulative Urinary Excretion Rates (% of Dose) for Unchanged and Total Formoterol (after twice daily dosing for 12 weeks)

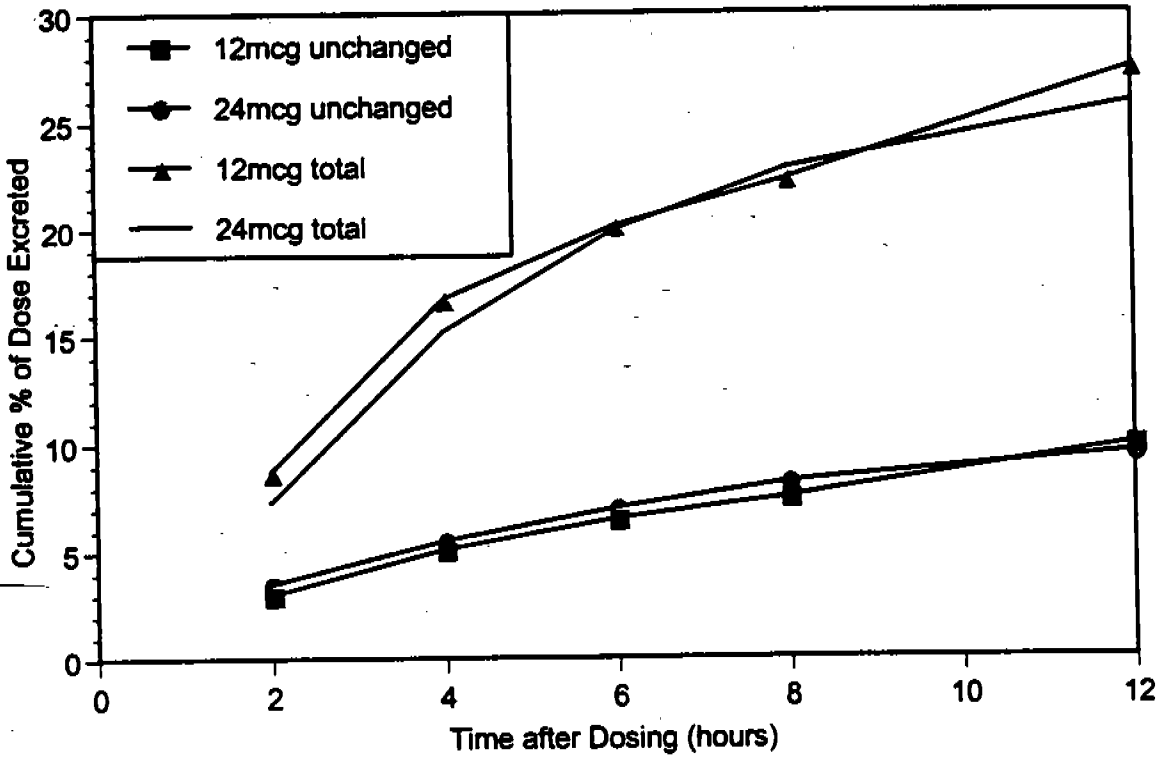


Table 1. Mean (%CV) Urine Pharmacokinetic Parameters for Unchanged and Total Formoterol After Multiple Inhaled Doses of 12 µg (n=7) and 24 µg (n=9) Formoterol Fumarate Dry Powder (after twice daily dosing for 12 weeks)

		12µg	24µg
Unchanged Formoterol	ER_{max} (nmol/hr)	0.48 (35)	1.4 (33)
	$A_{e\,(0\text{-}12)}$ (% of Dose)	9.87 (37)	10.4 (24)
	$t_{1/2}$ (hours)	5.60 (36)	—
Total Formoterol	$A_{e\,(0\text{-}12)}$ (% of Dose)	27.4 (17)	25.7 (39)

COMMENTS

1. Assay accuracy and precision could be demonstrated more accurately if quality control samples were more evenly distributed along the quantifiable range of the assay.
2. The sponsor is requested to submit blank and representative ——— to demonstrate assay specificity.
3. The sponsor accounting of study dropouts is not clear from the report submitted. They are requested to provide an accounting of all subjects enrolled.

