CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-592

MEDICAL REVIEW(S)

DIVISION MEMORANDUM

Date:	December 14, 2006
To:	NDA 21-592
From:	Sally M. Seymour, MD Team Leader, Division of Pulmonary and Allergy Products
Through:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products
Product:	Foradil Certihaler (formoterol fumarate inhalation powder)
Applicant:	Novartis

Administrative and Introduction

This is the fourth 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] b(4)

On October 17, 2003, the Division took an Approvable action on the application because of several CMC deficiencies that precluded approval. On June 24, 2004, the Applicant submitted a Complete Response to the October 17, 2003, action letter. The Applicant's responses to these deficiencies were reviewed by the CMC Reviewer, Dr. Craig Bertha, and found to be acceptable. However, on December 14, 2004, the Division took an Approvable action on the application because of clinical data suggesting patients were not able to operate the device successfully; therefore, the Division requested revised instructions for patients and a patient use study.

On October 10, 2005, the Applicant submitted a Complete Response to the December 14, 2004, action letter. The Applicant revised the patient instructions for use and conducted a patient use study, which suggested that the revised instructions improved patient's ability to operate the device successfully. However, during the review period, the Applicant submitted reports of inadvertent overdosing of patients who used the Certihaler device (which had been approved and marketed in Germany for several months) that resulted in a voluntary recall of the device. Because of the safety concerns with the overdosing reports, the Division took an Approvable action on April 11, 2006. The action letter cited two deficiencies: 1) modification of the device to address the safety issue of overdosing of patients; and 2) revised labeling, including a Medication Guide, to address risk of severe asthma episodes and death in asthma patients who use long acting beta agonists.

On June 15, 2006, the Applicant submitted a Complete Response to the April 11, 2006, action letter. In the Complete Response, the Applicant modified the Certihaler device to

address the overdose issue and the Applicant submitted revised labeling, which included a Boxed Warning and Medication Guide.

Chemistry, Manufacturing, and Controls

In the April 11, 2006, Approvable letter, deficiency comment #1 referred to modification of the device to address the safety issue of overdosing of patients. In the June 15, 2006, Complete Response, the Applicant analyzed the devices returned from patients who received an overdose in Europe and indicated that the overdosing was due to unintentional patient mishandling of the drug product. In order to address unintentional patient mishandling, the Applicant, in coordination with the drug product manufacturer, SkyePharma, and the device manufacturer, Riwisa, proposed four modifications to the Certihaler device. The modifications were reviewed by the CMC reviewer, Dr. Craig Bertha, who concluded that the proposed modifications should significantly mitigate the risk of overdosing in the event of unintentional patient device misuse. In addition, the Applicant submitted in vitro testing of the modified drug product. Dr. Bertha reviewed the in vitro data and concluded that the in vitro performance of the modified drug product is sufficiently comparable to the unmodified Foradil Certihaler drug product utilized in the clinical trials. The EES was acceptable. The CMC team has determined that the previously identified deficiency has been adequately addressed and the application is adequate to support Approval.

Clinical

The Applicant submitted a safety update in the June 15, 2006, Complete Response. The safety update included safety data collected since the safety update in the October 10, 2005, Complete Response. The safety data was reviewed by Dr. Anthony Durmowicz in a review dated November 15, 2006. The review of the safety update did not identify any new safety signal for Foradil Certihaler. Dr. Durmowicz's recommendation for this Complete Response is for Approval.

Labeling Issues

In the June 15, 2006, Complete Response, the Applicant submitted revised labeling, which included a Boxed Warning and Medication Guide. The Division of Medication Errors and Technical Support (DMETS) provided input on the product label in a review by Dr. Kristina Arnwine dated August 10, 2006. The DMETS review team continues to find the proposed product name, Foradil Certihaler, acceptable. In addition, DMETS recommended the Applicant develop web-based instructions for the Foradil Certihaler. Additional comments from DMETS were considered in the labeling review. The Division of Drug Marketing, Advertising, and Communications (DDMAC) provided input on the revised product label in a review dated October 17, 2006, by Michelle Safarik. The recommendations from DDMAC were considered during the labeling review. The Medication Guide was reviewed by Jeanine Best of the Division of Surveillance, Research, and Communication Support (DSRCS) in a review dated August 2, 2006, and the recommendations were considered during the labeling review.

The review team reviewed the proposed Foradil Certihaler label in detail and proposed additional changes to the product label to provide consistency with the related Foradil Aerolizer product label. The Division interacted with the Applicant during the review cycle to arrive at acceptable labeling.

The review team recommended changes to the carton/container labels, including removal of a graphic associated with the proprietary name. The Applicant agreed to the carton/container label changes and the revised carton/container labels are acceptable.

Pediatrics

The proposed indication for Foradil Certihaler is for children 5 years of age and older. Foradil Certihaler does not contain a new active ingredient because there is a marketed product, Foradil Aerolizer, which also contains formoterol fumarate. In addition, the dosage form (dry powder inhaler), route of administration (oral inhalation) and dosing regimen (twice daily) for Foradil Certihaler are the same as Foradil Aerolizer. Finally, the indication for Foradil Certihaler is also one of the indications for Foradil Aerolizer. Because this NDA is not for a new active ingredient, dosage form, route of administration, dosing regimen, or indication, this application does not trigger PREA and a pediatric assessment in children < 5 years of age is not required.

Recommendation and Discussion

The CMC issue regarding modification of the device to address the safety issue of overdosing of patients has been adequately addressed. The revised product label submitted in the Complete Response included a Boxed Warning and Medication Guide, which adequately addressed the labeling deficiency. The carton/container labeling issues have been adequately addressed. Acceptable labeling has been agreed upon by both the Division and the Applicant. Given that all of the deficiencies identified in the previous review cycles have been adequately addressed by the Applicant and there are no outstanding issues, the action on this application will be Approval.

