

**Clinical Team Leader Review**

**NDA:** 20,831  
**Product:** Foradil Aerolizer (formoterol fumarate inhalation powder)  
**Indications:** -maintenance treatment of asthma  
-prevention of exercise induced bronchospasm  
**Date:** 2/2/01  
**Reviewer:** Marianne Mann, Deputy Director, DPADP

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This is the secondary clinical review of NDA 20,831 for Foradil.

**Overview:**

Foradil is a new molecular entity, formoterol fumarate in an inhalation powder, which is a long-acting, selective beta<sub>2</sub> agonist, similar to Serevent. Like Serevent, Foradil has demonstrated efficacy for up to 12 hours. Foradil is packaged as a capsule and is intended for oral inhalation using an Aerolizer device, provided with the drug product. The product capsules are individually packaged in blister packs, and are removed just prior to use. The capsules are then placed in the Aerolizer capsule chamber and punctured, with the dry powder inhaled by the patient via the Aerolizer mouthpiece. Each capsule contains 12 mcg of formoterol fumarate. One \_\_\_\_\_ recommended for use every 12 hours, with total daily dosing not to exceed \_\_\_\_\_mcg (\_\_\_\_ capsules).

Foradil was originally submitted to the Division for NDA approval on June 26, 1997. Following review, the application was felt to be approvable, with the outstanding issues being primarily chemistry in nature. The sponsor has since responded to these deficiencies and submitted their complete response on August 18, 2000. The information in this complete response is primarily the necessary chemistry information, although there is a clinical safety update and labeling also provided. The complete response has adequately addressed all chemistry issues and the new updated safety information leads to no new safety concerns. However, a review of the pivotal clinical trials for asthma (trials 040 and 041 in patients 12 years of age and older and trial 049 in children age 5 through 12) raise concerns about the safety of the higher dose of Foradil of 24 mcg bid.

Clinical trials were performed to support two indications:

1. For long-term, twice daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting, beta<sub>2</sub> agonists.
2. For the acute prevention of exercise-induced bronchospasm (EIB) in patients 12 years of age and older, when administered on an occasional, as-needed basis.

## Clinical Overview

### Maintenance Treatment of Asthma

Previous submissions outlined two nearly identical U.S. trials (040 and 041) that supported the asthma indication in children age 12 and older and in adults. These trials enrolled over 1100 adult and adolescent asthmatic patients ages 12 through 75. Each trial evenly randomized patients to receive: placebo, albuterol 180 mcg qid, Foradil 12 mcg bid, or Foradil 24 mcg bid. The two 12-week trials demonstrated superiority of Foradil 12 and 24 mcg taken twice daily over placebo for the primary efficacy endpoint of the 12-hour post-treatment FEV<sub>1</sub> value. The trials also demonstrated superiority of Foradil 12 and 24 mcg twice daily over albuterol 180 mcg four times a day. The added benefit of Foradil 24 mcg over Foradil 12 mcg in these trials was marginal, but was replicated in two trials.

Adverse events in these trials were those typical of beta agonists, and included tremor, muscle cramps, insomnia, nervousness, and tachycardia. Tremor was more common in the Foradil 24 mcg arm in Trial 040 (10.4% with Foradil 24 versus 2.9% with Foradil 12). Tachycardia, muscle cramps, insomnia, and nervousness were all slightly more common in the high dose Foradil arm than the lower dose arm. Trial 041 also showed a greater frequency of muscle cramps, insomnia, nervousness, and tremor in the Foradil 24 mcg arm compared to the Foradil 12 mcg arm. Again, the most dramatic difference was with tremor, affecting 7.4% of Foradil 24 mcg patients versus 2.9% of Foradil 12 mcg patients.

