CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-592

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Patent Submission

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA #21-592

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: FORADIL® CERTIHALER™
- Active Ingredient(s): Formoterol Fumarate
- Strength(s): 10 mcg/metered dose
- Dosage Form: Multi-dose dry powder inhaler
- Approval Date:

A. This information should be provided for each individual patent submitted.

U.S. Patent Number: 6,182,655

Expiration Date: December 5, 2016

Type of Patent--Indicate all that apply:

1. Drug Substance(Active Ingredient) ___Y ___N
2. Drug Product(Composition/Formulation) __√_Y ___N
3. Method of Use ___Y ___N

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent:_____

Name of Patent Owner: Jago Research AG

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required by 21CFR 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.

The undersigned declares that the above stated United States Patent Number 6,182,655 covers the composition, formulation and/or method of use of FORADIL® CERTIHALER™ (name of drug product). This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- _√__the subject of this application for which approval is being sought.)

Signed: Carol A. Loeschorn

Carol A. Loeschorn
Senior Patent Attorney
Telephone Number: (862)778-7881
Date: December 4, 2002

The above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the ***The Orange Book***,* the above information may be provided to the Orange Book Staff at the address below. You may also contact the Orange Book Staff directly at **(301)827-5846** regarding listing of patent information.

Mailing address: **(US Mail or FedEx deliveries)**

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs/HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

OR faxed to: (301)-827-5911

* - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the ***The Orange Book***.

EXCLUSIVITY SUMMARY

NDA # 21-592 SUPPL # HFD # 570

Trade Name Foradil Certihaler

Generic Name formoterol fumarate

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known December 15, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

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 ☒ 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 ☐ NO ☒

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

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

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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# 21-929 Symbicort

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#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 8.

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.

(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 8:

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 ☒

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

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 ☒

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

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"):

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 # 60,254	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND # 60,254	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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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:

Name of person completing form: Akilah Green
Title: Senior Regulatory Management Officer
Date: December 11, 2006

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Badrul Chowdhury
12/15/2006 01:34:39 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-592 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: June 16, 2006 PDUFA Goal Date: December 16, 2006

HFD-570 Trade and generic names/dosage form: Foradil Certihaler (formoterol fumarate) Inhalation Powder

Applicant: Novartis Pharmaceuticals Corporation Therapeutic Class: 3

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☐ Yes. Please proceed to the next question.
- X No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only):_____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s):_____

Indication #1: _____

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- ☐ No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Akilah Green,
Senior Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Akilah Green
12/15/2006 11:41:11 AM

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

NDA No. 21-592
New Drug Application

Foradil® Certihaler™
(formoterol fumarate inhalation powder)

NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

NOVARTIS PHARMACEUTICALS CORPORATION 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.

December 9, 2002
Date

Ann Shea
Ann Shea
Associate Director
Drug Regulatory Affairs

DIVISION DIRECTOR'S MEMORANDUM

Date: October 17, 2003

To: NDA 21-592

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Foradil Certihaler (formoterol fumarate) Inhalation Powder, 10 mcg

Applicant: Novartis

Administrative and Introduction

Novartis submitted an NDA for Foradil Certihaler (formoterol fumarate) Inhalation Powder, 10 mcg as a 505(b)(2) application that was received by the Agency on December 18, 2002. The PDUFA action due date on this application is October 18, 2003. Foradil Certihaler is being developed by Novartis as a line extension to the Foradil Aerolizer product, which is a single dose dry powder inhaler containing the same active drug substance. Foradil Certihaler is a multi-dose dry powder inhaler device that contains 60 metered dose of the powder formulation. The proposed indication is maintenance treatment of asthma and prevention of bronchospasm in patients 5 years of age and older. Foradil Aerolizer is currently approved and marketed in the United States for use in patients with asthma and chronic obstructive pulmonary disease (COPD). Of note, the currently marketed and approved dose of Foradil Aerolizer in the United States is 12 mcg to be sued twice daily. The 24 mcg twice daily dose was not approved for asthma primarily because of increased asthma exacerbation seen with the 24 mcg twice daily dose, and because of no significant efficacy advantage of the 24 mcg twice daily dose to the 12 mcg twice daily for both asthma and COPD. Since formoterol is already approved for asthma , the clinical program to support this NDA is relatively brief and included two dose ranging studies in adults and children, two 12-week efficacy and safety studies in subjects 13 years of age and older, and one 12-week efficacy and safety study in children ages 5-12 years. These studies support the efficacy and safety of Foradil Certihaler for the treatment of asthma. The major issue with this application that will preclude approving this application in this first review cycle is in chemistry and manufacturing as detailed in the CMC discipline review and commented briefly below.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The CMC aspects of this application are discussed in the CMC review of Dr. Bertha. The CMC team issued a Discipline Review letter on May 7, 2003, and received a response from Novartis on August 29, 2003. The review of the response is ongoing. The major outstanding issues identified the CMC team include inadequate control, testing methods, and specifications of various aspects of the drug product, including device and formulation components. In addition, there is a major concern on device performance

and durability as discussed briefly below. The Sullivan's Medial Team Leader memorandum discusses the device durability problem in detail.

In the pivotal clinical studies 10,000-15,000 devices were utilized. Of these, 174 complaint devices were returned for testing, of which 111 devices were found to have failure, the most common (n=101) was an increase in the flow rate required to trigger an actuation. The devices used in the clinical studies were produced using [redacted] technique. Novartis subsequently transitioned from [redacted] and instituted certain design modifications to address the problems that led to device failures in the clinical studies. In consultation with the CMC team, Novartis conducted limited simulated patient use study of some new devices using their personnel as test subjects. Preliminary review of the limited use study by the CMC team show that there still is a small increase in the actuation flow rate with device use. In addition there are also some failures of the dose-counter. It is very likely that Novartis will need to conduct an actual patient use study to demonstrate reliability of the device in patients' hand.

b(4)

Pharmacology and Toxicology

This application refers extensively to the preclinical data submitted in support of the Foradil Aerolizer NDA (20-831) to support the use of formoterol in this drug product. Because formoterol is already approved, there are no outstanding preclinical issues on formoterol. The Foradil Certihaler drug product contains magnesium stearate as an excipient. Although magnesium stearate is generally recognized as safe (GRAS), this determination does not cover inhalation exposure. For that reason, Novartis conducted 1-month inhalation study in rat and dog, and a 6-month inhalation study in rat to support the use of magnesium stearate by the inhalation route. The toxicology data were reviewed by Dr. Robison and he has concluded that the data were support to support approval of use of magnesium stearate as an excipient and I concur with that conclusion.