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/s/

Sally Seymour
12/14/2006 04:33:22 PM
MEDICAL OFFICER

Badrul Chowdhury
12/15/2006 09:43:42 AM
MEDICAL OFFICER
I concur with this summary review

MEDICAL TEAM LEADER MEMORANDUM

Date: October 15, 2003
To: NDA 21-592
From: Eugene J. Sullivan, MD, FCCP
Acting Medical Team Leader
Division of Pulmonary and Allergy Drug Products (HFD-570)
Subject: Secondary medical review of NDA for Novartis' Foradil Certihaler

Administrative

NDA 21-592 was submitted by Novartis on December 18, 2002. The PDUFA action date for the application is October 18, 2003. The NDA was submitted 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,

b(4)

The drug substance, formoterol fumarate, is already approved in the US as a single dose dry powder inhaler called the Foradil Aerolizer (Novartis). The Foradil Aerolizer 12mcg BID was approved for asthma on February 16, 2001, (NDA 20-831) and for COPD on September 25, 2001 (NDA 21-279). Of note, the applications for both the asthma and the COPD indications for the Foradil Aerolizer requested approval of a second, higher dose of formoterol (24mcg BID). The 24mcg dose was not approved for asthma, primarily because of a suggestion of increased serious asthma exacerbations with this dose. In addition, the 24mcg dose was not approved for COPD, primarily because the data did not suggest an efficacy advantage of the higher dose, which was associated with more frequent adverse events.

Chemistry, Manufacturing, and Controls

The active pharmaceutical ingredient in this product is formoterol fumarate. The Certihaler is a plastic, breath-actuated, multi-dose dry powder inhaler device that contains 60 metered doses of the powder formulation. Each metered dose contains 10mcg of formoterol fumarate, as well as the inactive ingredients lactose monohydrate and magnesium stearate. The device includes a dose-counter.

The CMC aspects of this application are discussed in detail in the separate CMC review completed by Dr. Bertha. The CMC team issued a Discipline Review letter on May 7, 2003, and received a response from the Applicant in a submission dated August 29, 2003. The CMC review of this recent submission is ongoing. At this time, the CMC team has

identified several deficiencies in the application that will preclude approval. These include 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, an earlier design of the Certihaler ([redacted] tooling) was noted to be associated with increasing airflow rate requirement upon multiple dosing. This issue is discussed in the section below ("Device Durability").

Device durability

The Applicant estimates that 10,000-15,000 devices were utilized in the "pivotal" safety and efficacy studies (2302, 2303, and 604) and one long term safety study (603). From these studies, a total of 174 complaint devices were returned for testing. Thirteen of these could not be tested because they were somehow damaged by abuse. A total of 111 devices were found to have a failure, the most common of which was an increase in the actuation flow rate (n=101). The actuation flow rate is the inspiratory flow rate required to trigger an actuation. The Applicant states that this increase in actuation flow rate was due to the accumulation of powder residues on gliding parts, resulting in increased friction. The second most common finding was failure of the dose counter, which was found in 15 devices.

The devices used in the 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, the Application did not provide data to demonstrate that these design modifications were sufficient to correct the problem. Therefore, in a May 7, 2003, Discipline Review letter from the CMC review team, the following deficiency was conveyed: "Provide a summary of the efforts that have been taken to assure that drug product prepared with [redacted] tooled devices will have acceptable performance and will not display the same counter and actuation flow rate (or other) problems outlined in your included report in attachment 11 of section 3.2.P.2 and attachment 2 of this section in the March 17, 2003, amendment. Provide supporting data demonstrating the decrease in the percentage of complaints."

A telephone conference was held on July 2, 2003, to discuss various items in the May 7, 2003, Discipline Review letter. In the briefing package submitted for this telephone conference, the Applicant outlined a proposal for a "simulated patient-use" study. In this proposal, employees of the firm would carry devices with them during their day-to-day activities, and would bring the devices to the testing facility daily for *in vitro* activation. During the July 2, 2003, telephone conference, the Division agreed to this study design, but indicated that the planned number of devices to be tested (60) was insufficient. The Division stated that the number of devices should be increased to 500-1,000. The Division also found the Applicant's proposal to provide post-approval data on this issue derived from open-label study and AERs data to be acceptable.

As stated above, the Applicant has submitted further data in a submission dated August 29, 2003. This submission has not yet been formally reviewed. The submission includes data on the "simulated patient-use" study investigating 60 devices, and states that the Applicant plans an additional "simulated patient-use" study to investigate a larger number of devices, as discussed in the July 2, 2003, telephone conference. Of note, the data from the smaller study is reported to show a "slight" increase in actuation flow rate, and 3 dose-counter failures. Two of these involved count-not-fire errors, and one involved fire-not-count error. Thus, it appears that there are two potentially significant device durability issues that have not yet been resolved. Clinical data, rather than "simulated" clinical data may well be needed to establish that these issues have been adequately resolved. The CMC team will compose a comment on this issue, which will be included in the action letter. The comment will refer to preliminary review of the 60-device study and will state that clinical data may be required to establish that the device issues that were raised in prior clinical studies (increasing actuation flow rate, and dose-counter failure) have been resolved.

Clinical

A total of eight clinical studies were submitted with the original NDA, and one long-term safety study (603) was submitted in the 4-month safety update. The most important of these were the two dose-ranging studies (601 and 602), the two pivotal clinical studies in adults and adolescents (2302 and 2303), and the pivotal study in pediatric patients aged 5 to 12 years (604). Four additional studies were submitted in support of safety: 1) a 12-week multicenter trial intended to demonstrate non-inferiority of formoterol delivered by the MDDPI versus formoterol delivered by the Aerolizer device (605); 2) a small safety/tolerability study examining the effects of Foradil Aerolizer, 24mcg BID, on glucose control in 17 type 2 diabetic patients (2301); 3) a small active controlled safety/tolerability study examining the effects of Foradil Aerolizer 36mcg TID in 16 asthma patients (701); 4) a 12-month open-label safety study (603). The clinical program is described in detail in the Medical Officer Review performed by Dr. Richard Nicklas. The following is a brief summary of the important studies, and conclusions that may be drawn from them.

Dose-Ranging Studies

Dose-ranging studies were performed in adults aged ≥20 years (Study 601) and in children 5-12 years of age (Study 602). Study 601 was performed in Denmark and the Netherlands. The study was a repetitive dose, randomized, double-blind, crossover study in 67 asthmatic patients. Treatments studied were formoterol multidose dry powder inhaler (MDDPI) 5, 10, 15, and 30mcg BID, Foradil Aerolizer 12mcg BID, and placebo. Formoterol MDDPIs corresponding to 5 and 15mcg per actuation were utilized. An incomplete block design was utilized, such that each patient received four of the six possible treatments. Treatments were administered Q12 hours for one week, with a one-week washout period between treatments. The primary efficacy endpoint was the FEV_1 $AUC_{0\text{-}12\ hours}$ after one week of treatment. All doses of formoterol were statistically superior to placebo. The 10mcg dose was numerically greater than the 5mcg dose, and there was no remarkable difference between the 10mcg, 15mcg, and 30mcg doses. The 10mcg dose was similar to the Foradil Aerolizer 12mcg dose. In regard to individual

serial FEV_1 values, the 5mcg dose was not statistically superior to placebo after 10 hours, whereas statistical significance was maintained throughout the 12-hour period for the other doses of formoterol MDDPI. Therefore, in this age group, the 10mcg appeared to be a reasonable dose to pursue in Phase 3. It should be noted that the 5mcg dose did show efficacy (albeit without statistical significance at the end of the dosing interval), and it might have been reasonable to explore this dose in Phase 3 as well.