In Trial 040, urticaria were reported in 1.5% of subjects in the low dose formoterol arm and in 3.0% of patients in the higher dose arm versus a background incidence of 0.7% in the placebo-treated subjects. Trial 041, while not describing urticaria as an adverse event, did describe a 26 year old male who had an episode of urticaria and anaphylaxis after two days of treatment with formoterol 24 mcg bid. Formoterol may clearly be immunogenic in nature, and may, in rare cases, provoke hypersensitivity responses. Labeling for Foradil adequately describes this potential in the Warnings section, stating that "Immediate hypersensitivity reactions may occur after administration of Foradil, as demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm." Careful postmarketing monitoring for such events is nonetheless recommended as the ongoing safety profile of Foradil is made clear.

Serious adverse events (SAEs) in the two pivotal asthma trials are summarized: Study 041 had a total of 13 patients experiencing SAEs:

Placebo:	2 of 141 patients (1.4%) had an asthma exacerbation 1 of 141 patients (0.7%) had an elective cholecystectomy
Albuterol 180 qid	1 of 138 patients (0.7%) had hemorrhagic pancreatitis 1 of 138 patients (0.7%) had elective urologic surgery

Foradil 12 bid 1 of 139 patients (0.7%) had an asthma exacerbation

Foradil 24 bid 1 of 136 patients (0.7%) had urticaria and anaphylaxis  
6 of 136 patients (4.4%) had exacerbations of asthma

The 6 Foradil 24 mcg patients who experienced exacerbations of asthma are described in more detail below:

- A 45 y/o female was hospitalized with exacerbation of previously diagnosed sarcoidosis after 3 weeks of treatment. She required corticosteroids during her hospitalization.
- A 19 y/o female was hospitalized for an asthma exacerbation after 10 days of treatment.
- A 66 y/o female had a severe asthma exacerbation leading to respiratory arrest, a cardiac arrest, and death after 19 days of treatment.
- A 49 y/o male had increasing respiratory symptoms and a respiratory arrest after 25 days of treatment (during a bronchodilator washout period).
- A 33 y/o female developed status asthmaticus after 13 days of treatment
- A 13 y/o female was hospitalized for status asthmaticus 2.5 months after treatment.

Study 040 had a total of 9 patients experiencing SAEs:

Placebo: 1 of 136 patients (0.7%) was hospitalized for dizziness/ataxia

Albuterol 180 qid 2 of 134 patients (1.5%) had an asthma exacerbation

Foradil 12 bid 1 of 136 patients (0.7%) had a mucinous adenocarcinoma

Foradil 24 bid 1 of 135 patients (0.7%) had a cellulitis of the leg  
4 of 135 patients (3.0%) had an asthma exacerbation

The 4 Foradil 24 mcg bid patients who experienced asthma exacerbations are described below:

- A 36 y/o female was hospitalized for an asthma exacerbation after 1 month of treatment
- A 24 y/o female was hospitalized for an asthma exacerbation, pneumonia, and sinusitis after 2 months of treatment
- A 23 y/o male was hospitalized with status asthmaticus requiring intubation and mechanical ventilation after 5 weeks of treatment
- A 36 y/o female was hospitalized for an asthma exacerbation after 2 months of treatment

**Conclusions:** Both controlled studies in adults and adolescents over age 12 show a signal of concern in that the highest dose of Foradil 24 mcg bid was associated a slightly higher incidence of serious asthma exacerbations when compared to all other treatment arms. Notably, these exacerbations were quite serious in that two patients receiving Foradil 24 mcg bid required mechanical ventilation, one suffered a respiratory arrest, and one suffered a cardio-respiratory arrest ending in death. Most of the patients were female. Foradil 24 mcg bid offers only marginally better clinical efficacy over Foradil 12 mcg bid, so this safety signal, while subtle, is nonetheless very concerning.