Clinical and Statistical

The core clinical program includes two dose ranging studies in adults and children, two 12-week efficacy and safety studies in subjects 13 years of age and older, and one 12-week efficacy and safety study in children ages 5-12 years. These studies are reviewed in detail in Dr. Nicklas's medical review and also summarized in Dr. Sullivan's clinical team leader memorandum.

The dose ranging studies were performed in adults 20 years of age and older (study 601) and in children 5-12 years of age (study 602). These two studies were conducted outside the United States. Both studies were repetitive dose, randomized, double-blind, crossover study in asthmatic patients. Doses tested were Foradil Certihaler 5, 10, 15, and 30 mcg twice daily, Foradil Aerolizer 12 mcg twice daily, and placebo. The primary efficacy endpoint was the FEV1 AUC 0-12 hours after one week of treatment. In the studies the 10 mcg dose was numerically superior to the 5 mcg dose, and the 10 mcg Foradil Certihaler dose was comparable to the 12 mcg Foradil Aerolizer dose. These studies in general support the selection of the Foradil Certihaler 10 mcg twice daily dose.

The two pivotal efficacy and safety studies were performed in adults and adolescents ages 13 years and older (studies 2302 and 3203). These studies were multi-center, randomized, double-blind, double dummy, parallel group, US studies comparing Foradil Certihaler 10 mcg twice daily, albuterol MDI, and placebo over 12-week treatment period in patients with asthma. The primary efficacy endpoint was change from baseline FEV1 AUC 0-12 hours after 12 weeks of treatment. Varity of secondary efficacy variables, and the typical safety variables were also measured. These two studies support the efficacy and safety of Fordail Certihaler in patients with asthma.

The pediatric efficacy study was performed in children ages 5-12 years (study 604). This study was multi-center, randomizd, double-blind, placebo-controlled, parallel group, US study compaign Foradil Certihaler 10 mcg twice daily and placebo over 12-week treatment period. The primary efficacy endpoint was change from baseline FEV1 AUC 0-12 hours after 12 weeks of treatment. Varity of secondary efficacy variables, and the typical safety variables were also measured. This study supports the efficacy and safety of Fordail Certihaler in patients with asthma. Of note, the difference between Foradil Certihaler and placebo was rather small and was not consistent at all treatment visits.

Based on the submitted clinical data the Clinical and Biometrics team has concluded that Novartis has submitted adequate data to support the efficacy and safety of Foradil Certihaler and I concur with that conclusion.

The Clinical and Biometrics team has concluded that Novartis's proposal to add a text in the label that [redacted] is not supported by the submitted data and I concur with that conclusion. Novartis will be asked to amend this section of the label. b(4)

Clinical Pharmacology and Biopharmaceutics

Four studies had pharmacokinetic data. These were the two dose-ranging studies (studies 601 and 602) and the two efficacy and safety studies (studies 2302 and 3203). The pharmacokinetic data are reviewed in detail in Kim's review. No major issues were identified and the Office of Clinical Pharmacology and Biopharmaceutics team has recommended approval and I concur with that recommendation.

Data Quality, Integrity, and Financial Disclosure

No DSI audit of clinical study sites was requested or conducted for this application. Formoterol is not a new molecular entity and a formulation of the drug is already marketed in the United States, and during the review process of this application no irregularities that would raise question on the data integrity were found. No ethical issues are present. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues are present. The applicant submitted an acceptable financial disclosure statement and statements of good clinical practice.

Pediatric Consideration
Novartis has submitted data down to the age of 5 years. Although asthma occurs in children below 5 years of age, the current formulation is not appropriate for very young children. Typical dry powder devices are not suitable for patients below 4 years of age.

Product Name
The proprietary name of Foradil is approved and used by Novartis for the currently approved product. The suffix of Certihaler appears appropriate. A nomenclature consult was obtained with the Office of Drug Safety and the product name was determined to be acceptable. There may be some confusion in the market place when the Aerolizer and the Certihaler are co-marketed. Novartis will be asked to address this issue.

Labeling
Novartis has submitted a product label that conforms to the general requirements of labeling. The labeling was not extensively reviewed because the application is not heading towards an approval action because of CMC deficiencies. Some labeling comments from various disciplines will be communicated to Novartis.

Recommendation and Action
The clinical studies submitted with this application are sufficient to support efficacy and safety of Foradil Certihaler for use in asthma patients. There are outstanding CMC issues and device performance issues that need to be addressed before this application can be approved. The latter will likely require actual patient use study. Therefore, the action on this application will be APPROVABLE.

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

/s/

Badrul Chowdhury
10/17/03 04:26:18 PM
MEDICAL OFFICER
Div Dir memo

DIVISION DIRECTOR'S MEMORANDUM

Date:	December 10, 2004
To:	NDA 21-592
From:	Eugene J. Sullivan, MD, FCCP Deputy Director Division of Pulmonary and Allergy Drug Products (HFD-570)
Through:	Badrul A. Chowdhury, MD PhD Director, Division of Pulmonary and Allergy Drug Products
Product:	Foradil Certihaler (formoterol fumarate inhalation powder)
Applicant:	Novartis

Administrative and Introduction

This is the second review cycle for NDA 21-592, which was initially submitted by Novartis on December 18, 2002, for Foradil Certihaler (formoterol fumarate inhalation powder) for the proposed indication of "long-term, twice daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older, [redacted]. On October 17, 2003, the Division took an Approvable action on the application. On June 24, 2004, the Applicant submitted a Complete Response to the October 17, 2003, action letter. b(4)

The October 17, 2003, action letter cited several CMC deficiencies that precluded approval. These included inadequate controls, testing methods, and specifications of various aspects of the drug product, including device and formulation components (lactose and magnesium stearate), as well as control of foreign particulate matter in the drug product. In addition, the letter stated that the Applicant must provide a summary of the efforts that have been taken to assure that the design improvements that had been implemented during the course of drug development have been successful in correcting the performance problems that had been identified with earlier versions of the drug product. The letter also included two comments that were not considered deficiencies that would preclude approval. These comments asked the Applicant to consider studies to establish a more extensive database in adolescent and elderly patients, and to provide plans for educational activities intended to minimize confusion that may arise in the marketplace as a result of Foradil Aerolizer and Foradil Certihaler being marketed concurrently. Finally, the letter included several labeling comments.