CONCLUSION These data demonstrate that at least 25% of the administered dose is absorbed and excreted in the urine. While dose proportionality cannot be directly assessed from this study, it appears that similar fractions of drug are excreted when both 12μg and 24μg of formoterol dry powder are administered.

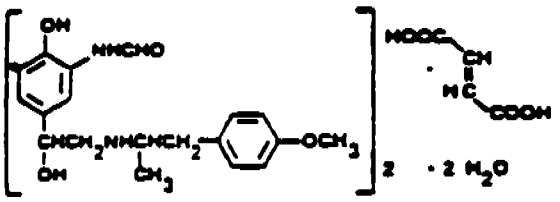
Absorption and disposition of [^{3}H]-labelled formoterol fumarate after single peroral doses in two healthy volunteers

Study 26/1986 **Volume** 1.72 **Pages** 015 - 048

Background Biotransformation studies in rats and dogs showed a marked conversion of formoterol to the phenolic O-glucuronide conjugate. No other metabolites were detected in urine or in rat liver preparations. In human studies, plasma levels of non-labeled drug were detected only after administration of doses of 120µg or greater. In urine about 5% of the dose was excreted as unchanged drug while after enzymatic treatment with α-glucuronidase, 10-15% of the dose could be attributed to formoterol.

Objectives To characterize the mass balance of [^{3}H]-labeled formoterol fumarate

Formulation [^{3}H]-labeled formoterol fumarate (radiolabel in the 3-position of the formanilide ring), Batch K-612.5A-1. It had a specific radioactivity of ——— and a chemical and radioactive purity of ≥99%.



Formoterol fumarate
(I•fumarate)

• ^{3}H-label

Study Design This open-label, single-dose study enrolled two healthy volunteers. After an overnight fast, subjects received a single capsule containing a 80.3 µg dose of [^{3}H]-labeled formoterol fumarate (total radioactivity: 166µCi). Serial blood samples were collected just prior to, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 96 hours after dosing. Urine and feces were also collected for periods of 104 and 96 hours, respectively, after dosing. During the first 24 hours after dosing, urine was collected during the following intervals: 0-2, 2-4, 4-8 and 8-24 hours after dosing.

Enzymatic Cleavage Samples of urine, blood and plasma were diluted with Sorensen buffer pH 6.8 mixed with α-glucuronidase, then incubated at 37°C to assess total formoterol.

Analysis of Unchanged Formoterol and Possible Metabolites Unchanged formoterol and 2 possible metabolite concentrations were determined in blood, plasma (1 and 1.5 hr samples) and urine by ———

Assay Aliquots of whole blood and feces were combusted and then radioactivity counting was performed on urine, plasma, whole blood and feces using a ———

Pharmacokinetic Evaluation C_{max}, T_{max}, AUC_{0-t}, $A_{e\,(0\text{-}48h)}$, CL_R, $t_{1/2}$

Results Both subjects completed the trial. Blood (dry) concentration equivalent versus time profiles for subjects A and B are presented in Figure 2. Dry blood concentrations were used because it is hypothesized that plasma concentration estimates were inflated due to the presence of tritiated water. Individual equivalent blood and urine pharmacokinetic parameter estimates are presented in Table 2. Total radioactivity excretion in urine and feces is presented in Table 3. Unchanged formoterol exposure (area under the curve based on dry blood concentrations both before and after treatment with α-glucuronidase) are compared to that of total [^{3}H]-labeled formoterol in Table 4. The concentrations of the two possible metabolites were below the limit of detection in all blood samples. Urinary excretion, as measured by total radioactivity and — is presented in Table 5.