Efficacy in children age 5 through 12 was evaluated in a single phase 3 trial (Trial 049) comparing 12mcg Foradil bid, 24 mcg Foradil bid, and placebo in a total of 518 patients age 5 through 12. This trial was one year in duration, although efficacy assessments were performed after 3 months. The primary efficacy variable was FEV<sub>1</sub> AUC measured after 3 months of treatment, with both Foradil doses showing superiority over placebo. Foradil 24 mcg bid offered slightly better efficacy compared to Foradil 12 mcg bid.

Serious adverse events are summarized as follows:

- Placebo: 2 of 176 patients (1.1%) had pneumonia  
1 of 176 patients (0.6%) had injury
- Foradil 12: 8 of 171 patients (4.7%) had exacerbation of asthma  
1 of 171 patients (0.6%) had pneumonia
- Foradil 24: 11 of 171 patients (6.4%) had exacerbation of asthma  
1 of 171 patients (0.6%) had syncope

The 11 Foradil 24 mcg patients who experienced asthma exacerbations are described below:

- A 9 y/o female experienced an asthma exacerbation on study day 50.
- An 8 y/o male experienced an asthma exacerbation on study day 73.
- A 7 y/o female experienced an asthma exacerbation on study day 215.
- A 9 y/o male experienced an asthma exacerbation on study day 99.
- A 12 y/o female experienced an asthma exacerbation on study day 61.
- A 10 y/o male experienced an asthma exacerbation on study day 210.
- An 8 y/o male experienced an asthma exacerbation on study day 78.
- A 10 y/o female experienced an asthma exacerbation on study day 81.
- An 11 y/o male experienced an asthma exacerbation on study day 297.
- A 7 y/o male experienced an asthma exacerbation on study day 150.
- A 10 y/o female experienced an asthma exacerbation on study day 84.

**Conclusions:** The primary pediatric trial again shows a potential signal of concern that higher doses of Foradil 24 mcg bid were associated with a relatively

*high rate (6.4%) of asthma exacerbation. Even the Foradil 12 mcg bid dose in this study had a somewhat high rate (4.7%) of serious asthma exacerbation compared to placebo. It is somewhat comforting to note that in a separate 12-week pediatric trial (TrialDP/PD2), the rate of asthma exacerbations in a Foradil 12 mcg bid dosage arm was very similar to the rate in the active comparator arm who received salbutamol 400 mcg tid.*

### Clinical Overview

#### EIB

Two randomized trials supported the efficacy of single doses of Foradil 12 and 24 mcg in the prevention of EIB, in adults and in adolescents age 12 and up. The larger dose of Foradil 24 mcg provided somewhat greater protection against EIB than the Foradil 12 mcg dose at the 4-hour and 12-hour timepoints, but not for the initial 15-minute exercise challenge. Safety and tolerability data of Foradil in these clinical trials of limited exposure were not remarkable.

### Clinical Summary and Addendum

Based on the aforementioned concerns, a teleconference was held with the sponsor on 1/25/01. Novartis responded to the FDA concern that patients dosed with Foradil 24 mcg twice daily experienced more serious asthma exacerbations in the three pivotal controlled clinical trials: Study 040, 041 and 049. The sponsor did not disagree with the data from these trials, and had noted this potential signal of concern as well.

The sponsor responded by noting 3 additional studies, all of which involved a Foradil 24 mcg arm. These studies are DPRD2, DPRD3, and — 03. The first study, DPRD2 was not considered relevant because adverse events had to be considered at least possibly attributable to drug in order to be considered valid and recorded. The remaining two studies, DPRD3 and — 03 were controlled clinical trials that included a Foradil 24 mcg arm, and which demonstrated no signal for concern regarding serious asthma exacerbation in the Foradil 24 mcg treatment arms. I therefore agree with the sponsor that there are indeed two controlled studies which showed no signal of concern in the Foradil 24 mcg arm.