Chemistry, Manufacturing, and Controls

Comments 1-12 of the October 17, 2003, action letter referred to the various CMC deficiencies the precluded approval of the application. The Applicant's responses to these deficiencies have been reviewed by the CMC Reviewer, Dr. Craig Bertha, and found to be acceptable. One additional issue that has come to the attention of the

Division relates to the presence of lactose in the formulation. Patients who are allergic to milk proteins and who are extremely sensitive, might develop an allergic reaction to the trace amounts of milk protein that remain in the lactose after it is purified. Because the amount of these proteins in the formulation is quite low, it is expected that such an occurrence would be exceedingly low. These residual milk proteins are not considered to be a component of the formulation and therefore would not customarily be listed in the Description section of a product label. However, given the potential clinical importance, albeit rare, the Division will ask the Applicant to refer to the presence of these proteins in the Description section of the label.

Device durability

During the clinical trials that were performed to support approval of this product certain device performance issues arose. The most common issue was an increase in the inspiratory flow rate required to trigger an actuation ("actuation flow rate"). The second most common issue was failure of the dose counter. The devices used in these clinical trials were produced using [redacted] In the subsequent transition from [redacted] the Applicant instituted certain design modifications intended to address the problems identified with actuation flow rate and dose counter failures. However, in the original submission the Applicant had not provided data to demonstrate that these design modifications were sufficient to correct the problems. For this reason, the October 17, 2003, action letter instructed the Applicant to provide evidence to demonstrate that the design modifications successfully corrected the problems (Comment 1[a]). In order to address this issue, the Applicant has now submitted results of four studies. Two of these were "simulated patient use" studies (Studies 8521-19, and 8521-21), and two were patient use studies (Studies 2304, and 2306).

b(4)

Two "simulated patient use" studies: 8521-19 and 8521-21

Study 8521-19

In this study, 10 employees of SkyPharma or Novartis were assigned to carry a total of 60 devices (six devices per employee) throughout their daily personal routines. Each day (Monday through Friday), the employee brought the devices to the laboratory for twice daily *in vitro* activation, using a "dosing unit sampling apparatus" set at 60 L/min. An additional 15 devices were stored under ambient conditions in the laboratory and underwent twice daily actuation. Dose counter function was assessed with each actuation, and actuation flow rate (AFR) was measured with every tenth actuation. In addition, the device lockout feature was assessed. The Applicant reports that six devices were stolen from one of the employees. Data from these devices were included for the period prior to the theft.

The dose counter on this product is designed to advance each time the protective cap is closed following a dose. In this study, four of the 75 devices exhibited a dose counter malfunction: failure to advance when the protective cap was closed in two devices, and advancing twice (double-counting) when the protective cap was closed in two devices. The Applicant states that, when actuated at low flow rates (30 L/min) the airflow may be insufficient to trigger the counter mechanism. The Applicant expects this would be a

very rare occurrence. In addition, the Applicant has determined that the counter may not advance if the device is manipulated in two distinct ways: the cap is forcefully closed, then forcefully opened, or the cap is closed only half way, then re-opened. In both cases, the counter will not advance when the cap is subsequently closed. However, dosing would not occur. The Applicant was unable to identify the mechanism by which double-counting occurred, and attributed this to "operator failure (i.e. 'wrong observation'). **Reviewer's Comment: This study identified dose counter malfunction in four of 75 devices. These apparently related to the way the device was handled by the operator. Because the operators were trained laboratory technicians, it might be expected that dose counter malfunction would be more common in the clinical setting.**

The Applicant states that there was a mean increase in the actuation flow rate of approximately 5 L/min. The Applicant did not provide summary data regarding the number of devices that required actuation flow rates in excess of 40 L/min. The Applicant did state that the range of AFRs was generally 30-45 L/min, with one device requiring and AFR of 50 L/min.

No failures of the device lockout feature were noted.

Study 8521-21

This study was performed as a follow-up to Study 8521-19. In this study, a laboratory shaker device was used in order to simulate patient use, rather than the "simulated patient" approach utilized in Study 8521-19. A total of 210 devices were examined. Two hundred of the devices were subjected to mechanical agitation using a laboratory shaker, in order to simulate patient use. The devices were subjected to one hour of agitation between actuations, and were actuated up to six times daily. The remaining 10 devices were not agitated. In this study, the dose counter failed to function in 5 out of 12,810 actuations. In these cases, the counter did not advance "for one or two attempts," but subsequently functioned correctly. Subsequent examination of the five devices did not reveal a mechanical malfunction, and the Applicant attributed these events to "mis-manipulation by the operators" such that the protective cap was not correctly opened to the full 90 degree angle. **Reviewer's Comment: Although rare, the fact that trained technicians failed to manipulate the device correctly raises the possibility that patients may have difficulty using the device appropriately.** Consistent with the findings of the previous study, there was an increase in the mean AFR of approximately 5 L/min over the course of the life of the device.

Two patient use studies: 2304 and 2306

Study 2304: "A 3-week, open label, uncontrolled, multicenter study evaluating the functionality of the Foradil Certihaler device in patients with asthma."

This study was conducted at 11 centers in the US. The first patient was enrolled on January 7, 2004, and the last patient completed the study on February 5, 2004. This was an open label study in asthmatic patients aged ≥5 years. The study entailed two clinic visits. At visit 1, after confirmation of eligibility criteria, patients began a 3-week treatment period of Foradil Certihaler 10mcg BID (Novartis batch # X113 0702).

Notable inclusion criteria were the diagnosis of asthma requiring treatment for the past 2 months, baseline FEV_1 ≥40% predicted, documented history of FEV_1 reversibility, and documented ability to use and activate a training device (empty Certihaler device) and ability to understand the directions for device usage, evaluating device function, and completing the patient diary. The first dose of study medication was taken under observation at the study center after training in the use of the device. Diary information and device collection occurred at the end of the study (Visit 2). All collected devices had at least 14 remaining doses. Following device collection, technical assessment of the devices was performed by SkyePharma. This included assessment of dose counter function, actuation flow rate, and lock-out mechanism. The patient diaries included the following questions:

— Did the dose counter decrease by one?
— Did you get the dose?
— Did you notice any difference in triggering the device?
— Any comments?