Discussion Peak plasma radioactivity levels are attained rapidly (0.5-1.0 hours) after oral dosing with a total of approximately 60% excreted in the urine. When combined with the fecal fraction, greater than 93% of the administered dose was recovered. It is unclear what part of the fecal fraction is unabsorbed drug and what portion was excreted via the biliary route. The elimination half-life was about 3 hours. It is clear that while [^{3}H]-labeled formoterol is rapidly metabolized, the metabolites formed are minor moieties. Additionally, it is evident that both parent drug and metabolites are largely glucuronidated.

Figure 2. Dry Blood Concentration Equivalent versus Time Profiles for Subjects A and B After Administration of 80μg of [^{3}H]-Labeled Formoterol Fumarate (total radioactivity: 166μCi)

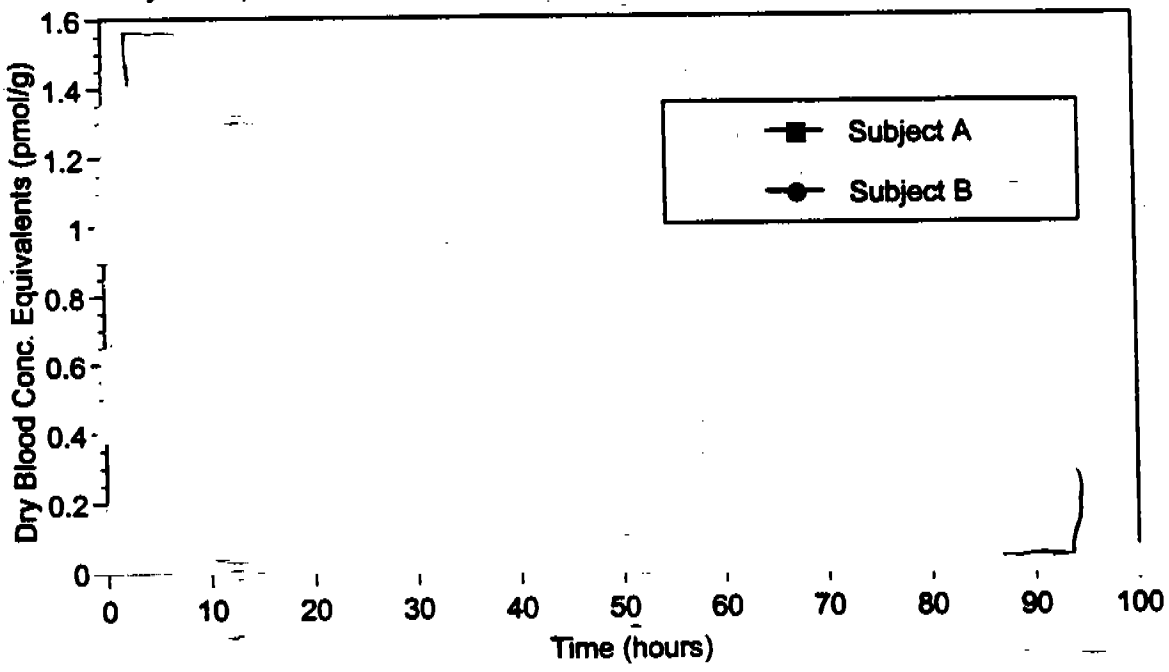


Table 2. Pharmacokinetic (dry blood and urine) Parameters After A Single Oral Dose of [^{3}H]-labeled formoterol fumarate (total radioactivity: 166μCi)

Parameter		*Subject A*	*Subject B*
C_{max}	(pmol/g)	0.583	0.147
T_{max}	(hr)	1	0.5
AUC_{0-12}	(pmol·hr/g)	1.548	0.724
$t_{1/2}$	(hr)	3.5	3.0
CL_R	(mL/min)	149	150

Table 3. Excretion of Total Radioactivity in Urine and Feces After a Single Oral Dose (80μg) of [^{3}H]-Labeled Formoterol Fumarate (total radioactivity: 166μCi) to Two Healthy Volunteers (% of Dose)

