

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-831

ADMINISTRATIVE DOCUMENTS

NOVARTIS

Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 201 503 7500
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September 19, 1997

NDA 20-831
Foradil™
(formoterol fumarate)
dry powder capsules for inhalation

COPY 1

NDA Amendment

Center for Drug Evaluation and Research (HFD-570)
Document Control Room 10B-03
5600 Fishers Lane
Rockville, Maryland 20857

Attn: John Jenkins, MD, Director
Division of Pulmonary Drug Products

Dear Dr. Jenkins: _____

Please refer to our New Drug Application for Foradil™ (formoterol fumarate) dry powder capsules for inhalation. In accordance with the Revised Policies and Procedures for compliance with the National Environmental Policy Act, we are requesting withdrawal of the Environmental Assessment provided in Volume 1.9A of Foradil™ NDA 20-831 on June 24, 1997. At this time, we are providing a claim for categorical exclusion from the Environmental Assessment requirements under 21 CFR 25.31(b). This provides for action on an NDA whereby the use of the active moiety may be increased, but the estimated concentration of the active moiety formoterol at the point of entry into the aquatic environment will be below 1 part per billion.

Should you have any comments or questions regarding this submission, please contact me directly at (908) 277-7044.

Sincerely,

Joyce Ann Sinno, Ph.D.

Joyce Ann Sinno, Ph.D.
Drug Regulatory Affairs

Attachment
Submitted in duplicate

cc: Ms. Regina Brown
New Jersey District Office, North Brunswick Resident Post





Memorandum

Date May 17, 2000

From Steven R. Koepke, /S/
Deputy Director, Division of New Drug Chemistry II,
Office of New Drug Chemistry

Subject NDA 20-831
Floradil (formoterol fumarate powder for inhalation)
Novartis

There are serious CMC deficiencies related to particle size and degradation products in the stability data submitted in this application. Up to 30% of the drug substance is unaccounted for in mass balance in the accelerated stability studies. In addition, there are significant changes in particle size and emitted dose over time. The sponsor has submitted limited refrigerated stability data to attempt to address some of these issues, but it is unclear that there is any significant improvement in this data. It is recommended that the sponsor be reminded that the Agency has recommended protective overwraps or other protective packaging be investigated to address these issues.

Overall CMC recommendation: There are remaining serious CMC deficiencies as of CMC review #6. We concur with the overall recommendation of Approvable.

Environmental assessment: Categorical exclusion was claimed (see CMC review #1) – adequate.

Facility Inspections: Acceptable 12-May-2000

Tradename: Acceptable 16-Jul-1997 from LNC. Has this been reexamined by OPDRA?

Labeling: Acceptable from CMC

APPEARS THIS WAY
ON ORIGINAL

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 6, 2000

NDA NUMBER: 20-831

NAME OF DRUG: Foradil Aerolizer (formoterol fumarate powder for inhalation)

NDA HOLDER: Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

I. INTRODUCTION

This consult was written in response to a request from the Division of Pulmonary Drug Products (HFD-570) for assessment of the tradename Foradil Aerolizer. A specific request was made by HFD-570 to evaluate the inclusion of Foradil Aerolizer, as proposed by the sponsor.

The name Foradil was previously reviewed by the Labeling and Nomenclature Committee (LNC) and found to be acceptable. Inclusion of the delivery device name "Aerolizer" in the proprietary name for this product was not previously proposed by the sponsor and, therefore, was not addressed by the LNC.