A total of 157 patients aged 8-68 years (mean 31.9) were enrolled. Of these, 43% were male, and 88% were Caucasian. The mean baseline FEV_1 was 2.72 liters (range 1.24–5.78), and the mean baseline peak inspiratory flow was 245 L/min (range 34-900). Seven patients discontinued prior to completion of the study. The reasons for discontinuation were device failure/malfunction in 5 patients, and adverse event in 2 patients (one with moderate tremor and one with moderate asthma exacerbation). The five patients who discontinued due to device failure/malfunction can be summarized as follows, based on the subsequent technical device assessments:

— subsequent technical device assessment revealed device failure in 3 devices. The 3 device failures were all related to the same phenomenon: misalignment of the dosing bar and the sliding shelter of the device, leading to blockage of the dosing mechanism. All three of these patients had reported being unable to trigger the device. The dose counter read 53, 51, and 49 at the time. **Reviewer Comment: After discovering this phenomenon, the Applicant further modified the design of the device in an attempt to prevent this malfunction. The modification includes the addition of two small studs to the guiding rail to prevent misalignment. Dr. Craig Bertha, the CMC reviewer believes that this design modification should be expected to prevent this misalignment malfunction in the future. In addition, in order to test the success of this design modification, the Applicant performed a second clinical patient use study (#2306) using the re-designed devices.**

— subsequent technical device assessment revealed normally functioning device in 2 devices. Although no device malfunction was found, these patients are worth further discussion because they apparently had difficulty triggering the device. The first patient was a 47 year-old man (baseline FEV_1 2.38 L, baseline PIF 128 L/min) who first noted that, although he believed he received a dose, the dose counter did not decrease from 51 to 50. He then tried to take approximately 10 inhalations, but was unable to trigger a dose or get the dose counter to advance. At the clinical site, the device appeared to function normally after two attempts.

The patient was then discontinued from the study. The second patient was a 66 year-old female (baseline FEV_1 1.39 L, baseline PIF 214 L/min) who noted difficulty triggering the device on Day 12 and was no longer able to trigger the device on Day 17.

The diary data revealed reported problems with the device as follows:

— "Did the dose counter decrease by one?": 22 (14%) answered NO.

— "Did you get the dose?": 21 (13.4%) answered NO.

— "Did you notice any difference in triggering the device?" 81 (51.6%) answered YES.

— Any comments? 107 (68.2%) had comments.

Reviewer's Comment: Failure of the device to deliver the dose and failure of the dose counter to advance were reported fairly frequently (13.4% and 14%, respectively).

Technical device assessment was performed on 157 returned devices. Among these:

— 3 frank device failures were identified. These involved misalignment of the dosing bar, and are discussed above.

— 1 device was damaged by laboratory personnel during the assessment. The damage occurred when the device was accidentally knocked off the lab bench to the floor. After this incident, the device continued to actuate, but the counter no longer advanced. The Applicant states that the impact resulted in the counter being tilted out of position such that it was no longer aligned with the driving spring of the dosing bar and was no longer functional. **Reviewer's Comment: This is a potentially important event because it demonstrates that with a relatively benign insult, the dose counter may be damaged.**

— 153 were reported to be "without problems" during the technical assessment. Although these were reported as being "without problems," it should be noted that several devices required actuation flow rates higher than the release requirement for the device. The release requirement is that — must actuate at — L/min. A total of 9 devices did not actuate at ≤40 L/min but did actuate at 45 L/min, and 1 device did not actuate at ≤45 L/min but did actuate at 50 L/min.

b(4)

Study 2306: "A 3-week, open label, uncontrolled, multicenter study evaluating the functionality of the Foradil Certihaler device in patients with asthma."

This study was performed in order to investigate whether the design modification instituted following Study 2304 would successfully prevent the specific malfunction that was observed in that study. The devices studied were from Novartis production batch number X007 0104. The study design was identical to that of Study 2304, with a few minor revisions. Specifically, the diary question that previously read "Did you notice any difference in triggering the device?" was revised to read "Did you have to breathe any harder in order to make the device work? If yes, please comment." This change was made because of perceived ambiguity of the previous wording. In addition, in Study 2306 patients were asked to write in the diary comment field when and how they cleaned the

device. Finally, some of the drawings of the patient instruction leaflet were improved, and some explanatory text was added to clarify the correct use of the device.

A total of 154 patients aged 5-79 years (mean 31.7) were enrolled. Of these, 49% were male, and 87% were Caucasian. The mean baseline FEV_1 was 2.81 liters (range 1.11 – 4.82), and the mean baseline peak inspiratory flow was 273 L/min (range 60-611). Nine patients discontinued prior to completion of the study. The reasons for discontinuation were device problems in 8 patients, adverse events in 1 patient (headache), and "other" in 1 patient (device destroyed by a dog). The eight patients who discontinued due to device problems can be summarized as follows:

- Device failure/malfunction with normal use in 6 patients. Subsequent technical assessment did not reveal a device malfunction in any of these cases.
    - 75 year-old male (baseline FEV_1 2.56 L, baseline PIF 342 L/min) reported on Day 15 that the device would not work at all. Upon inhalation, the holes in the device did not move or open, and the dose counter did not advance. At the discontinuation visit on Day 16, the study coordinator reported witnessing that the device holes did open, but that the dose counter did not advance.
    - 21 year-old male (baseline FEV_1 3.26 L, baseline PIF 428 L/min) reported on a number of occasions that the dose counter did not advance although he did receive the dose. This began on the evening of Day 1. The patient discontinued the study on Day 9.
    - 18 year-old female (baseline FEV_1 2.96, baseline PIF 290 L/min) began to notice that she had to breathe in harder to actuate the device on Day 9. On Day 14 and subsequently, she could not actuate the device despite repeated attempts, and the dose counter did not advance.
    - 41 year-old male (baseline FEV_1 3.28, baseline PIF 533 L/min) began to notice that he could not get a dose, and the dose counter was not advancing despite multiple attempts.
    - 36 year-old male (baseline FEV_1 3.6 L, baseline PIF 461 L/min) began noticing difficulty actuating the device and the dose counter was not advancing on Day 5. This continued until Day 9 (although during that period he was able to receive at least 2 doses), when he was seen at the study center and, despite demonstrating proper technique in using the device, was unable to trigger a dose, and was discontinued by the investigator.
    - 14 year-old female (Center 0501, Subject 00001): "could not get the proper doses from the device." The device would not dispense medication and the counter did not change for 4 days. The device did not work in the clinic when she came in to discontinue. **Reviewer's Comment: This is clearly a patient-reported device malfunction. However, in the Applicant's summary of the results of this study did not include this as an "apparent malfunction," but instead described this case only as "the subject experienced problems using the device and therefore missed multiple doses of study medication."** Technical device

assessment was performed (Vol. 8, page 70). The dose counter read "34" upon receipt. The assessment did not reveal any malfunction.

Reviewer's Comment: There seems to be a discrepancy between the clinical experience of these six patients and the findings of the in vitro testing. The devices, which apparently fail in the patients' hands are not found to be malfunctioning during in vitro testing.

