CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-279

CHEMISTRY REVIEW(S)

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-279 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 21-DEC-00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	22-SEP-00	25-SEP-00	20-JUL-97

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

DRUG PRODUCT NAME

Proprietary: Foradil Aerolizer™
Nonproprietary/USAN: formoterol fumarate inhalation powder
Code Names/#s:

- Atock (Japan)
- BD40A
- CGP 25827A
- Eformoterol (England)
- Foradil (USA/Europe)
- FORADIL/A. S. fumarate
- FORADIL/A.S. fumarate, —
- FORADIL/W.S. fumarate
- (±)-2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dehydrate
- 2-Hydroxy-5-[(1RS)-1-hydroxy-2-{[(1RS)-2-p-methoxyphenyl)-l-methylethyl]-amino}ethyl]formanilide fumarate dehydrate
- (±)-2'-Hydroxy-5'-[(IRS)-l-hydroxy-2-{[(IRS)-2-p-methoxy-a-phenethyl-amino-ethyl formanilide fumarate dehydrate
- (R*, R*)-(±)-N-[2-Hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butenedioate (2:1) (salt)
- YM-08316
- YM-8316

Chemical Abstracts registry number is 43229-80-7.

Chem.Type/Ther.Class: 1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: β_2-adrenergic bronchodilator for — bronchoconstriction in patients with — COPD

DOSAGE FORM: Capsule containing powder for inhalation

STRENGTHS:

- 12 mcg per capsule
- The recommended dose is one to two capsules every 12 hours
- The emitted dose is 10 mcg when tested at 60L/min with 2 activations for 2 seconds each

ROUTE OF ADMINISTRATION: oral inhalation for use with the Aerolizer™ Inhalation Device only

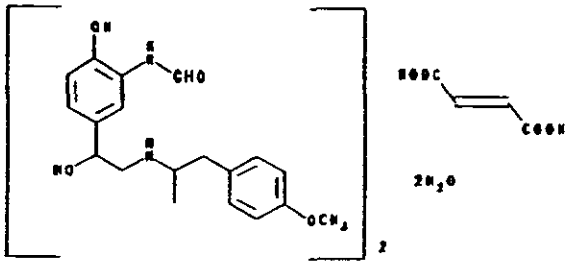
SPECIAL PRODUCTS: __ Yes _X_ No

DISPENSED: _X_ R_x ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

±2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate

Molecular Weight: 840.9
Molecular Formula:
$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$



SUPPORTING DOCUMENTS:

N20-831 and associated DMFs.

RELATED DOCUMENTS (if applicable): See seven chemistry reviews and addenda for N20-831.

CONSULTS: N/A

REMARKS/COMMENTS:
The current application N21-279 is being submitted as per Appendix E of PDUFA for a new indication — bronchoconstriction in patients with — chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis. This is being done while the original application N20-831 is still under review. It is noted that as per the second addendum to chemistry review #7 dated 12/8/00, the application N20-831, as amended on 07-DEC-00 was considered sufficient from a CMC perspective for **approval (AP)**.

In terms of the chemistry, manufacturing, and controls (CMC) information in N21-279, there were no changes made to the DESCRIPTION or HOW SUPPLIED sections of the labeling or the patient's instructions for use. The applicant states on p. 4-2 of vol. 3 that the CMC section of N21-279 is "fully cross-referenced and supported by the CMC information submitted to NDA 20-831. The only items included here are the environmental assessment, and a statement concerning the formulations of the capsules and Aerolizer™ used in the COPD trials as compared to the commercial formulations."

Environmental Assessment Information (vol 3, p. 4-4)
The applicant certifies that the current application, with the potential for "increased use", as defined in 21 CFR 25.5(a), will still qualify for a categorical exclusion in accordance with 21 CFR 25.31(b) as the concentration of the active moiety (formoterol) introduced at the point of entry into the aquatic environment will be less than 1 ppb in concentration. They further state that, to the best of their

knowledge, no other extraordinary circumstance is known to exist which may impact significantly on the environment and require the preparation of an environmental assessment.

Evaluation: Satisfactory.

Formulation/Device Modification Comments (vol. 3, pp. 4-5, 6)
The applicant indicates that the formulation of the drug product used in clinical studies 041, 056, and 058, supporting this application were the same as the to be marketed formulation for N20-831 except that there were "minor variations" to the capsule shell. Table 1 and 2 are reproduced from the application below.