The sponsor also notes in their response that there were a higher rate of asthma-related premature discontinuations (combining the data from the 6 trials: 040, 041, 049, DPRD2, DPRD3, and — 03 together) in the placebo arm. They feel that this could result in under-representation of patients at risk for serious asthma exacerbation in the placebo arm, amplifying the ultimate rate of SAEs in the Foradil treatment arms. Of note, the sponsor addressed this only by combining the 6 trials together, and then separating out patients with baseline FEV<sub>1</sub> % predicted values below 75% to show that placebo patients had more premature discontinuations related to asthma. I disagree with the sponsor's assertion that the early removal of patients in placebo-arms due to asthma reduced that treatment arm's ultimate risk for serious asthma exacerbations. A review of the 3 pivotal studies 040, 041, and 049 all reveal fairly similar and balanced rates of

premature discontinuation (even due to asthma) for the Foradil 12 mcg arm, the Foradil 24 mcg arm, and the placebo arms. Nonetheless, it is the Foradil 24 mcg arm that had the highest rate of serious asthma exacerbation, and this finding was consistent in all 3 studies.

**Reviewer Summary**

*Foradil 12 mcg bid has proven efficacy and safety for both the maintenance treatment of asthma in patients age 5 and older and for the prevention of EIB in patients age 12 and older. I agree with the approval of Foradil 12 mcg taken twice a day for maintenance treatment of asthma. I also agree with the approval of Foradil 12 mcg taken as a single capsule prior to exercise for the acute prevention of EIB.*

*Foradil 24 mcg bid did demonstrate somewhat better prevention of EIB when compared to Foradil 12 mcg bid, and it was clearly superior to placebo.*

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*Foradil 24 mcg bid demonstrated a marginal increase in efficacy (about 100 ml improvement in FEV<sub>1</sub>) over Foradil 12 mcg bid for the maintenance treatment of asthma. Approval of Foradil 24 mcg would clearly be acceptable if there were no safety concerns with this dose, given this slight benefit. However, there were three "pivotal" randomized clinical trials performed, and all three demonstrated that Foradil 24 mcg bid was associated with a subtle but persistently greater incidence in severe asthma exacerbations when compared to placebo, and also when compared to Foradil 12 mcg bid. The signal is subtle, and it is not present in two other controlled trials, which argues against its validity. However, there is a biologic rationale to support this concern. Higher doses of Foradil are associated with greater tachyphylaxis, and this may result in more recalcitrant asthma exacerbations in some patients. In addition, there has been historical concern raised with various long-acting beta agonists and their possible link to increased mortality via serious asthma exacerbations. This has led to great controversy in the pulmonary literature, and it has led to the withdrawal of one long-acting beta agonist           . The controversy is heightened by the unfortunate fact that monitoring of events post-marketing has been unable to reliably detect a signal of concern because the safety event of interest is also the underlying disease.*



*I support a large, simple Phase 4 study commitment to evaluate more definitively the occurrence of serious asthma exacerbations in patients treated with Foradil 24 mcg bid. Three treatment arms would be enrolled: Foradil 24 mcg bid plus pm albuterol, Foradil 12 mcg bid plus pm albuterol, and Placebo bid plus pm albuterol. Patients would be followed for a duration of 16 weeks, and the outcome variable of interest would be serious asthma exacerbations.*

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Marianne Mann, M.D.  
Deputy Director, DPADP

APPEARS THIS WAY  
ON ORIGINAL

/s/

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Marianne Mann  
2/13/01 02:24:56 PM  
MEDICAL OFFICER -

Robert Meyer  
2/14/01 09:16:01 AM  
MEDICAL OFFICER

I agree with Dr. Mann's secondary review. For reasons of consistency and due to insufficient data to fully support the advantage of 24 mcg of formoterol in the EIB use, I believe we should label this drug for 12 mcg as the sole dose for all indications.