Formoterol fumarate (Foradil) is a highly selective beta₂-adrenergic bronchodilator. The drug is indicated for the prevention and maintenance treatment of asthma and bronchoconstriction in patients 5 years of age and older with reversible obstructive airways disease. This includes patients with nocturnal asthma. Formoterol fumarate is also indicated for the prevention of exercise-induced bronchospasm in adults and children ages 12 years and above. It is supplied in one strength, as a capsule containing 12 mcg of formoterol fumarate in a dry powder form. Foradil comes supplied with a disposable inhaler device, the Aerolizer™. There is no propellant in the Aerolizer product. The device punctures the capsule and the patient inhales the powder when ready. The usual dosing for most indications is inhalation of the contents of one 12-mcg capsules every 12 hours. For exercise-induced bronchospasm, inhale contents of one at least 15 minutes before exercise. Total daily dose greater than is not recommended.

Foradil appears to be marketed in several other countries, including the United Kingdom.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii,iii} as well as several FDA databases^{iv} for existing drug names which sound alike or look alike to Foradil to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

A group discussion was held by OPDRA to gather professional opinions on the safety of a proprietary name. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Error staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Because no other dosage forms of Foradil are currently available in the U.S., it seems unlikely that physicians will include the additional delivery device name "Aerolizer" in communicating prescriptions. Therefore, the proprietary name was discussed with a concern for the name "Foradil", not "Foradil Aerolizer". Two product names were identified in the OPDRA Expert Panel discussion that were thought to have some potential for confusion with Foradil: Tofranil and Toradol. Tofranil is supplied as 10-, 25-, and 50-mg oral tablets. Toradol is an NSAID that is supplied as 10-mg oral tablets and 1-mL and 2-mL vials and syringes containing 1 mL or 2 mL of 15 mg/mL or 30mg/mL solution.

Of the two products, Toradol oral tablets were considered to be most likely confused with Foradil. Both Foradil and Toradol solid dosage forms are supplied in one strength, which may increase the potential for errors since a mg- or mcg- strength would not be required to clarify a prescription prior to dispensing.

The FDA-approved Toradol oral dosing is one or two tablets initially, followed by one tablet every 4 to 6 hours as needed. The dose should not exceed 40mg per 24-hour period and combined therapy of IV/IM Toradol and oral Toradol is not to be continued beyond 5 days total, although in usual clinical practice settings, the 5-day length of therapy is not strictly adhered to. Foradil is intended for use as a twice-daily inhalation dose of the capsule contents via the Aerolizer delivery device.

ⁱ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

ⁱⁱ American Drug index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

^{iv} Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-99, and the electronic online version of the FDA Orange Book.

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A study was conducted within FDA employing a total of 94 health care professionals (nurses, pharmacists, physicians) to determine the degree of confusion of Foradil with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote inpatient and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Foradil (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
<i>Inpatient:</i> Foradil 1 cap BID	<i>Inpatient:</i> Foradil, one cap BID
<i>Outpatient:</i> Foradil cap, 1 BID, #60, No refills	

2. Results

Results of this exercise are summarized below:

Study	No. of participants	# of responses (%)	"Foradil" response	Other response
Written: Inpatient	31	19 (58%)	1 (5%)	18 (95%)
Outpatient	32	20 (62%)	4 (20%)	16 (80%)
Verbal: Inpatient	31	18 (58%)	3 (17%)	15 (83%)
Total	94	57 (61%)	8 (14%)	49 (86%)

Among verbal prescription study participants, the majority of study participants provided misspelled variations of the drug name. Most of the name interpretations were phonetic variations of "Foradil". Three of 18 (17%) study respondents correctly interpreted the name as "Foradil".

Among participants in the written prescription studies, the majority of the respondents provided misspelled variations of the drug name; most of the name interpretations were phonetic variations of "Foradil". Five of 39 (13%) study respondents correctly interpreted the name as "Foradil". Notably, two (2) respondents to the outpatient written prescription studies mentioned Toradol as a closely related name. One specifically interpreted the study drug name as Toradol. The second respondent interpreted the name as Foradil but believed that Foradil could be mistaken for Toradol, depending on the handwriting clarity, although they felt that a pharmacist might distinguish the products based upon dissimilar dosing.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Foradil Aerolizer", the primary concerns were related to drug product names that look-alike or sound-alike to Foradil, without the delivery device name "Aerolizer". One product name in particular, Toradol, was identified in the Expert Panel discussion that was

thought to have potential for confusion with Foradil. We conducted prescription studies to simulate the prescription ordering process. In this case, there was some confirmation that Foradil could be confused with Toradol, as two study participants independently noted this similarity in handwritten, inpatient drug orders.