— Device failure as a result of misuse: 1 patient
  - A 79 year-old female had difficulty opening the cap, and damaged it while attempting to open it with a screwdriver. Although she had been trained at the start of the study, the subject forgot that the device must be in the proper orientation in order to open. The investigator was able to open the device in the clinic, when in the proper orientation. The patient suggested that since the device is so different from currently marketed devices, it might be helpful to have written instructions on the device to hold level in order to open. This device did not undergo subsequent technical assessment.

— Device destroyed by a dog: 1 patient. This device did not undergo subsequent technical assessment.

The diary data revealed reported problems with the device as follows:

— "Did the dose counter decrease by one?": 28 (18.2%) answered NO.

— "Did you get the dose?": 16 (10.4%) answered NO.

— "Did you have to breathe in any harder to make the device work?" 63 (40.9%) answered YES.

Reviewer's Comment: Failure of the device to deliver the dose and failure of the dose counter to advance were reported fairly frequently (18.2% and 10.4%, respectively). In addition, although subsequent technical assessment revealed a relatively minor increase in actuation flow rate, a significant number of patients reported noticing that they had to breathe in harder to actuate the device.

A total of 154 devices were returned for assessment. Two of these were severely damaged and could not be completely assessed (one had been destroyed by a dog, and could not be opened, and one had been destroyed by the patient who had attempted to open the device with a tool). Thus, a total of 152 devices underwent technical assessment. Of these, 151 devices were reported to be "without technical problems" during the technical assessment. One device was found to have a malfunction. On three consecutive attempts, the malfunctioning device delivered a dose, but the dose counter did not advance. Based on the weight of the powder in the reservoir, the Applicant estimates that a total of about 25 shots had been delivered without counting (including patient use and *in vitro* testing). By drilling a hole in the device and inserting an endoscope, the Applicant was able to observe that the [redacted] The Applicant hypothesizes

b(4)

that some type of impact of compressive pressure had deformed the body of the device, bringing the counting mechanism out of alignment. It should be noted that, although the majority of devices were reported as being "without problems," several devices required actuation flow rates higher than the release requirement for the device. The release requirement is that [redacted] must actuate at [redacted] L/min. A total of 12 devices did not actuate at ≤40 L/min but did actuate at 45 L/min. b(4)

Labeling Issues

Comments 15-23 of the October 17, 2003, action letter were the Division's comments on the proposed labeling. The Medical Reviewer, Dr. Nicklas, has reviewed the Applicant's response to these labeling comments. In general, the Applicant has agreed to make the suggested changes. Although the Division had instructed the Applicant to remove language referring to [redacted] the Applicant continues to propose the inclusion of such language. It is the Division's opinion that the data do not adequately support a claim of [redacted] b(4)

Additional Comments in the October 17, 2003, Action Letter

In addition to the deficiencies and labeling comments, the October 17, 2003, action letter contained two recommendations (Items 13 and 14). First, the Division recommended that the Applicant develop a more extensive database in adolescent and elderly patients. Second, the Division asked the Applicant to provide its plans for educational activities intended to minimize confusion that may arise in the marketplace as a result of Foradil Aerolizer and Foradil Certihaler being co-marketed. In the current submission, the Applicant has submitted protocol summaries for clinical studies in adolescent patients and in COPD patients, a significant portion of whom are expected to be elderly. In addition, the Applicant has proposed educational materials related to the differentiation of the two products. These materials will be reviewed by the Division of Medication Errors and Technical Support.

Recommendation and Discussion

The overall recommendation is for an Approvable action. The CMC issues that previously precluded approval have been adequately addressed. However, data from the two patient use studies that were performed to address the issues surrounding device durability have raised important questions regarding the ability of patients to use the device. These data indicate that a substantial number of patients are not able to operate this device successfully. This is a concerning observation, particularly because participation in these studies required that patients demonstrate their ability to understand and demonstrate the correct use of the device after careful instruction. In fact, the second patient use study (2306) utilized instructions to patients were amended in order to improve their clarity. Despite this, the problems persisted in the second study. It is likely that difficulties using the device such as those observed in the patient use studies would be more common in an unselected patient population. The fact that most of the devices that patients reported to be problematic were found to function normally in *in vitro*

testing likely indicates that the devices themselves are not malfunctioning. Rather, it would appear that the failure lies in the ability of patients to understand the directions for use, and implement them effectively. The Applicant will need to develop improved mechanisms to instruct patients in the use of the device, and demonstrate that these improved mechanisms are effective.

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

/s/

Eugene Sullivan
12/10/04 11:24:59 AM
MEDICAL OFFICER

Badrul Chowdhury
12/14/04 12:11:22 PM
MEDICAL OFFICER
I concur

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 21-592	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: Foradil Certihaler Established Name: formoterol fumarate Dosage Form: 10 mcg, inhalation powder		Applicant: Novartis Pharmaceuticals Corporation	
RPM: Akilah Green		Division: Pulmonary and Allergy Products	Phone # 301-796-1219

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 20-831 Foradil Aerolizer (formoterol fumarate inhalation powder) Provide a brief explanation of how this product is different from the listed drug. This application provides for a change in device. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☒ Confirmed ☐ Corrected Date: November 1, 2006

❖ User Fee Goal Date ❖ Action Goal Date (if different)	December 15, 2006
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None AE: October 17, 2003, December 14, 2004, and April 11, 2006,
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☐ Requested in AP letter ☐ Received and reviewed N/A

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 5

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

APPEARS THIS WAY
ON ORIGINAL

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☐ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	October 15, 2003, December 14, 2004
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	November 17, 2006
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	December 11, 2006
• Original applicant-proposed labeling	December 17, 2002
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	November 17, 2006
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	December 11, 2006
• Original applicant-proposed labeling	June 15, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	December 12, 2006
• Most recent applicant-proposed labeling	December 13, 2006

❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS May 7, 2003, December 1, 2004, February 3, 2005, January 31, September 20, 2006 ☒ DSRCS January 30, and August 2, 2006 ☒ DDMAC October 17, 2006 ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	November 1, and 20, 2006, and December 11, and 132006,
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	January 6 and 30, February 28, and May 7, 2003, August 24, October 5, and November 10, and 17, 2004, March 7 and 9, April 22, May 17, and November 17, 2005, April 24, (2) May 9, July 21, August 18, November 17, December 5, and 11, 2006
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg April 25, and May 10, 2002
• EOP2 meeting *(indicate date)*	☐ No mtg January 29, 2001
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☐ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	April 28, 2003, Augut 11, November 16, and December 7,

	2004, March 9, July 7, and November 29, 2006
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☐ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	August 11, 2004
• ☐ Review & FONSI *(indicate date of review)*	
• ☒ Review & Environmental Impact Statement *(indicate date of each review)*	August 11, 2004
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: December 8, 2003, January 13, 2004, and November 22, 2006 ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☒ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	September 29, 2003
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☒ None requested

APPEARS THIS WAY
ON ORIGINAL

Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	October 15, and 16, 2003, April 10, November 15, and December 13, 2006
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☐ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☐ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☐ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies[11]	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None September 26, 2003
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None September 24, 2003

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.