APPEARS THIS WAY  
ON ORIGINAL

## TEAM LEADER MEMORANDUM

TO:  
THROUGH:  
FROM:  
RE:  
DATE:

NDA 20-831

John K. Jenkins, MD

Peter K Honig, MD

Foradil® (formoterol fumarate)

June 5, 1998

15/6/98

15/

6/12/98

### Background:

Formoterol as a dry powder formulation for inhalation is approved in 13 countries in Western Europe and worldwide. This licensing application is for single-dose dry powder delivery. The clinical trials of this drug product included two large multicenter studies in adult asthmatics as well as a pediatric program and several studies investigating the role of formoterol in the prevention of exercise-induced exacerbation of asthma.

### Clinical Program:

Studies 40 and 41 were similar in design and investigated nearly 1100 mild to moderate asthmatics older than 12 years of age. Formoterol at doses of 12 mcgs and 24 mcgs twice daily versus albuterol 180 mcgs QID were compared to placebo in a double-blind, double-dummy fashion over 12 weeks. Serial spirometry conducted at regularly scheduled visits during the course of the trial demonstrated that formoterol produced significant bronchodilatation was near maximal and as good or better than that produced by albuterol within 30 minutes. The duration of action of formoterol also supported the proposed dosing interval with 20-25% improvement at the 12-hour timepoint over the pre-treatment baseline at the final treatment visit. Secondary endpoints (PEFRs, nocturnal awakenings, daytime asthma symptoms, rescue beta-agonist use, etc.) all demonstrated statistical superiority to placebo. The onset-of-action and appropriateness of the dose and dosing interval was further characterized in a small, single-dose, crossover, placebo controlled trial in which specific airway resistance and FEV1 was measured early and often after dosing. Formoterol at doses of 6, 12 and 24 mcgs were compared to albuterol at 400 mcg. The two higher doses of formoterol produced similar effects to albuterol as early as and were superior to formoterol dosed at 6 mcg.

The role of formoterol in the management of exercise-induced asthma exacerbation was also investigated in adult asthmatics. Studies 45 and 46 demonstrated both formoterol doses to confer protection as early as 15 minutes after dosing which lasted throughout a 12 hour dosing interval. The results indicated that formoterol at either dose was numerically superior to albuterol at early timepoints and significantly superior as early as four hours after dosing.

The pediatric program was limited to one 12-week active controlled trial and one EIB trial in children below the age of 12 years. The 12-week trial (Study DP/PD2) investigated 200 children aged 5-13 randomized to 6 or 12 mcgs of formoterol dosed twice daily or a European dry powder formulation of albuterol dosed at 400 mcg TID. Although the higher dose of formoterol demonstrated statistically significant superiority to the other two treatments, no difference between treatments was demonstrated for any of the secondary efficacy endpoints. This study suffers from not exploring the effective dose range of formoterol and the lack of a placebo control which is necessary to determine the appropriateness of the proposed dosing interval and onset of action in pediatric patients. The EIB study in children (Study DP/PD3) studied single 12 mcg doses of formoterol versus albuterol DPI (400 mcg) versus DPI placebo in a blinded, crossover fashion. Exercise challenge was conducted at baseline and 3 and 12 hours after each treatment. Although formoterol demonstrated efficacy in EIB at both timepoints, there are several problems with this study. First, the youngest patient was 10 years old and, as such, the sponsor did not adequately study patients at the lower end of the proposed indication age range. Second, and more importantly, the dose of formoterol studied may not be the appropriate dose for pediatric patients. The failure of the sponsor to adequately characterize the optimal pediatric dose does not allow this study to support an EIB claim because 12 mcgs may not be the appropriate dose for children.

The sponsor also conducted trials designed to evaluate the potential for tachyphylaxis development with the short-term, regular use of formoterol. Study DP/SP2 demonstrated a dramatic loss of protection against methacholine challenge versus placebo after two weeks of treatment with formoterol (24 mcgs BID). Study FO/UK2 evaluated the cumulative dose-response to formoterol after 4-6 weeks of treatment with formoterol or placebo. The baseline FEV1 was higher, the change to maximum FEV1 lower, and the fall from maximum to the end of the dose-response test was greater after chronic formoterol dosing than after the placebo period. The findings of these studies will probably need to be reflected in product labeling.