Study 602 was a dose ranging study performed in children 5-12 years of age in the Czech Republic, Norway, Russia, and South Africa. The study was a repetitive dose, randomized, double-blind, crossover study in 77 children with asthma. Treatments studied were formoterol multidose dry powder inhaler (MDDPI) 5, 10, 15, and 30mcg BID, Foradil Aerolizer 12mcg BID, and placebo. Formoterol MDDPIs corresponding to 5 and 15mcg per actuation were utilized. An incomplete block design was utilized such that each patient received 4 of the 6 possible treatments. Treatments were administered Q12 hours for one week, with a one-week washout period between treatments. The primary efficacy endpoint was the FEV_1 $AUC_{0\text{-}12\ hours}$ after one week of treatment. All doses of formoterol were statistically superior to placebo. Although the effect size of the 30mcg dose was slightly greater than that of the 5mcg dose, there was no remarkable difference between any of the doses on this endpoint. Therefore, in this age group, based on this data, it might have been reasonable to proceed with the 5mcg dose, rather than the 10mcg dose, in this population in Phase 3. However, it should be noted that the systemic exposure (measured by 12-hour urine excretion) using the 10mcg dose was quite similar to the exposure using the currently approved Foradil Aerolizer 12mcg. This will be discussed in more detail in the Biopharmaceutics section below.

Pivotal Safety and Efficacy Trials (Adult/Adolescent)

Two pivotal safety and efficacy studies were performed in adults and adolescents aged 13 years and older (Studies 2302 and 2303). The study designs were identical, with the exception that pharmacokinetic assessments were performed in Study 2303, but not in Study 2302. These studies were multi-center, randomized, double-blind, double-dummy, parallel group, US studies comparing the effects of Foradil Certihaler (10mcg BID), albuterol MDI (180mcg QID), and placebo, administered over a 12-week treatment period in asthmatic patients. The primary efficacy endpoint was the change from baseline FEV_1 $AUC_{0\text{-}12\ hours}$ after 12 weeks of treatment. Secondary efficacy measures included serial measures of FEV_1 and FVC, morning and evening pre-dose PEFR, use of rescue medication (albuterol), asthma exacerbations, symptom scores, and the health-related quality of life instrument, the mini-AQLQ (Asthma Quality of Life Questionnaire). Safety assessments included adverse events, laboratory tests, vital signs, ECGs, and physical examination.

These two studies supported the efficacy of Foradil Certihaler as a bronchodilator in asthmatic patients aged 13 years and older. In both studies, Foradil Certihaler was statistically superior to placebo on the primary endpoint, change from baseline FEV_1 $AUC_{0\text{-}12\ hours}$ after 12 weeks of treatment. Interestingly, albuterol was found to be superior to placebo on this endpoint in Study 2302, but not Study 2303. The secondary

endpoints generally served to support efficacy. For instance, in both studies Foradil Certihaler was statistically superior to placebo for the change from baseline FEV_1 $AUC_{0\text{-}12\ hours}$ after one dose, and after 1 month of treatment. In addition, in both studies, Foradil Certihaler was statistically superior to placebo on nearly all of the 12-hour serial FEV_1 measurements on Day 1, Month 1, and Month 3. Finally, in both studies, Foradil Certihaler was statistically superior to placebo for AM and PM PEFR (averaged over all treatment days), and for rescue medication use.

The results of the patient-reported outcomes, the mini-AQLQ and the asthma symptom scores, were not consistent between trials. Foradil Certihaler was statistically superior to placebo on the mini-AQLQ (total score) at 3 months in Study 2303, but not in Study 2302. The effect size seen in Study 2303 (0.33) was in the range that would be considered to be "small" by the developers of the instrument. Likewise, in Study 2303, but not Study 2302, Foradil Certihaler was statistically superior to placebo for AM total symptom score, PM total symptom score, and an assessment of sleep quality called the nocturnal symptom score.

Although submitted by the Applicant for support of safety, the efficacy results of Study 605 should also be noted. The primary objective of Study 605 was to determine if 10mcg of formoterol delivered by the MDDPI BID is comparable to 12mcg of formoterol delivered by the Aerolizer device BID, in asthmatic patients aged ~~13 years~~ and older. This study enrolled a total of 365 patients who were treated with either Foradil Certihaler 10mcg BID, Foradil Aerolizer 12mcg BID, or placebo, for a treatment period of 12 weeks. The primary endpoint in this study was the pre-dose FEV_1 after 12 weeks of treatment. In this study, neither the Certihaler nor the Aerolizer were demonstrated to be superior to placebo on the primary endpoint ($p=0.42$, and $p=0.55$, respectively). It should be noted that the study was underpowered because the primary variable was changed in the middle of the study, without adjustment of the sample size.

Pivotal Safety and Efficacy Trial (Pediatric)

One pivotal safety and efficacy study was performed in asthmatic children aged 5-12 years (Study 604). This study was a multi-center, randomized, double-blind, placebo-controlled, parallel group, US study comparing the effects of Foradil Certihaler (10mcg BID) and placebo, administered over a 12-week treatment period in asthmatic patients. The primary efficacy endpoint was the change from baseline FEV_1 $AUC_{0\text{-}12\ hours}$ after 12 weeks of treatment. Secondary efficacy measures included serial measures of FEV_1 and FVC, morning and evening pre-dose PEFR, use of rescue medication (albuterol), asthma exacerbations, and symptom scores. Safety assessments included adverse events, laboratory tests, vital signs, ECGs, and physical examination.

The results of this study support the safety and efficacy of Foradil Certihaler 10mcg BID as a bronchodilator in asthmatic patients aged 5-12 years, based on statistical superiority over placebo on the primary endpoint, FEV_1 $AUC_{0\text{-}12\ hours}$ ($p=0.01$). However, it should be noted that the differences between Certihaler and placebo were rather small, and that statistical superiority over placebo was not maintained after 6 hours at the 3-month visit.