(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.

(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).

(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.

(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).

(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.

(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: December 12, 2006

To: Ann Shea
Senior Associate Director, Regulatory Affairs

Fax: (973) 781-2565

Phone: (862) 778-4567

From: Akilah Green, RN, MS
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: NDA 21-592; Labeling comments

Thank you.

NDA 21-592
Foradil Certihaler

We have reviewed your carton and container labeling dated December 7, 2004, and we have the following comments:

1. According to the HOW SUPPLIED section of your proposed Package Insert, the target net content (fill weight) is approximately 560 mg of formoterol powder blend; however, according to the carton/container label, the fill weight is — ng. Correct this discrepancy. b(4)

2. Revise the font size utilized for the modifier "Certihaler" so that it is identical to the font size of the root name "Foradil." The current presentation highlights "Foradil" not Certihaler." Ensure that the font of the established name (formoterol fumarate inhalation powder) is at least 1/2 the size of the proprietary name. See 21 CFR 201.10(g)(2).

3. Remove the yellow graphic around the proprietary name as it obscures and crowds the proprietary name. The presence of the graphic increases the prominence of the proprietary name and decreases the relative prominence of the established name. See 21 CFR 201.15 (a)(6) and 21 CFR 201.10(g)(2).

If you have any questions, you may contact Ms. Akilah Green, Senior Regulatory Management Officer, at 301-796-1219.

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/s/

Akilah Green
12/12/2006 03:58:37 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: December 11, 2006

To: Ann Shea
Senior Associate Director, Regulatory Affairs

Fax: (973) 781-2565

Phone: (862) 778-4567

From: Akilah Green, RN, MS
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: NDA 21-592; labeling comment

Thank you.

NDA 21-592
Foradil Certihaler (formoterol fumarate) Inhalation Powder

We have reviewed your revised Package Insert dated December 7, 2006, and we have the following additional comment:

> In the CLINCAL TRIALS Section, the definition of the FEV1 adjustment made in Figures 1-3 is too complex. Change the FEV1 adjustment definition under the Figures to "Plotted means are least squares means adjusted for baseline".

If you have any questions, you may contact Ms. Akilah Green, Senior Regulatory Management Officer, at 301-796-1219.

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/s/

Akilah Green
12/11/2006 10:03:29 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: December 5, 2006

To: Ann Shea
Senior Associate Director, Regulatory Affairs

Fax: (973) 781-~~3966~~ 2565

Phone: (862) 778-4567

From: Akilah Green, RN, MS
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: NDA 21-592; Labeling comments

# of Pages: 3

Thank you.

NDA 21-592
Foradil Certihaler

We have reviewed your revised Package Insert and Medication Guide dated November 28, 2006, and we have the following additional comments:

1. In the CLINICAL PHARMACOLOGY SECTION - Metabolism subsection:

   a. Replace the sentence starting with " [redacted] ..." with the following sentence "In vitro studies showed that multiple isozymes catalyze the glucuronidation (UGT1A1, 1A8, 1A9, 2B7 and 2B15 were the most predominant isozymes) and O-demethylation (CYP2D6, 2C19, 2C9, and 2A6) of formoterol." b(4)

   b. Correct the misspelled word "relevant" in the first paragraph.

2. Your proposal to delete the phrase regarding [redacted] in the ADVERSE REACTIONS Section is acceptable. b(4)

3. In the CLINICAL TRIALS SECTION:

   a. Include figures from Studies 2302 and 2303 showing the adjusted mean FEV1 versus time for the first and last treatment day. Include an explanation of the adjustment in the legend.

   b. Update the legend of the pediatric figures to include an explanation of the adjustment.

4. In the Medication Guide:

   a. Include trademark information for Brovana and Symbicort, if necessary.

Submit the revised label incorporating all of the changes in by Friday, December 8, 2006, SPL format.

If you have any questions, you may contact Ms. Akilah Green, Senior Regulatory Management Officer, at 301-796-1219.

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/s/

Akilah Green
12/5/2006 02:28:37 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
OFFICE OF DRUG EVALUATION II

Memorandum of Facsimile Correspondence

Date: November 17, 2006

To: Eric Floyd, Ph.D
Drug Regulatory Affairs

Fax: (973) 781-3966

Phone: (862) 778-5657

From: Akilah Green, RN, MS
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: NDA 21-592; labeling comments

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

48 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Akilah Green
11/17/2006 04:37:14 PM
CSO

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: October 17, 2006

To: Anthony Durmowicz, MD, Medical Officer
Akilah Green, MS, RN, Regulatory Project Manager
Division of Pulmonary and Allergy Products

From: Michelle Safarik, PA-C, Regulatory Review Officer
Iris Masucci, PharmD, Labeling Reviewer
Division of Drug Marketing, Advertising, and Communications

Subject: NDA 21-592
DDMAC labeling comments for Foradil Certihaler (formoterol fumarate inhalation powder)

Per your consult requests dated August 29, 2006, and October 12, 2006, DDMAC has reviewed the proposed product labeling (PI), proposed Medication Guide and Instructions for Using Foradil Certihaler, and proposed carton and container labeling for Foradil Certihaler, and we offer the following comments.

PI

b(4)

3 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Michelle Safarik
10/17/2006 02:43:08 PM
DDMAC REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-592

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Attention: Ann Shea
Senior Associate Director
Drug Regulatory Affairs

Dear Ms. Shea:

We acknowledge receipt on June 16, 2006 of your June 15, 2006, resubmission to your new drug application for Foradil Certihaler (formoterol fumarate inhalation powder).

We consider this a complete, class 2 response to our April 11, 2006, action letter. Therefore, the user fee goal date is December 16, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for children 6 months - 4 years of age. Your request is currently under review. Once the application has been filed we will notify you whether we have waived or deferred the pediatric study requirement for this application.