Although there are limitations to the predictive value of these studies primarily due to the sample size, we have acquired some safety concerns due to the positive interpretations with these drug products. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors in the general population. The potential for a serious outcome could be associated with the inadvertent administration of Toradol to a patient with asthma. Toradol and other NSAIDs have precautions for use in patients with asthma, as they may have an increased risk of bronchospasm.

However, we acknowledge the fact that the prescriptions in our studies did not convey the FDA-approved, standard dosing regimen of Toradol (e.g., every 4 to 6 hours). In addition, Toradol and Foradil Aerolizer would likely physically be stored in different sections of a pharmacy, although that does not eliminate the possibility of medication errors associated with the misinterpretation of prescriptions for either product. In communicating outpatient prescriptions, a specification of quantity to dispense would likely distinguish the two drug products.

III. RECOMMENDATIONS

We do not object to use of the name "Foradil Aerolizer", but with the following commitment from the manufacturer:

OPDRA recommends that the firm be required to treat all Foradil Aerolizer postmarketing reports of medication errors or reports of potential errors as Expedited (15-Day) reports during the first 6 months of distribution of the product, regardless of patient outcome.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

/S/

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/

3/14/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Pulmonary Drug Products		HFD-570
Attention: Parinda Jani Project Manager		Phone: (301) 827-1064
Date: May 7, 1997		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: Foradil		IND: _____
Established name, including dosage form: formoterol fumarate dry powder capsules for inhalation		
Name of the firm: Novartis Pharmaceuticals Corp.		
Indications for Use (may be a summary if proposed statement is lengthy): for the maintenance treatment and prevention of acute bronchospasm in patients — years of age and older with reversible obstructive airway disease.		
Initial Comments from the submitter (concerns, observations, etc.): The NDA will be submitted, May 1997 (assigned number 20-831). The sponsor understands that tradename will be re-evaluated during the NDA approval process.		

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original 20-837; HFD-570/division file; HFD-570/J.Parinda; HFD-570/ Schumaker, Poochikian

Rev. December 95

APPEARS THIS WAY
ON ORIGINAL

Consult #811 (HFD-570)

FORADIL

formoterol fumarate dry powder caps

The Committee found no look-alike/sound-alike conflicts or misleading aspects with the proposed proprietary name. However, the recommended established name for this product should be (formoterol fumarate for inhalation).

The Committee had no reason to find the proposed name unacceptable.

IS/ 7/16/97, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

Novartis Pharmaceuticals Corporation

NDA 20-831

Foradil™
(formoterol fumarate)
Capsules for Inhalation

PATENT INFORMATION

Pursuant to 21 CFR 314.53(c)(3), the applicant declares that it believes that there are no relevant unexpired patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-831 SUPPL # _____

Trade Name Foradil Generic Name formoterol fumarate inhalation powder

Applicant Name Novartis HFD- 570

Approval Date 2/16/01

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES / X / NO / ___ /
- b) Is it an effectiveness supplement? YES / ___ / NO / X /

If yes, what type(SE1, SE2, etc.)? _____

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

- _____
- d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / ___ / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other

than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / ___ / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / ___ / NO / ___ /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___ / NO / ___ /

If yes, explain: _____

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / ___ / NO / ___ /

If yes, explain: _____

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval: _____

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES / ___/ NO / ___/

Explain: _____

Investigation #2

IND # _____ YES / ___/ NO / ___/

Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / / Explain _____

NO / / Explain _____

Investigation #2

YES / / Explain _____

NO / / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / /

NO / /

If yes, explain: _____

 / S /

Signature of Preparer

 2/5/01

Date

Title: ~~Project~~ Manager

 / S /

Signature of Office of Division Director

 2/14/01

Date

Novartis Pharmaceuticals Corporation

NDA 20-831

Foradil™ (formoterol Fumarate) Capsules for Inhalation

DEBARMENT CERTIFICATION STATEMENT

Novartis Pharmaceuticals Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act, in connection with this application.