The interpretation of the study results is hampered by the unexplained observation of increases in serial FEV_1 in the placebo group at Month 1 and Month 3. These increases may have contributed to the failure to achieve statistical significance during the second half of the dosing interval. Pre-dose PEFR data generally support bronchodilator efficacy, although statistical significance was not demonstrated (AM PEFR p=0.05, PM PEFR p=0.06). Twenty-four hour rescue medication use was not statistically different between groups (p=0.1), but night-time rescue medication use was statistically lower in the Foradil Certihaler group (p=0.04). Perhaps consistent with a slightly more notable effect overnight, the Foradil Certihaler group was statistically superior to placebo on the "nocturnal symptoms" score, a measure of sleep quality. However, no differences were noted between groups for either the morning (p=0.10) or the evening (p=1.24) assessments of asthma symptom scores, with Foradil numerically inferior to placebo on the evening assessment.

Tachyphylaxis

In the proposed label, as in the currently approved label for the Aerolizer device, the Applicant has included a section under Clinical Pharmacology titled Tachyphylaxis/Tolerance. In this section the proposed text states that "there was no suggestion of bronchodilatory tolerance following regular twice-daily use with Foradil Certihaler over a 12-week period" in the adult/adolescent and pediatric confirmatory trials. This may be too strongly stated. The Biometrics Reviewer (Dr. Zhou) plotted the serial FEV_1 values on Day 1, Month 1, and Month 3 for each of the three confirmatory studies, without imputed values. These plots demonstrated that in one of the two adult/adolescent studies (2303), there was evidence of decreasing effect size during the last half of the dosing interval over the course of the study. Firm interpretation is limited because in this study, albuterol failed to show its expected efficacy as well. In addition, in the pediatric study, efficacy in the second half of the dosing interval clearly declined during the course of the study. However, firm interpretation of this finding is also limited because the apparent loss of efficacy may have been related to an unexplained increase in FEV_1 seen in the placebo group over time. Based on these observations, the Applicant will be asked to delete this section of the proposed label.

Safety

The safety database provided with the application was sufficient to allow adequate estimation of the safety profile of this drug product. In addition, given that the systemic exposures using the Aerolizer and the Certihaler devices are not substantially different, the safety data used to support approval of the Aerolizer product can be used as additional support of the current application. The safety data did not suggest a specific safety concern with this product. The incidence of certain adverse events that might be expected with a $beta_2$-agonist, such as tachycardia, palpitations, and tremor, were somewhat more frequent among patients treated with Foradil Certihaler than those treated with placebo. The most prominent of these was tremor, which occurred in 7% of patients treated with Foradil Certihaler and 1% of placebo patients. Of note, tremor was also less common in the Foradil Aerolizer (3%) and albuterol MDI (1%) groups.

Clinical Summary

In summary, these studies demonstrate adequate support for the safety and efficacy of the proposed dose of formoterol fumarate (10mcg BID) delivered by the Certihaler device. The results of the primary and many secondary analyses support the bronchodilator efficacy in the two adult/adolescent trials. These trials did not demonstrate convincing evidence of treatment effect in terms of patient-reported outcomes (e.g. symptoms, mini-AQLQ). The data from the pediatric study (604) were less impressive, although they may have been affected by an unexpected increase in the FEV_1 values in the placebo group over the course of the study. The secondary endpoints provided only weak support of efficacy in this study.

Pharmacology/Toxicology

Because the drug substance, formoterol fumarate, has already been approved, the application did not contain extensive toxicology data. Rather, the Applicant referenced its data submitted with the Foradil Aerolizer NDA (#20-831). The application did contain toxicologic data for one of the excipients, magnesium stearate. Although magnesium stearate is considered to be Generally Recognized as Safe (GRAS), this determination does not cover inhalational exposure. There has never been any use of this excipient by the inhalation route in approved drug products. For that reason, the Applicant conducted 1-month inhalation studies in the rat and the dog, and a 6 month inhalation study in the rat in order to support the use of magnesium stearate in this inhalation drug product. The toxicology data were reviewed by the Division's Pharm/Tox Reviewer (Dr. Robison), who found that the toxicology data were sufficient to support approval. There was no evidence of local toxicity in the chronic rat study. His findings are included in the separate Pharm/Tox review.

Biopharmaceutics

Four studies with pharmacokinetic data were submitted. These were two dose-finding studies (Study 601 in adults/adolescents, and Study 602 in pediatric patients aged 5-12 years), and two Phase 3 safety/efficacy studies that included PK sampling (Study 2303 in adults and adolescents, and Study 604 in pediatric patients aged 5-12 years). The pharmacokinetic data are reviewed in depth in the OCPB Review performed by Dr. Kim.

In Studies 601 and 602, four doses of formoterol delivered by multiple-dose dry powder inhaler (MDDPI) (5, 10, 15, and 30mcg BID) were compared to formoterol 12mcg administered with the Aerolizer device BID for a period of one week. In Study 601, examination of mean urinary excretion of formoterol, suggested that systemic exposure with the Aerolizer at a dose of 12mcg was lower than that with the Certihaler at a dose of 10mcg, and greater than that with the Certihaler at a dose of 5mcg. In Study 602, systemic exposure, as assessed by urinary excretion, was similar between the Aerolizer at a dose of 12mcg and the Certihaler at a dose of 10mcg.

Pharmacokinetic data from Studies 604 and 2303 indicated rapid absorption, with Cmax occurring at 10 minutes (first sampling) after inhalation. In both studies, the amount of

formoterol excreted unchanged in the urine was 1.6-fold higher at steady state, compared to first dose.

Ethical and Statistical Integrity Issues

The studies submitted with this application were performed in accordance with Good Clinical Practices, and appropriate ethical standards. Analyses of the data from the confirmatory studies did not raise suspicion regarding data integrity. DSI audits of clinical studies were not performed. The application included appropriate financial disclosure documentation. The financial disclosure information did not raise doubts about the ability to draw conclusions based on the data submitted.

Nomenclature

The USAN name, formoterol fumarate, has been previously established for the currently approved Foradil Aerolizer formulation. The proprietary name Foradil, has also been established for the currently approved product. A nomenclature consult was obtained from the Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS), for the name Foradil Certihaler. This name was found to be acceptable. DMETS recommended that the Applicant commit to providing an educational campaign at the launch of this product in order to minimize confusion that may arise as a result of Foradil Aerolizer and Foradil Certihaler being co-marketed. The action letter will request that the Applicant address this issue.