The safety database was large but not without limitations. First, the number of children at the lower end of the proposed indicated age range is inadequate as only 19 children less than 7 years of age were studied of which 6 received single-doses only. Second, the analysis of the available ECG database was inadequate. ECG interval analysis was not conducted and the categorical analysis (abnormal/normal) requires clarification. Finally, a complete accounting of all serious adverse events and dropouts due to adverse events as well as a complete submission of CRFs for all deaths and dropouts due to adverse events were not available for review. From the available data, it can be concluded that the safety profile was generally consistent with that seen for other beta-agonists. Hyperglycemia is a known finding with beta-agonists; however, the degree seen with formoterol was numerically higher than that seen with the active control comparator, albuterol. Foreign spontaneous post-marketing safety report data were reviewed by Dr. Anthracite and did not reveal any particular, unusual, or unexpected problem associated with this drug.

DSI investigations of four sites selected by the Medical Officer did not reveal any data integrity issues.

**Team Leader Conclusion and Recommendation:**

I agree with Dr. Anthracite's conclusion that formoterol is approvable for the treatment of asthma and EIB in adults and adolescents greater than 12 years of age. Submission of additional clinical safety data and reanalyses as recommended by the reviewer will be required prior to approval. Formoterol is not approvable for the pediatric indication because the appropriate dose and dosing interval has not been demonstrated. The pediatric EIB claim is not supported by the study because the number of patients at the lower age range is not adequate and the appropriate dose may not have been necessarily been studied. The sponsor should be made aware that the EIB study should involve the lowest dose approved in pediatric patients. Several other concerns should also be communicated to the sponsor.

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They should also be encouraged to study the role of less frequent dosing (e.g once daily) in the management of asthma, particularly in light of the finding of sustained efficacy with no loss of bronchodilation after 12 hours as shown in Studies 40 and 41. Labeling will be the concern of a separate review. It will also be requested that translated copies of foreign labeling will be submitted for review.

CC:  
NDA20-831/Division File  
HFD-570/MO/Anthracite/Honig  
HFD-570/PM/Jani

**APPEARS THIS WAY  
ON ORIGINAL**



# PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

**NDA Number:** N 020831  
**Trade Name:** FORADIL (FORMOTEROL FUMARATE)12MCG CAPS  
**Generic Name:** FORMOTEROL FUMARATE  
**Supplement Number:** 000 **Supplement Type:** N  
**Dosage Form:**  
**Regulatory Action:** AP **Action Date:** 2/16/01  
**COMIS Indication:** PREVENTION AND MAINTENANCE TREATMENT OF  
 BRONCHOCONTRICION IN PATIENTS WITH REVERSIBLE OBSTRUCTIVE AIRWAYS  
 DISEASE/ INCLUDING PATIENTS WITH SYMPTOMS OF NOCTURNA

Indication #1: for the long-term, twice daily, administration in the maintenance treatment of asthma and in prevention of bronchospasm in patients 5 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting, beta2-agonists

**Label Adequacy:** Adequate for some pediatric age groups

**Formulation Needed:**

**Comments (if any)** The PPSR submitted did not address all the pediatric age groups, and therefore, was considered inadequate. Sponsor is planning to submit another PPSR. (4-27-00)  
 Sponsor will submit another PPSR post-approval (1-19-01)

	Lower Range	Upper Range	Status	Date
Comments: See the comment above.	6 months	4 years	Deferred	2/28/02
Sponsor will submit the developemnt plans post-approval	0 months	5 months	Waived	

Indication #2: For the prevention of exercise-induced bronchospasm in adults and children 12 years of age and older.