Signed Stephenie Barba Date 6/11/98.

Stephenie Barba
Executive Director
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

NDA 20-831

Foradil®
(formoterol fumarate inhalation powder)

**Complete Response to FDA's
May 24, 2000 Approvable Letter**

Appendix 4. Financial Disclosure Information

Document type: Health Authority Response

Document status: Final

Release date: Aug 11, 2000

**Property of Novartis Pharmaceuticals Corporation
Confidential**

**May not be used, divulged, published or otherwise disclosed
without the consent of Novartis Pharmaceuticals Corporation**

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

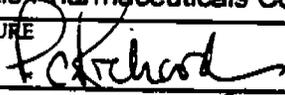
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Peter Richardson, MD MScP	TITLE Vice President
FIRM/ORGANIZATION Novartis Pharmaceuticals Corporation	
SIGNATURE 	DATE 07/11/00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

4 PAGE(S) REDACTED



Memorandum

Date February 15, 2001

From Steven R. Koepke, **/S/**
Deputy Director, Division of New Drug Chemistry II,
Office of New Drug Chemistry

Subject NDA 20-831
Foradil Aerolizer (formoterol fumarate powder for inhalation)
Novartis

There were serious CMC deficiencies related to particle size and degradation products in the stability data submitted in this application as of CMC review #6. The applicant submitted early stability studies (see CMC review #7) that addressed the earlier deficiencies with a protective overwrap of the drug product and refrigerated storage conditions. The stability data are reviewed in CMC reviews #7 addendum #1 and 2. These studies support storage conditions of 2-8°C for 18 months or 25°C with a 4 month period of use and a reduction of the specification of unaccounted for in mass to — The Applicant agreed to these conditions in the 01-DEC-00 submission.

Overall CMC recommendation: There remaining CMC deficiencies were resolved as of CMC review #7 addendum #2. We concur with the overall recommendation of Approval from a CMC perspective with labeling comments.

Microbiology: Acceptable 12-Dec-98

Environmental assessment: Categorical exclusion was claimed (see CMC review #1) — adequate.

Facility Inspections: Acceptable 27-Oct-2000

Tradename: Acceptable 16-Jul-1997 from LNC.

Labeling:

Carton: Delete — from established name.
Change yellow print to a more prominent color.

Division Director's Memorandum

Date: Thursday, May 04, 2000
NDA: 20-831
Sponsor: Novartis
Proprietary Name: Foradil (formoterol fumarate powder for inhalation)
From: Robert J. Meyer, MD Director, Division of Pulmonary and Allergy Drug Products. /S/

Introduction: This is a resubmission of the Foradil NDA to answer an "approvable" letter issued in June 1998. The response was received 11/23/99. There were numerous 11/24 deficiencies identified in this action letter related to the CMC, clinical, and biopharmaceutics review areas, as well as in labeling. While many of these deficiencies have been successfully answered at this point, the lack of data to support stability of this product on storage preclude approval at this time.