Pediatric Considerations

The application included clinical data to support an Indication for adults, adolescents, and children ≥ 5 years of age. Although asthma occurs in younger children, this multi-dose dry powder formulation may not be appropriate for very young children. Of note, Serevent (salmeterol xinafoate) Diskus, a currently approved dry powder formulation of a long-acting beta$_2$-agonist, is indicated for children 4 years of age and older.

Recommendation

From a clinical perspective, the application is considered adequate for approval. However, unresolved CMC issues preclude approval during this review cycle. Therefore, the overall recommendation is for an Approvable action.

Labeling Issues

The Applicant's proposed product label very closely resembles the currently approved label for the Foradil Aerolizer product. Although this is appropriate, a few specific changes should be made:

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Additional Comments for Action Letter

The Action Letter will contain comments addressing the above labeling issues. In addition the action letter will contain a comment asking 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.

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/s/

Eugene Sullivan
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MEDICAL OFFICER
NDA Clinical Team Leader Memo

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-592
Submission Code	N000
Letter Date	June 15, 2006
Stamp Date	June 16, 2006
PDUFA Goal Date	December 16, 2006
Reviewer Name	Anthony G. Durmowicz MD
Review Completion Date	November 14, 2006
Established Name	formoterol fumarate
(Proposed) Trade Name	Foradil Certihaler
Therapeutic Class	beta agonist bronchodilator
Applicant	Novartis
Priority Designation	Standard

Formulation	Certihaler (inhalation powder)
Dosing Regimen	10 µg bid
Indication	maintenance treatment of asthma and the prevention of bronchospasm
Intended Population	adults and children 5 years and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical recommendation is for Approval for the Foradil Certihaler MDDPI. This decision is made on the basis that recent structural modifications to the Certihaler MDDPI delivery device made as a result of post-marketing reports of inadvertent overdosing of formoterol by patients in Germany are felt to be sufficient by the CMC review team to sufficiently mitigate the risk of overdosing due to unintended misuse of the device by patients (see CMC review #6 by Craig Bertha, Ph.D., dated July 05, 2006). In addition, during the previous Complete Response dated October 10, 2005, Novartis had addressed clinical concerns regarding the ability of patients' understanding of how use the device appropriately by extensively revising the patient instructions for use of the Certihaler, including figures, in order to improve patient comprehension and conducted a patient use study (F2309) which demonstrated improved ability of patients to use the Certihaler.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

In addition to the recent structural modifications of the device to prevent inadvertent overdosing due to unintended misuse of the device, the risk management plan for patient support upon approval and commercialization of the Certihaler mimics the patient support that was available in the patient use study (F2309) which demonstrated improved ability of patients to use the Certihaler. These include revised instructions for use now contained in the Medication Guide, provision of a toll free number and web site to call or access if difficulties arise in using the device, and access to a Certihaler instructional video (in DVD or VCR format).

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

In the approvable letter of October 17, 2003, the Division recommended the applicant establish a more extensive database to further evaluate the Foradil Certihaler in adolescent and elderly populations.

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1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This is the fourth 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] " Previously, on October 17, 2003, December 14, 2004, and April 11, 2006, the Division took Approvable actions on the application and noted requirements to address CMC and device malfunction issues (October, 2003 letter) including the fact that a substantial number of patients in the clinical program were not able to operate the Certihaler device successfully despite the finding on in vitro testing that the devices themselves were not malfunctioning (December, 2004 letter). These aspects were addressed successfully in the Complete Response dated October 10, 2005. However, late in the review cycle of the October 10, 2005, response, post-marketing reports from Germany of inadvertent overdosing by patients using the Foradil Certihaler, apparently due to unintended misuse of the product, were received. As a result, the FDA stated in an Approvable Letter dated April, 11, 2006, that the Certihaler be modified in such a way that mishandling leading to inadvertent overdosing could no longer occur. Data supplied with the current Complete Response dated June 15, 2006, regarding structural changes made to the device have been reviewed by the CMC reviewers and found to be acceptable from the CMC perspective to substantially mitigate the risk of overdosing due to unintended misuse and have lead to a recommendation of Approval from the CMC reviewers.

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The original evaluations of the safety and efficacy of the Foradil Certihaler (formoterol fumarate inhalation powder) are contained in the initial NDA review, dated October 7, 2003, by Richard Nicklas, M.D. A subsequent review of the Complete Response, dated June 24, 2004, which addressed device malfunction problems, was also conducted by Dr. Nicklas (dated December 10, 2004). The clinical review by Anthony Durmowicz, M.D. of the Complete Response dated October 10, 2005 including review of improved patient instructions, patient use study F2309, and labeling is dated April 10, 2006.

The drug substance, formoterol fumarate, is already approved in the US as a single dose dry powder inhaler called the Foradil Aerolizer (Novartis). The Foradil Aerolizer 12mcg BID was approved for asthma on February 16, 2001, (NDA 20-831) and for COPD on September 25, 2001 (NDA 21-279). This NDA is for the approval of the Foradil Certihaler inhalation powder device. The Certihaler is a multi-dose dry powder inhaler whereas the already approved Aerolizer is a single-dose delivery device.

A total of eight clinical studies were submitted with the original NDA, and one long-term safety study (603) was submitted in the 4-month safety update. The most important of these were the two dose-ranging studies (601 and 602), the two pivotal clinical studies in adults and adolescents

(2302 and 2303), and the pivotal study in pediatric patients aged 5 to 12 years (604). Four additional studies were submitted in support of safety: 1) a 12-week multicenter trial intended to demonstrate non-inferiority of formoterol delivered by the MDDPI versus formoterol delivered by the Aerolizer device (605); 2) a small safety/tolerability study examining the effects of Foradil Aerolizer, 24mcg BID, on glucose control in 17 type 2 diabetic patients (2301); 3) a small active controlled safety/tolerability study examining the effects of Foradil Aerolizer 36mcg TID in 16 asthma patients (701); 4) a 12-month open-label safety study (603). The clinical program is described in detail in the Medical Officer Reviews performed by Richard Nicklas, M.D.

Two pivotal safety and efficacy studies were performed in adults and adolescents aged 13 years and older (Studies 2302 and 2303). These two studies supported the efficacy of Foradil Certihaler as a bronchodilator in asthmatic patients aged 13 years and older. In both studies, Foradil Certihaler was statistically superior to placebo on the primary endpoint, change from baseline FEV_1 $AUC_{0\text{-}12\ hours}$ after 12 weeks of treatment. The secondary endpoints generally served to support efficacy. One pivotal safety and efficacy study was performed in asthmatic children aged 5-12 years (Study 604). The results of this study support the safety and efficacy of Foradil Certihaler 10mcg BID as a bronchodilator in asthmatic patients aged 5-12 years, based on statistical superiority over placebo on the primary endpoint, FEV_1 $AUC_{0\text{-}12\ hours}$ ($p=0.01$).