Table 1 Foradil clinical study formulation information

Clinical study	Batch number	Batch size (capsules)	Formulation number	Dosage form
Protocol 041	T2/95 (E-15491)		Q874 (H-3831)	12 µg clear capsule with imprint
Protocol 056	B970020,		KN 3746732.00.003	12 µg Clear capsule with
	B970097		KN 3746732.00.003	
Protocol 058	B970020		KN 3746732.00.003	12 µg Clear capsule with

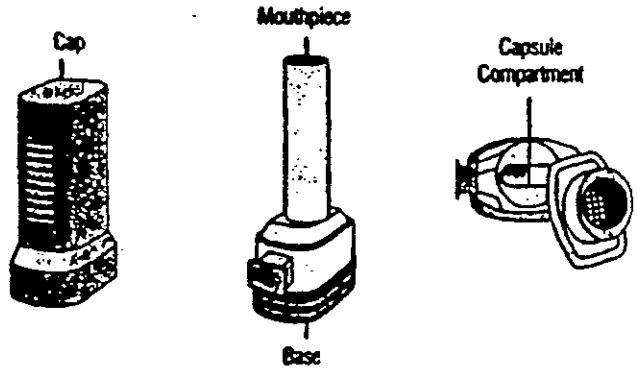
Table 2 Foradil market formulation (used in clinical studies)

Component	Quantity per capsule
Formoterol fumarate	0.012 mg
Lactose	to 25 mg
Capsule shell size clear or as specified above)	1

Evaluation: Satisfactory. The changes to the capsule shell are minor in nature and involve the imprint, presumably for ID purposes. Also, the use of a shell is not specified in the final drug product specifications (see p. 15 of addendum #2 of CR#7), which only lists the appearance of the dosage unit in a clear capsule imprinted in black ink with CG/FXF. These changes are not expected to have altered the stability or performance properties of the drug product in any significant manner.

The applicant indicates that the Aerolizer design that was indicated in NDA-831 was used for their clinical studies 041, 056 and 058 for support of the current application, but subsequently, "minor improvements were made to the commercial Aerolizer." Figure 1 reproduced below is a drawing of the Aerolizer device. Table 3 from the application is reproduced below which summarizes the changes made.

Figure 1 **Commercial Aerolizer**



A comparison of the Aerolizer used for clinical studies 041, 056 and 058, and the improvements made to the commercial Aerolizer, is outlined in the table below:

Table 3 **Differences between Aerolizers used in the referenced clinical studies and the commercial Aerolizer**

Development Aerolizer (used in clinical studies 041, 056 and 058)	Current commercial Aerolizer
The capsule piercing pins (located in the capsule compartment) are made of	The capsule piercing pins are made of a , improves capsule piercing performance.
No	step was added to the manufacturing process for the Aerolizers. This step ensures consistent quality of the Aerolizers.
Push-buttons	Push-buttons were added to improve the patient's handling of the Aerolizer.

Evaluation: Satisfactory. The change in the composition of the piercing pins of the device is stated to improve the "piercing performance" although no data is provided in support of this. The applicant has *not* indicated a

CONCLUSIONS & RECOMMENDATIONS:

The application N21-279 is considered sufficient from a CMC perspective for **approval (AP)**.

cc:
Orig. NDA 20-831
HFD-570/Division File
HFD-570/CBertha/12/21/00
HFD-570/PJani
HFD-570/GPoochikian

R/D Init by:

Craig M. Bertha, Ph.D., Review Chemist
filename: **00-09-22.rev**

APPEARS THIS WAY ON ORIGINAL

/s/

Craig Bertha
12/22/00 01:38:48 PM
CHEMIST

Guiragos Poochikian
12/22/00 03:23:21 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

The environmental assessment was reviewed as part of chemistry review #1, dated December 21, 2000, page 2.

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 20831/000**
Stamp: **26-JUN-1997** Regulatory Due: **18-FEB-2001**
Applicant: **NOVARTIS PHARMS**
59 RT 10
EAST HANOVER, NJ 079361080

Priority: **1S** Org Code: **570**
Action Goal: District Goal: **24-FEB-1998**
Brand Name: **FORADIL AEROLIZER(FORMOTEROL FUMARATE IN**
Established Name:
Generic Name: **FORMOTEROL FUMARATE**
Dosage Form: **PDR (POWDER)**
Strength: **12 MICROGRAMS**

FDA Contacts: **P. JANI (HFD-240) 301-827-7248 , Project Manager**
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation:

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

Establishment: [redacted]
DMF No: [redacted]
AADA No.

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **05-SEP-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

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

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

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Profile: **ADM** 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

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

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

DMF No: [redacted]
AADA No:

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

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

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

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:
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:
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:
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:

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