**Label Adequacy:** Adequate for some pediatric age groups

**Formulation Needed:** No new formulation is needed

**Comments (if any)** The PPSR submitted did not address all the pediatric age groups, and therefore, was considered inadequate. Sponsor is planning to submit another PPSR post-approval

	Lower Range	Upper Range	Status	Date
Comments: Sponsor will submit the development plans post-approval.	4 years	11 years	Deferred	2/28/02
	0 months	3 years	Waived	

This page was last edited on 2/16/01

\_\_\_\_\_  
 JS/  
 Signature

\_\_\_\_\_  
 2-16-01  
 Date



# PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

**NDA Number:** N 020831  
**Trade Name:** FORADIL AEROLIZER  
**Generic Name:** FORMOTEROL FUMARATE INHALATION POWDER  
**Supplement Number:** 000 **Supplement Type:** N

**Dosage Form:**  
**Regulatory Action:** AP **Action Date:** 2/16/01  
**COMIS Indication:** PREVENTION AND MAINTENANCE TREATMENT OF  
 BRONCHOCONTRICION IN PATIENTS WITH REVERSIBLE OBSTRUCTIVE AIRWAYS  
 DISEASE/ INCLUDING PATIENTS WITH SYMPTOMS OF NOCTURNAL ASTHMA

Indication #1: for the long-term, twice daily, administration in the maintenance treatment of asthma and in prevention of bronchospasm in patients 5 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting, beta2-agonists

**Label Adequacy:** Adequate for some pediatric age groups

**Formulation Needed:**

**Comments (if any)** The PPSR submitted did not address all the pediatric age groups, and therefore, was considered inadequate. Sponsor is planning to submit another PPSR. (4-27-00)  
 Sponsor will submit another PPSR post-approval (1-19-01)

Lower Range	Upper Range	Status	Date
6 months	4 years	Deferred	2/28/04

**Comments:** See the comment above.  
 Sponsor will submit the development plans post-approval

Indication #2: For the prevention of exercise-induced bronchospasm in adults and children 12 years of age and older.

**Label Adequacy:** Adequate for some pediatric age groups

**Formulation Needed:** No new formulation is needed

**Comments (if any)** The PPSR submitted did not address all the pediatric age groups, and therefore, was considered inadequate. Sponsor is planning to submit another PPSR post-approval.

Lower Range	Upper Range	Status	Date
4 years	11 years	Deferred	2/28/02

**Comments:** Sponsor will submit the development plans post-approval.

This page was last edited on 2/15/01

IS/

2-16-01

Signature

Date

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-831

Supplement # \_\_\_\_\_ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 579 Trade and generic names/dosage form: Foradil (Formoterol) fumarate capsules for Inhalation  
Applicant Novartis Therapeutic Class 15 Action: AP  AE  NA

Indication(s) previously approved \_\_\_\_\_  
Pediatric information in labeling of approved indication(s) is adequate  inadequate   
Proposed indication in this application \_\_\_\_\_ (See attached)

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS?  Yes (Continue with questions)  No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)  
 Neonates (Birth-1month)  Infants (1month-2yrs)  Children (2-12yrs)  Adolescents(12-16yrs)

- 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required. NO
- 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required. Yes - 12-16 years
- 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
  - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
  - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
  - c. The applicant has committed to doing such studies as will be required.
    - (1) Studies are ongoing,
    - (2) Protocols were submitted and approved.
    - (3) Protocols were submitted and are under review.
    - (4) If no protocol has been submitted, attach memo describing status of discussions.
  - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER?  Yes  No  
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Dr. Anthracite (e.g., medical review, medical officer, team leader)  
IS/ Project Manager June 5, 1998  
Signature of Preparer and Title Date

cc: Orig NDA/BLA # 20-831  
HF D579 Div File  
NDA/BLA Action Package  
HFD-006/ KRoberts

(revised 10/20/87)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

1 PAGE(S) REDACTED

Draft

Labeling