The safety database provided with the application was sufficient to allow adequate estimation of the safety profile of this drug product. In addition, given that the systemic exposures using the Aerolizer and the Certihaler devices are not substantially different, the safety data used to support approval of the Aerolizer product can be used as additional support of the current application. The safety data did not suggest a specific safety concern with this product. The incidence of certain adverse events that might be expected with a $beta_2$-agonist, such as tachycardia, palpitations, and tremor, were somewhat more frequent among patients treated with Foradil Certihaler than those treated with placebo. The most prominent of these was tremor, which occurred in 7% of patients treated with Foradil Certihaler and 1% of placebo patients. Of note, tremor was also less common in the Foradil Aerolizer (3%) and albuterol MDI (1%) groups.

On October 17, 2003, the Division took an Approvable action on the application. 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. The Applicant's responses to these deficiencies at the time were reviewed by the CMC Reviewer, Dr. Craig Bertha, and found to be acceptable. However, 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. For this reason, the October 17, 2003, action letter instructed the Applicant to provide evidence to demonstrate that design modifications (manufacturing) successfully corrected the problems. In b(4)

order to address this issue, the Applicant performed and submitted the results of four studies in a Complete Response dated June 24, 2004. Two of these were "simulated patient use" studies (Studies 8521-19, and 8521-21), and two were patient use studies (Studies 2304, and 2306). While these studies addressed the device performance issues, important questions were raised in the patient use studies regarding the ability of patients to operate the device successfully. The fact that most of the devices that patients reported to be problematic were found to function normally in *in vitro* testing likely indicated that the devices themselves were not malfunctioning. Rather, the failure was in the ability of patients to understand the directions for use, and implement them effectively. Thus, in the Approvable action taken by the Division on December 14, 2004, in order to gain approval for this drug product, the Applicant was to develop a more effective patient education program about the use of the device, including instructions for use, and then demonstrate that patient difficulty in using the Certihaler device can be minimized by use of this improved patient education about the use of the device. The results of that study (study F2309) were submitted in the Complete Response dated October 10, 2005. In that study, the percentage of patients who felt that they did not receive a dose from the Certihaler was 3.9% compared to 14-17% in previous patient use studies. It showed that while the Certihaler may be cumbersome to use for some select individuals, that the difficulties encountered by patients in previous patient use studies could be mostly overcome with more effective instruction.

However, late in the review cycle, post-marketing reports from Germany of inadvertent overdosing by patients using the Foradil Certihaler, apparently due to unintended misuse of the product, were received. As a result, the FDA stated in the Approvable Letter dated April, 11, 2006, that the Certihaler be modified in such a way that mishandling leading to inadvertent overdosing could no longer occur. Data supplied with the current Complete Response dated June 15, 2006, regarding structural changes made to the device have been reviewed by the CMC reviewers and found to be acceptable from the CMC perspective to substantially mitigate the risk of overdosing due to unintended misuse and have lead to a recommendation of Approval from the CMC reviewers.

1.3.2 Efficacy

The data reviewed as part of this Complete Response did not assess efficacy. See the brief summary above and the initial review of NDA# 21-592 by Richard Nicklas, MD, dated October 7, 2003 for the full evaluation of efficacy.

1.3.3 Safety

The previous two Complete Responses of this NDA dated October 10, 2005, and June 15, 2006 have addressed safety concerns regarding patient use of the Foradil Certihaler. Study F2309 was performed to address whether patient difficulty in using the Foradil Certihaler device observed in previous studies could be minimized by the use of improved patient education materials about how to use the device. This study was submitted in the October, 2005 Complete Response and reviewed previously (clinical review by Anthony Durmowicz, M.D., dated April, 2006). In that study, the percentage of patients who felt that they did not receive a

dose from the Certihaler was 3.9% compared to 14-17% in previous patient use studies. It showed that while the Certihaler may be cumbersome to use for some select individuals, that the difficulties encountered by patients in previous patient use studies could be mostly overcome with more effective instruction.

The Complete Response dated June 15, 2006 was in response to an Approvable Letter that required the Certihaler be modified in such a way that mishandling leading to inadvertent overdosing could no longer occur. This requirement was the result of post-marketing reports from Germany of inadvertent overdoses of Foradil from the Certihaler apparently due to unintended misuse of the product. Those reports had lead to a voluntary recall of the Certihaler from Germany and Switzerland on January 23, 2006, approximately four months after the Certihaler was marketed in those countries. Data supplied with this submission regarding structural changes made to the device are acceptable from the CMC perspective to substantially mitigate the risk of overdosing due to unintended misuse and have lead to a recommendation of Approval from the CMC reviewers.

7 INTEGRATED REVIEW OF SAFETY

The original clinical review of safety was performed by Richard Nicklas, M.D. at the time of the original NDA submission (document date December 17, 2002) and may be found in his review dated October 07, 2003. Additional safety reviews were performed at the time of Complete Responses (document dates June 24, 2004, and October 10, 2005, by Richard Nicklas, M.D. and Anthony Durmowicz, M.D., respectively). The review of safety for this, the third Complete Response to reviews of this NDA, includes a safety update from clinical trial F2402 which was ongoing at the time of the October 10, 2005 Complete Response and is currently in the reporting phase. The cutoff dates for inclusion of data in this report are August 1, 2005 through May 10, 2006

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.9 Safety Update

A safety update has been submitted that includes a summary of safety data that has become available since the safety update submitted with the previous Complete Response on October 10 2005. The cutoff dates for inclusion of data in this report are August 1, 2005 through May 10, 2006, inclusive. The update includes:

- Additional information from Study F2402, a randomized, multi-center, placebo-controlled study in 844 adults with COPD to compare the efficacy and safety of formoterol via the Certihaler, tiotropium via the HandiHaler, and tiotropium via the HandiHaler in combination with formoterol via the Certihaler administered to patients with stable COPD for 24 weeks. This study was ongoing at the time of the October 2005 safety update and is now in the reporting phase.

- Narratives for SAEs from the post-marketing experience in Germany and Switzerland where inadvertent overdosing of Foradil delivered by the Certihaler were reported are provided.
- Narratives and deaths reported from a post-marketing surveillance in Germany.