CMC: The sponsor's resubmission was received with only 3 months of complete, relevant stability data. The resubmission was later amended with the addition of the 6 month data (and very recently 9 months from one site). Serious, clinically concerning issues remain with the CMC stability data submitted that preclude approval. At various conditions on storage (most notably 40°C/75% RH), there is a dramatic loss of drug detectable in their drug assay. The sponsor has failed to identify the degradation products resulting from this loss, so that the full mass balance cannot be accounted for - up to 30% unaccounted for at 40°C/75% RH at 6-months. This means that in accelerated stability testing, there is not only a loss of potency, but a large accumulation of presumed degradation products that have been neither identified nor characterized. Therefore, any safety or efficacy issues related to these accumulated degradants cannot be assessed. While the loss of drug substance in the assay, and the impact of this loss on the emitted dose testing is improved by storage at lower temperatures (including refrigerated conditions), it may not be reasonable to assume that the product will never be subject to higher temperatures between manufacturing, shipping, distribution and ultimate use.

A second critical issue relates to the particle size distribution, as characterized by _____ testing. _____ data show that Foradil undergoes substantial shifts in individual stages of the _____ on stability testing, even at room temperature and refrigerated conditions. This is particularly notable on some of the more 'relevant' stages covering the respirable fractions of the dose - from approximately _____ microns. These kind of shifts would be expected to have clinical consequences in terms of efficacy. It is not clear if an overwrap or other protective packaging would help stabilize the _____ profile during storage since, despite more than 2 years of advice from DPADP, the sponsor has never conducted secondary protective packaging stability studies. In our April 6, 2000, meeting with the company, they argued that this product showed no problems in the clinical studies, despite these concerns. We pointed out that clinical studies only define mean responses to an average dose and are not designed to (nor can they) assess the impact on an individual patient of the loss of drug substance, an increase in degradation products or a shift in the particle size distribution in a particular dose. However, careful studies with monodispersed aerosols of bronchodilators show

that particle size has a critical and substantial effect on the resulting bronchodilator response.

Since there are substantial CMC concerns outstanding, and since the sponsor has not provided adequate data to support appropriate packaging, storage conditions nor the length of expiration dating, this product cannot be approved at this time.

Pharm/Tox: The four carcinogenicity studies previously submitted were reconsidered by the ECAC this cycle, due to incomplete internal records of the prior CAC discussion and recommendation on these studies. The findings of these studies ultimately will lead to revisions of the labeling to better describe some of the tumors found in both rats and mice, but the ultimate assessment of the Division is that the findings do not preclude approving this product, when the other issues are resolved. See Dr. Huff's memo and Dr. Pei's review for details.

Biopharmaceutics: The deficiencies included in the original approvable action have been successfully addressed to OCPB's satisfaction. Incorporation of some of the resulting biopharmaceutics data into the product labeling will be needed.

Clinical / Stastical: There were 7 clinical deficiencies contained in the June 1998 action letter. These have been addressed by the sponsor in the response of Nov. 1999. One of the major deficiencies was the lack of adequate data for children 6 to 11 years of age for both the maintenance treatment indication and the protection against exercise-induced bronchospasm. The former has been addressed through the submission of a additional study (#049), the latter will be part of the pediatric written request. Otherwise, the issues were successfully addressed by the sponsor (see Dr. Anthracite's review of 4/11/2000):

The data from the 12-month pediatric safety and efficacy trial (#049) support the approvability of Foradil for the prevention and maintenance treatment of bronchospasm in children. Of concern in this trial was a higher rate of serious asthma-related adverse events in the active treatment group, compared to placebo. Although this signal does not preclude approving the drug for this age range, this finding must be reflected in the product labeling under the Pediatric Use subsection and the Adverse Event Section of the labeling.

Labeling: Further comments from the Clinical, Biopharm and Pharm/Tox disciplines will be provided in this action letter. However, final labeling comments will await full resolution of the CMC issues and the sponsor's response to the comments provided in this action.

Conclusions: From my perspective, I cannot recommend approval of this product currently, since we do not have data to provide for a reasonable expiration dating period. The sponsor must first demonstrate that product produced and packaged appropriately at all the relevant sites remains sufficiently stable at recommended storage conditions (particularly with regard to drug assay, emitted dose and particle size distribution), to allow for a reasonable expiration dating period.