	Subject A		*Subject B*	
Time Interval (hr)	*Urine*	*Feces*	*Urine*	*Feces*
0-2				
2-4				
4-8				
8-24				
24-48				
48-72				
72-96				
96-104				
0-104 Total				

Table 4. Area Under the Curve (AUC) of Total [^{3}H]-Labeled Formoterol and of Unchanged Formoterol (based on dry blood concentrations both before and after treatment with α-glucuronidase) After an Oral Dose of 80μg of [^{3}H]-Labeled Formoterol Fumarate

	Subject A			*Subject B*		
	Total ^{3}H	Before hydrolysis	After hydrolysis	Total ^{3}H	Before hydrolysis	After hydrolysis
AUC_{0-12} (pmol·hr/g)	4.869	1.584	2.338	6.578	0.724	2.064

Table 5. Excretion in Urine of Total [^{3}H] Radioactivity, Formoterol (I) and Two Possible Metabolites (II & III) Measured by — Both Before and After α-Glucuronidase Incubation (0 - 96 hours after dosing)

		% of Urinary Radioactivity					
Subject	Total [^{3}H] (% of Dose)	I Pre-Hyd	I Post-Hyd	II Pre-Hyd	II Post-Hyd	III Pre-Hyd	III Post-Hyd
A	58.9	14.2	48.0	0.4	1.5	0.1	1.0
B	62.1	6.5	57.0	0.2	1.1	0.1	1.0

Conclusion Orally administered [^{3}H]-formoterol is rapidly absorbed and metabolized to a small extent, then glucuronidated before elimination mainly via the liver and possibly through biliary excretion. Nearly total excretion of drug and metabolites is complete 96 hours after dosing.

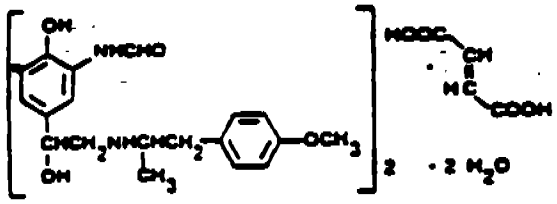
In Vitro **Binding of Formoterol to Serum Proteins**

Report No. R 41/1991 **Volume** 1.73 **Pages** 127 - 153

Objectives: To assess the extent of binding of formoterol to serum proteins using equilibrium dialysis

Materials:

[^{3}H]-formoterol hemifumarate (batch K-612.5B-3), 82 μCi/mg (Ciba-Geigy), radiochemical purity approximately 95%



Formoterol fumarate
(I•fumarate)

• ^{3}H-label

Blank human plasma from blood of healthy donors
Human serum albumin (HSA,) three references:

- S1: A 1653 (96 - 99% albumin)
- S2: A 1887 (essentially fatty acid free)
- S3: A 3782 (essentially fatty acid free, prepared from crystallized and lyophyllized essentially globulin free albumin)

α-1-acid glycoprotein (AAG,
γ-globulin (GG,
Sorensen phosphate buffer, 67 mmol/L, pH 7.4

Methods: Initially, the stability of formoterol in protein solutions (HSA, AAG and GG) compared to in serum was determined by incubating non-labeled formoterol fumarate in these media at 37°C. A apparatus with a membrane with a molecular cut off of daltons were used for dialysis. In each cell, 1 mL of [^{3}H]-labeled formoterol solution (pH 7.4) was dialyzed at 12 r.p.m. against 1 mL of serum or HSA, AAG or GG solution. All incubations were conducted with various drug concentrations at temperatures and within times shown to not permit formoterol degradation. Additionally, experiments were conducted to determine the incubation time needed to achieve equilibrium between the compartments. After dialysis, aliquots from each compartment were mixed with cocktail and radioactivity was determined by counting the samples for five minutes in a

The extent of formoterol protein binding was calculated as follows:

$$\%Binding = \frac{Ct - Cf}{Ct} x100$$