An in-depth review of the safety update follows below. In summary, review of the safety update did not suggest any new safety signals for the Foradil Certihaler.

Deaths

There have been 2 deaths reported in this study. The first was reported in the previous Safety Update and was that of a 68 year old male (patient 0117/00009, Netherlands) who was discontinued from the study after 1 month of treatment (formoterol + tiotropium group) due to dyspnea attributed to a COPD exacerbation. However, the patient was subsequently diagnosed with bronchial carcinoma localized to the mediastinum and right bronchus and died approximately 4 weeks after discontinuing from the study.

The second death was that of 71 year old male (patient 0054/00019) with a history of COPD, depression, benign prostatic hypertrophy, and radicular pain for which he was taking amitriptyline, alfuzosin, aspirin, and diclofenac. He was randomized to the placebo group and received his first dose of study medication on April 5, 2005. On [redacted] (study day 156) he fell while walking and hit his head resulting in cerebral bleeding. He died on the day of the accident. An autopsy was not performed. b(6)

Serious Adverse Events

There have been a total of 38 non-fatal SAEs reported for Study F2402, 8 in the formoterol treatment group, 11 in the placebo group, 10 in the tiotropium group, and 9 in the formoterol + tiotropium group. The seven SAEs listed below are new SAEs that were reported after the deadline for the previous safety update.

In the formoterol group:

- one patient experienced carotid artery stenosis

In the tiotropium group:

- one patient experienced COPD exacerbation
- one patient experienced myocardial ischemia

In the formoterol plus tiotropium group:

- one patient experienced myocardial ischemia
- one patient experienced COPD exacerbation

In the placebo group:

- one patient experienced gastrointestinal inflammation

- one patient experienced metastases to bone (primary site of cancer not reported)

The most frequently reported SAE during the entire study was for COPD (worsening/exacerbation) which was reported for 1, 3, 6, and 3 patients in the formoterol, placebo, tiotropium, and formoterol + tiotropium treatment groups, respectively. Other SAEs are consistent with an older population with long smoking histories and other concomitant illnesses and include bronchial carcinoma (5), angina/chest pain (3), coronary artery disease/syndrome (3), and CVA (2) *[Post-text table 2-2, Update of Clinical Safety-Appendix 1]*. No specific SAEs were reported substantially more frequently in any treatment group.

Discontinuations Due to Adverse Events

Adverse events leading to study discontinuation were experienced during the study by 6 patients in the formoterol treatment group, 8 in the placebo group, 11 in the tiotropium treatment group, and 8 in the formoterol + tiotropium treatment group. The most frequently reported AE leading to study discontinuation was COPD (worsening/exacerbation), which was reported for 2 formoterol, 2 placebo, 5 tiotropium, and 2 formoterol + tiotropium treated patients.

Adverse Events

The most frequently occurring AEs (≥1% of patients in any treatment group) are summarized by MeDRA preferred term in the following table.

Number (%) of patients with most frequent AEs (1% or higher in any treatment group) *[Table 2-2, Update of Clinical Safety, 05/24/2006]*

	Formoterol n (%)	Placebo n (%)	Tiotropium n (%)	Tio + For n (%)
Patients studied				
Total no. of patients	210 (100)	209 (100)	221 (100)	207 (100)
Any adverse event	72 (34.3)	82 (39.2)	79 (35.7)	70 (33.8)
Adverse event (MedDRA preferred term)				
Chronic obstructive pulmonary disease	20 (9.5)	34 (16.3)	28 (12.7)	16 (7.7)
Nasopharyngitis	15 (7.1)	11 (5.3)	11 (5.0)	13 (6.3)
Hypertension	4 (1.9)	5 (2.4)	5 (2.3)	3 (1.4)
Back pain	3 (1.4)	3 (1.4)	1 (0.5)	3 (1.4)
Bronchitis	3 (1.4)	1 (0.5)	4 (1.8)	1 (0.5)
Cough	3 (1.4)	4 (1.9)	5 (2.3)	5 (2.4)
Hypercholesterolemia	3 (1.4)	1 (0.5)	1 (0.5)	0
Influenza	3 (1.4)	5 (2.4)	1 (0.5)	2 (1.0)
Respiratory tract infection	3 (1.4)	3 (1.4)	4 (1.8)	1 (0.5)
Tremor	3 (1.4)	0	2 (0.9)	1 (0.5)
Dyspnea	2 (1.0)	2 (1.0)	1 (0.5)	3 (1.4)
Dyspnea exacerbated	2 (1.0)	3 (1.4)	1 (0.5)	0
Influenza like illness	2 (1.0)	3 (1.4)	1 (0.5)	2 (1.0)
Upper respiratory tract infection	2 (1.0)	3 (1.4)	0	1 (0.5)
Headache	1 (0.5)	0	0	4 (1.9)
Pyrexia	1 (0.5)	2 (1.0)	3 (1.4)	1 (0.5)
Diabetes mellitus non-insulin-dependent	0	0	0	3 (1.4)
Fall	0	3 (1.4)	1 (0.5)	1 (0.5)
Edema peripheral	0	0	0	4 (1.9)
Sinusitis	0	3 (1.4)	4 (1.8)	3 (1.4)
Tachycardia	0	1 (0.5)	4 (1.8)	1 (0.5)

A subject with multiple occurrences of an AE was only counted once for that AE.

There were no meaningful increases in AEs in formoterol-receiving treatment groups compared to tiotropium-only and placebo groups. Formoterol-receiving groups had fewer AEs in the respiratory, thoracic, and mediastinal disorder system organ class due to fewer AEs reported for COPD. There were no increased instances of AEs commonly reported for beta-2 agonists in the formoterol-receiving treatment groups such as tremor, increased serum glucose, palpitations, or ECG changes.

Adverse Events Due to Inadvertent Overdosing

Correspondences from Novartis on February 2 and March 1, 2006 notified the FDA that in January and February, 2006 there were 5 post-marketing CIOMS adverse reaction reports from Germany in which patients had inadvertently received overdoses of Foradil from the Certihaler which had been marketed in Germany and Switzerland since September 2005. Adverse reactions to the overdoses were serious in several of the cases with tachycardia to a heart rate of 150, hypertension to 200 mmHg (systolic), and tremor and insomnia lasting up to several days. All

subjects recovered from the overdoses. Narratives for these spontaneous case reports were included in this safety update [Update to Clinical Safety-Appendix 2].
Reviewer's Comment: All the submitted information has already been reviewed. The overdoses ultimately lead to a voluntary recall of the Certihaler from the German and Swiss markets on 1/23/06 and withholding of Approval of the Foradil Certihaler from the United States market.