If you have any questions, call Ms. Akilah Green, Senior Regulatory Management Officer, at (301) 796-1219.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Akilah Green
8/18/2006 03:09:21 PM
Signed for Sandy Barnes

MEMORANDUM

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

DATE: August 2, 2006

TO: Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Products

VIA: Akilah Green, Regulatory Project Manager
Division of Pulmonary and Allergy Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review #2 of Medication Guide for Foradil Certihaler (formoterol fumarate inhalation powder), NDA 21-592

Background and Summary

The sponsor submitted revised labeling (PI and MG) on June 15, 2006, Foradil Certihaler (formoterol fumarate inhalation powder), NDA 21-592 in response to an Approvable Action taken April 11, 2006. Also, refer to our Review of the Medication Guide and IFU dated January 30, 2006.

We have revised the submitted Medication Guide to mirror the Medication Guide text approved for Foradil Aerolizer on June 19, 2006, and have revised the *Instructions for Use* at the end of the MG to enhance patient comprehension.

We can provide a Word copy of the document and tracked changes of the revisions to the *Instructions for Use,* if requested by the review division.

13 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Jeanine Best
8/2/2006 01:03:36 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
8/2/2006 03:23:43 PM
DRUG SAFETY OFFICE REVIEWER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: July 21, 2006

To: Ann Shea Senior Associate Director, Drug Regulatory Affairs	From: Akilah Green Senior Regulatory Management Officer
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary and Allergy Products
Fax number: 973-781-3966	Fax number: 301-796-1219
Phone number: 862-778-4567	Phone number: 301-796-9718

Subject: NDA 21-592 Fax

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES X NO

NDA 21-592
Foradil Certihaler (formoterol fumarate) Inhalation Powder

Your submission to NDA 21-592 dated June 16, 2006, is currently under review and we have the following comments and requests for information:

We remind you of the agreements to complete the following below as listed in your October 4, 2004, amendment.

1

2.

b(4)

3.

c

4

5.

6. The following agreements pertain to the control of foreign particulates in the drug product components and subcomponents.

a.

b.

b(4)

c.

7. Provide the updated Mg stearate testing monograph including the revision tightening the specific surface area specification to — m^2/g. b(4)

8. Provide a methods validation package as outlined in comment 6j of the October 17, 2003, letter within 3 months following the approval of the application.

If you have any questions, you may contact, Ms. Akilah Green, Senior Regulatory Management Officer, at 301-796-1219.

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/s/

Akilah Green
7/21/2006 10:34:01 AM
CSO

NOVARTIS

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Ann Shea, Sr. Associate Director
Tel: 862-778-4567
Fax: 973-781-2565
Internet:ann.shea@novartis.com

June 15, 2006

Badrul Chowdhury, MD, PhD
Division Director
Food and Drug Administration
Division of Pulmonary and Allergy
Drug Products
Office of Drug Evaluation II
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 21-592

FORADIL® CERTIHALER®
(formoterol fumarate inhalation powder)

Complete Response to Approvable Letter dated April 11, 2006

Dear Dr. Chowdhury:

Reference is made to NDA 21-592 for Foradil® Certihaler® (formoterol fumarate inhalation powder) for long-term, twice-daily administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older, and the Approvable Letter dated April 11, 2006. Please find enclosed a Complete Response to the items outlined in the Approvable Letter.

Format and Content of the Complete Response

This complete response is provided electronically, and includes:

- Response document (Item 20)
- Proposed labeling (Item 2)
- CMC technical report (Item 4)
- Safety update (Item 9)
- Case Report Forms - Study F2402 (Item 12)

This submission is being provided in accordance with the guidance for industry titled, *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (April 2005). The relevant technical details of the electronic portions of this submission are as follows:

- **Submission size:** approximately 35 MB
- **Electronic media:** one compact disc
- **Virus scan:** Network Associates Incorporated VirusScan© version 7.1.0 (formerly known as the McAfee VirusScan). The submission is virus free.

Resubmission classification

In accordance with the Guidance for Industry: Classifying Resubmissions in Response to Action Letters, Novartis considers this Complete Response to be a Class 1 Resubmission, as it includes draft labeling, a safety update, and a CMC technical report demonstrating via *in vitro* testing that the modifications made to the device prohibit accidental mishandling, thereby preventing potential overdose.

If you have any questions concerning this submission, please contact me at 862-778-4567.

Sincerely,

Ann Shea
Sr. Associate Director
Drug Regulatory Affairs

Attachments: 1 CD

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: May 9, 2006

To: Ann Shea Senior Associate Director, Drug Regulatory Affairs	**From:** Akilah Green, MS, RN Senior Regulatory Management Officer
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary and Allergy Products
Fax number: 973-781-2565	**Fax number:** 301-796-1219
Phone number: 862-778-4567	**Phone number:** 301-796-9718

Subject: NDA 21-592 Response to questions in meeting request

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES X NO

NDA 21-592
Foradil Certihaler

Attached are the FDA responses to the questions (in bold italics) in your April 13, 2006, meeting package regarding Foradil Certihaler (formoterol fumarate) Inhalation Powder. We will be prepared to clarify any questions you have regarding our responses at the May 15, 2006, teleconference. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request.

Please let me know as soon as possible if you would like to cancel the teleconference.

Question 1:
On March 29, 2006, Novartis submitted a proposed plan to NDA 21-592 for modifying and testing the Certihaler inhaler in order to prevent potential overdose. Does the Agency agree with the proposed plan?

Refer to the facsimile correspondence dated April 24, 2006, regarding the comment and recommendation on your proposed plan. We do not have any further comments.

Question 2:
Novartis submitted proposed draft labeling to NDA 21-592 on March 30, 2006, which included a Boxed Warning. A proposed Medication Guide was provided to the Agency by email on April 10, 2006, followed by submission to the NDA on April 12, 2006. Novartis believes that the Agency's concerns, including the addition of a Boxed Warning and Medication Guide, have been addressed. Novartis would appreciate receiving feedback on the labeling submitted to date.

We are currently discussing with you the labeling for your currently marketed Foradil Aerolizer (formoterol fumarate) Inhalation Powder. Foradil Certihaler contains the same active ingredient, formoterol fumarate, as Foradil Aerolizer. In order to maintain consistency across labeling we intend to work with you to finalize labeling for Foradil Aerolizer and then apply the appropriate sections, including the additional warnings, to the label for Foradil Certihaler .

Question 3:
The safety update will include safety information for Foradil Certihaler which has become available subsequent to the safety update submitted in October 2005. Summary tables and listings for AEs, discontinuations due to AEs, and SAEs will be provided for study F2402 in COPD patients (the only Foradil Certihaler study with an ongoing clinical phase during this period). Narratives for SAEs from this study, which were not previously submitted with the October 2005 update, will also be provided. Additionally, narratives will be provided for SAEs from the post-marketing experience in Germany and Switzerland (where Foradil Certihaler has been marketed) for patients

identified as taking Foradil Certihaler or on unspecified formulation of Foradil. The format will be similar to that of the October 2005 safety update, and data is not planned to be integrated with previously submitted results from completed studies. Does the Agency agree?

