



NDA 20-831

Food and Drug Administration  
Rockville MD 20857

JAN 21 1999

Novartis Pharmaceuticals Corporation  
59 Route 10  
East Hanover, New Jersey 07936

Attention: Kathleen Creedon, Ph.D.  
Assistant Director  
Drug Regulatory Affairs

Dear Dr. Creedon:

Please refer to your pending new drug application dated June 24, 1997, received June 26, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Foradil (formoterol fumarate powder for inhalation).

We also refer to your submissions dated June 1, October 19 and November 10, 1998, and our meeting dated December 14, 1998.

We have completed our review of the chemistry, manufacturing and controls (CMC) section of your submission and have identified the following deficiencies.

For additional details on each comment, refer to items in the previous letters dated March 25 and June 26, 1998, as indicated in each comment.

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These comments are being provided to you as continuation of our meeting dated December 14, 1998, to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application.

If you have any questions, contact Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

/S/

Guirag Poochikian, Ph.D.  
Chemistry Team Leader for  
Division of Pulmonary Drug Products (HFD-570)  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

JUN 26 1998

Novartis Pharmaceuticals Corporation  
59 Route 10  
East Hanover, New Jersey 07936

Attention: Kathleen Creedon, Ph.D.  
Assistant Director  
Drug Regulatory Affairs

Dear Dr. Creedon:

Please refer to your pending new drug application dated June 24, 1997, received June 26, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Foradil (formoterol fumarate powder for inhalation).

We acknowledge receipt of your submissions dated August 7, 11, 15, 20, 28, and 29, September 19, October 16, 24, and 27, 1997, and January 30, February 5, 19, and 24, March 17, 20, and 25, and May 13 and 14, 1998. The user fee goal date for this application is June 26, 1998.

We also acknowledge receipt of your submission dated June 1, 1998. Please be advised that this submission has been accepted as correspondence and has not been reviewed prior to issuance of this letter.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, a satisfactory inspection of \_\_\_\_\_ will be required. In addition, it will be necessary for you to address the following deficiencies.

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B. The following comments and deficiencies have not been provided to you previously and must be adequately addressed prior to approval.

1. The indication prevention and maintenance treatment of asthma and bronchoconstriction in children 6 to 12 years of age is not supported by the available efficacy and safety data. Study DP/PD2, as presented, does not allow comparison of the primary endpoint over the entire treatment period and secondary endpoints are not supportive of an efficacy claim. An additional placebo-controlled study in this age group that adequately characterizes the optimal dose for this population is required for approval of the pediatric indication. In addition, the number of patients at the lower end of the proposed 6- to 12-year age range in the safety database is inadequate to support a pediatric claim. A reasonable number of children aged 6 and 7 years should be evaluated for safety, including characterization and quantification of variables such as vital signs, adverse events, clinical laboratory results, and ECGs to support approval. We encourage you to consult with the Division of Pulmonary Drug Products regarding the design and duration of the additional study(ies) necessary to support the proposed pediatric indication before it(they) is(are) initiated.
2. The indication protection against exercise-induced bronchoconstriction (EIB) for children \_\_\_\_\_ years of age is not supported by available data. The youngest patient studied in trial DP/PD3 was 10 years of age. Furthermore, the optimal dose for protection against EIB for the pediatric population has not been determined. An additional placebo-controlled trial that enrolls an appropriate number of pediatric patients over the entire age range proposed

for approval and that adequately characterizes the optimal dose for the management of EIB in this age group is required for approval (see item B.1 above). We encourage you to consult with the Division of Pulmonary Drug Products regarding the design of the study before it is initiated.

3. The Integrated Summary of Safety is incomplete in that it does not include analyses of, and case report forms (CRFs) for, all patients who prematurely discontinued participation in clinical trials due to adverse events and for patients who suffered serious adverse events in trials involving formoterol. Provide a complete accounting and index for previously submitted data as well as the CRFs that were not provided in this original NDA submission for all patients meeting the aforementioned criteria.
4. Provide an analysis of the demography of patient exposure by duration of treatment and by formoterol dose for the following age categories: 6 to 12 years, 12 to 18 years, and equal to or greater than 18 years. Clarify in which of the categories 12-year-old and 18-year-old patients are included.
5. The qualitative analysis of electrocardiographic (ECG) data from Studies #40 and #41 are inadequate without a complete description of the criteria and methodology used to categorize the data. Describe the ECG criteria for categorization, the methodology for assuring consistency and bias control in interpretation by readers, and the relative frequency of these interpretations within treatment groups. If these criteria and methodology were not applied to the original categorical analyses of the qualitative database, a reanalysis of the database is required.
6. The categorical analysis of electrocardiographic intervals (e.g., PR, QRS, QT/QTc) from the available ECG database is inadequate. Provide summary variables of central tendency (i.e., mean and standard deviations) as well as sensitivity analyses (e.g., change from baseline of 0-10%, 10-15%, 15-20%, 20-30%, etc.) to describe distributions and comparisons between treatment groups and formoterol doses. If not previously performed, ECGs should be read in a blinded fashion, QT should be corrected for rate using conventional methodologies (e.g., Bazett's formula), and QT/QTc analyses should include a presentation of mean change as well as mean maximum change from baseline, when available.
7. Provide original and English translations of approved product labels from countries in which formoterol is approved and/or marketed.
8. The incidence of some findings in the statistical analysis of the dietary carcinogenicity studies does not match that reported in the summary incidence tables. For example, in the mouse dietary study, the incidence of benign hepatomas reported in the incidence table (vol. 49, p. 176) differs from that

presented in the statistical analysis (vol. 49, p. 428), as illustrated in the following table.