We agree, your proposal is acceptable.

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/s/

Akilah Green
5/9/2006 03:12:51 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: April 24, 2006

To: Ann Shea Senior Associate Director, Drug Regulatory Affairs	**From:** Akilah Green, MS, RN Senior Regulatory Management Officer
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary and Allergy Drug Products
Fax number: 973-781-2565	**Fax number:** 301-796-1219
Phone number: 862-778-4567	**Phone number:** 301-796-9718

Subject: NDA 21-592 Re: March 29, 2006, submission

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES X NO

NDA 21-592
Foradil Certihaler

Your submission dated March 29, 2006, is currently under review and we have the following comment and recommendation:

> Perform drop test studies analogous to those that were originally reported in attachment 8 of 3.2.P.2 of the original application using the drug product with variant devices prepared with filled funnels from a recent commercial batch. We recommend that you repeat the same studies with the current commercial product to provide a more direct comparison of the data based predominantly on the device variations alone.

If you have any questions, you may contact Ms. Akilah Green, Senior Regulatory Management Officer, at 301-796-1219.

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/s/

Akilah Green
4/24/2006 10:22:07 AM
CSO

Akilah Green
4/24/2006 10:25:07 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-592

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Attention: Ann Shea
Associate Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sepracor Foradil Certihaler (formoterol fumarate) Inhalation Powder.

We also refer to your April 13, 2006, correspondence, received April 17, 2006, requesting a meeting to discuss the format of your safety update, and items 1, and 2 of the approval letter dated April 11, 2006.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: May 15, 2006
Time: 9:00-10:00 AM
Phone Arrangements: CALL-IN NUMBER AND PASSCODE TBD by Novartis.

CDER Participants: Badrul A. Chowdhury, M.D., Ph.D., Division Director,
Anthony Durmowicz, M.D., Clinical Reviewer
Blair Fraser, Ph.D., Division of Pre-Marketing Assessment I, Branch II, Branch Chief
Prasad Peri Ph.D., Division of Pre-Marketing Assessment I, Branch II, Pharmaceutical Assessment Lead
Craig Bertha, Ph.D., Division of Pre-Marketing Assessment I, Branch II, Chemistry, Manufacturing, and Controls Reviewer
Akilah Green, Regulatory Project Manager

If you have any questions, call Akilah Green, Regulatory Project Manager, at (301) 796-1219.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Akilah Green
4/24/2006 11:36:33 AM
Signed for Sandy Barnes

MEMORANDUM OF TELECON

DATE: March 6, 2006

APPLICATION NUMBER: NDA 21-592/Foradil Certihaler

BETWEEN:

Name: Eric Floyd, Ph.D., Drug Regulatory Affairs, US
Ann Shea, Drug Regulatory Affairs, US
Christopher Morrison, Ph.D., Drug Regulatory Affairs, Basel
Jill Horowitz, Ph.D., Project Management, US
Simon Hedgecock, Clinical Research Manager, Clinical Development, UK
Barbara Haeberlin, Ph.D., Technical Research and Development, Basel
Oliver Meier, Country Manager, Global Pharma QA, GQO, Basel
Volker Schaefer, Head of QA, Germany
Heinz Weidenthaler, M.D., Medical Expert, Clinical Safety & Epidemiology, Germany
Beda Fischer, Global Head, QA, Technical Research and Development, Basel
Mathias Hukkelhoven, Ph.D., Senior V.P., Global Head, Drug Regulatory Affairs

Phone: 1-866-866-5114

Representing: Novartis Pharmaceuticals Corporation

AND

Name: Eugene Sullivan, M.D., Deputy Director
Sally Seymour, M.D., Clinical Reviewer
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SUBJECT: Germany adverse event reports

BACKGROUND: This teleconference is in response to the post-marketing reports of overdosage in patients using Foradil Certihaler in Germany as noted in the submissions dated February 2, and March 1, 2006.

DISCUSSION: The Division began the teleconference by pointing out that we are concerned about the post-marketing reports from Germany regarding the accidental overdose of Foradil Certihaler. We consider this to be very a serious issue. Based on the description of the events in Germany, it is very difficult to ensure that device failure leading to accidental overdosing will not occur in the United States. Therefore, we are questioning whether we should allow Foradil Certihaler to be marketed in the United States. After reviewing the documentation submitted by Novartis, it was noted that mechanical issues likely caused the problems, i.e., incorrect opening and/or closing of the cap potentially leads to interference of internal components of the device leading to a gap between the reservoir and dosing plate, resulting in potential overdosing upon patient inhalation. In light of this, the Division questioned whether Novartis has plans to fix the device to prevent this from occurring again.

Novartis stated that they have not made plans to make any additional modifications to the device. Novartis noted that there are differences between the labeling in Germany and the labeling in the United States. As a result, they indicated that they plan to add two additional steps to the label regarding how to open and close the device. Novartis feels they can address the problems with the device through the label. In study 2309, the number of patients mishandling the device decreased due to the new labeling in the U.S.

The Division noted that this type of overdose was not observed during clinical development and the problem will not be addressed by improved labeling instructions. From the Division's perspective, it is clear that once the device hits the market there may be additional occurrences. Therefore, we have to assume that what happened in Germany will occur in the United States. This is a serious failure of the device, which can be potentially fatal, particularly in patients with underlying coronary disease.

This application is still under review, and we are not certain labeling changes are enough. If Novartis has additional information, the Division would like to see it. Novartis questioned whether the Division would be willing to discuss their detailed risk management plan to address the Agency's concerns in the next two weeks. The Division noted that the timeline for this review cycle will not allow for substantive review of a newly submitted risk management plan and the data that would be submitted to support the plan. The Division further added that preventing patients from experiencing an overdose is the goal.

The Division pointed out that the updated labeling to address the risks of long-acting beta-agonists for Foradil Aerolizer and Foradil Certihaler are still outstanding. The content of the Division's November 17, 2005, supplement request letter included a black box, etc.; however, Novartis did not adequately address this in their labeling supplement for Foradil Aerolizer. In addition, Novartis has not submitted relevant updated labeling for Foradil Certihaler, which makes it difficult to move forward on the application.

POST MEETING NOTE:
Novartis indicated that they will submit updated labeling to include the black box warning etc. on March 28, 2006.

Akilah Green, RN
Senior Regulatory Management Officer

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/s/

Akilah Green
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