**Incidence of Benign Hepatoma in the  
Incidence Table and Statistical Analysis**

Group	Volume 49	
	reference page 176	reference page 428
0	18/85	24/85
2	19/85	24/85
5	21/85	31/85
20	24/84	33/84
50	15/85	25/85

Clarify and explain these discrepancies.

9. Plasma exposure (AUC) data from preclinical studies play a critical role in the evaluation of the safety of formoterol fumarate. You have noted in your submission that there were difficulties with the method(s) used to evaluate plasma formoterol levels in animal studies. The values provided are much higher than would be expected given a drug of this type and class. In addition, we note that the C<sub>max</sub> identified in the mouse dietary carcinogenicity study is 6.3 nmol/L for a 50mg/kg/day dose, far below the number provided in the mouse drinking water study (C<sub>max</sub> = 1100 nmol/L and AUC = 4300 nmol/hr/L at a 60 mg/kg/day dose level) that was used for comparison to humans. The AUC values from the dietary study seem more realistic based on the administered dose and, thus, we are concerned that the claimed large-dose multiples between humans and animals are inaccurate. Specifically, we are concerned with reported exposure data (AUC, C<sub>max</sub>, etc.) associated with the carcinogenicity studies, reproductive and development studies, and the chronic toxicity studies.

Provide realistic exposure information for these studies, or provide an explanation of why such data are not attainable. We note that in humans levels as low as an AUC of 1.33 nmol/hr/L based on an inhaled dose of 120 µg, are measurable.

10. Report the estimated deposition factor used for the preclinical inhalation toxicology studies.
11. The following comments pertain to Study # — (US)1996/048. For your future reference, we remind you that assay accuracy and precision could be

demonstrated more accurately if quality control samples were more evenly distributed along the quantifiable range of the assay.

- a. Submit blank and representative \_\_\_\_\_ to demonstrate assay specificity.
  - b. Clarify whether the two lots of 12 and 24 µg capsules used in this trial were the to-be-marketed formulation/device with regard to composition, drug microcrystalline size distribution, method of manufacture, production size/scale, and site of manufacture.
  - c. Submit complete single-dose urinary excretion data.
  - d. The accounting of study dropouts is not clear from the report submitted. Provide an accounting of all subjects enrolled.
12. The following comments pertain to Study Protocol 054. For your future reference, we remind you that more meaningful results could have been obtained if both the parent and conjugated forms of formoterol were measured.
- a. Conduct a subset analysis, more fully investigating the effect of gender on formoterol disposition, e.g., clearance.
  - b. With regard to the plasma and urine assay performance validation, only summary data are reported. Submit data to fully demonstrate the linearity, accuracy, precision, and specificity of the method. Include complete standard curve data, independent quality control results, and representative \_\_\_\_\_. For further details on currently accepted assay validation, refer to Shah VP, et al., *Pharm Res* Vol 9, No. 4 (1992).
13. The draft package insert and carton and container labels should be modified to reflect the above comments and submitted. Further labeling comments are being reserved at this time pending resolution of the aforementioned deficiencies.
- C. Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.
1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in \_\_\_\_\_

your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus the time you submit your complete response to this letter will facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Provide details of any significant changes or findings.
4. Summarize worldwide experience on the safety of this drug.
5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

D. Although not required for approval, the following clinical comments are being provided to you in order to facilitate further development and evaluation of formoterol.

1. It is strongly recommended that the clinical significance of the effect of formoterol on blood glucose observed in the NDA studies be further evaluated by investigating the impact of formoterol on glucose control in a diabetic population.
2. Protection against exercise-induced bronchoconstriction has not been studied in the context of chronic formoterol administration in any age group. Given the findings suggesting tachyphylaxis to formoterol in the methacholine challenge trial DP/SP2, it is strongly recommended that the potential for the development of tachyphylaxis to the protective effects of formoterol in EIB after chronic dosing be studied.
3. Given the findings of the duration of action of formoterol versus placebo and albuterol over a 12-hour dosing interval and the improvement in pre-dosing baseline FEV<sub>1</sub> after chronic dosing of formoterol, it may be reasonable to explore the efficacy of formoterol when administered less frequently than every 12 hours.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or teleconference with the Division of Pulmonary Drug Products to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

U - JSI - 6/26/98

James Bilstad, M.D.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

cc:

- Original NDA 20-831
- HFD-570/Div. Files
- HFD-002/ORM
- HFD-92/DDM-DIAB
- HFD-570/P.Jani
- HFD-570/Anthracite/6-9-98/6-12-98
- HFD-570/Honig/6-10-98/6-12-98
- HFD-570/Zoetis/6-5-98/6-12-98
- HFD-570/Sheevers/6-5-98/6-12-98
- HFD-570/Guo/6-8-98/6-12-98
- HFD-570/Wilson/6-9-98/6-12-98
- HFD-570/Gillespie/6-8-98/6-12-98
- HFD-570/Uppoor/6-9-98/6-12-98
- HFD-570/Leak/6-5-98
- HFD-570/Poochikian/6-9-98/6-12-98
- HFD-570/Schumaker/6-5-98/6-12-98
- HFD-570/Jenkins/revised 6-12-98/6-12-98
- HFD-102/Bilstad
- HFD-102/Ripper/6-24-98
- HFD-101/L.Carter
- DISTRICT OFFICE
- HFD-40/DDMAC (with draft labeling)

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*for C. Schumaker 6/26/98*

*/S/ all noted  
 edits and su  
 edits per J  
 Substant on  
 approve with  
 date 6/26/98*

Drafted by: pj/June 5, 1998/

Initialed by:

Final:

APPROVABLE (AE)

**APPEARS THIS WAY  
ON ORIGINAL**