Adverse Events from Post-Marketing Surveillance Study

A post-marketing surveillance study which enrolled 5280 patients was conducted by Novartis in Germany from September 2005 through March 2006. During that time six SAEs, including two deaths, were reported as of May 10, 2006. The deaths were listed as due to a myocardial infarction in one patient and from gastric ulcer hemorrhage and cardiac failure in the other patient. The four non-fatal SAEs were reported as myocardial infarction, bacterial infection, pneumonia, and a cholecystectomy.
Reviewer's Comment: The usefulness of this data is very limited as all patients were being treated with the Foradil Certihaler. The SAEs, including deaths, reported from the surveillance study are not uncommon for an older population with COPD and other significant concomitant illnesses.

9 OVERALL ASSESSMENT

9.2 Recommendation on Regulatory Action

The clinical recommendation is for Approval for the Foradil Certihaler MDDPI. This decision is made on the basis that recent structural modifications to the Certihaler MDDPI delivery device made as a result of post-marketing reports of inadvertent overdosing of formoterol by patients in Germany are felt to be sufficient by the CMC review team to sufficiently mitigate the risk of overdosing due to unintended misuse of the device by patients (see CMC review #6 by Craig Bertha, Ph.D., dated July 05, 2006). In addition, during the previous Complete Response dated October 10, 2005, Novartis had addressed clinical concerns regarding the ability of patients' understanding of how use the device appropriately by extensively revising the patient instructions for use of the Certihaler, including figures, in order to improve patient comprehension and conducted a patient use study (F2309) which demonstrated improved ability of patients to use the Certihaler.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

In addition to the recent structural modifications of the device to prevent inadvertent overdosing due to unintended misuse of the device, the risk management plan for patient support upon approval and commercialization of the Certihaler mimics the patient support that was available in the patient use study (F2309) which demonstrated improved ability of patients to use the

Certihaler. These include revised instructions for use now contained in the Medication Guide, provision of a toll free number and web site to call or access if difficulties arise in using the device, and access to a Certihaler instructional video (in DVD or VCR format).

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments

9.3.3 Other Phase 4 Requests

In the approvable letter of October 17, 2003, the Division recommended the applicant establish a more extensive database to further evaluate the Foradil Certihaler in adolescent and elderly populations.

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9.4 Labeling Review

Much of the labeling for the Foradil Certihaler had been previously agreed upon during the previous three review cycles. One issue not previously agreed upon was the addition of a new Boxed Warning and a Medication Guide to alert health care professionals and patients to recent findings that LABAs may increase the chance of severe asthma episodes, and death in patients that use them. Novartis initial response was a refusal to include the Boxed Warning and Medication Guide. However, after negotiation of an appropriate label for the other marketed LABA, salmeterol, as well as for the single-dose formoterol DPI marketed by Novartis (Foradil Aerolizer), Novartis agreed to submit a revised label that would include a Boxed Warning and Medication Guide. In this complete response, the proposed label now includes a Boxed Warning and Medication Guide. Labeling for the Certihaler will be much the same as that for the Aerolizer in order to ensure consistency of the label across Novartis' formoterol portfolio.

The Division of Surveillance, Research, and Communication Support has developed a proposed Medication Guide for the Certihaler utilizing the product patient instruction sheet and incorporating the added warnings required for LABAs with an indication to treat asthma (Consults dated January 30, 2006 and August 2, 2006, by Jeanine Best).

The Division of Medical Errors and Technical Support was also consulted to review the label and had both specific and general comments, including more detailed explanations on device use and, possibly, the need for a device redesign if confusion still exists after more detailed label changes are made (review by Kimberly Petersen, December 15, 2005). An updated consult by DMETS dated August 10, 2006, has also been completed. It reaffirms the need for detailed instructions in how to use the Certihaler, including web-based instructions.

DMETS also suggested removing the abbreviation for "long-acting beta agonist" (LABA) from the Medication Guide. The Division does not agree with this suggestion as the abbreviation LABA has become recognized by both health care providers and patients as the standard term for this class of drugs.

At the time of finalization of this review, labeling negotiations are ongoing. The primary issues are the following: 1) inclusion of a tachyphylaxis/tolerance section; 2) deletion of dose finding information from the clinical trials section; 3) deletion of information regarding diabetic patients that is not currently in the Foradil Aerolizer label; and 4) selection of the appropriate figures for the clinical trials section.

9.5 Comments for the Action Letter

There are no clinical comments for the action letter at this time.

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/s/

Anthony Durmowicz
11/15/2006 08:08:19 AM
MEDICAL OFFICER
I fixed it

Sally Seymour
11/15/2006 08:16:47 AM
MEDICAL OFFICER
I concur

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-592
Submission Code	N000
Letter Date	October 10, 2005
Stamp Date	October 11, 2005
PDUFA Goal Date	April 11, 2006
Reviewer Name	Anthony G. Durmowicz MD
Review Completion Date	April 10, 2006
Established Name	formoterol fumarate
(Proposed) Trade Name	Foradil Certihaler
Therapeutic Class	beta agonist bronchodilator
Applicant	Novartis
Priority Designation	Standard
Formulation	Certihaler (inhalation powder)
Dosing Regimen	10 µg bid
Indication	maintenance treatment of asthma and the prevention of bronchospasm
Intended Population	adults and children 5 years and older

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The recommendation is for an approvable action for the Foradil Certihaler MDDPI. While the patient instructions for use, including figures, have been extensively revised in order to improve patient comprehension and a patient use study (F2309) has been conducted which demonstrated improved ability of patients to use the Certihaler, recent post-marketing reports from Germany of serious overdoses of formoterol due to device failures raise serious safety concerns regarding both the proper use of the device and the device itself. On the basis that mishandling of the device could result in serious or even fatal overdoses of formoterol in a population (elderly COPD) particularly sensitive to adverse events such as arrhythmias or stroke as a result of excess beta receptor stimulation, the applicant must take steps to redesign the internal components of the device in such a way that such mishandling could either no longer occur or if it is still possible, that it would not lead to the events that could cause overdosing. The device cannot be approved until such device failures are resolved.

Another deficiency is that the proposed labeling by Novartis remains inadequate. In response to recent findings that LABAs may increase the chance of severe asthma episodes, and death when those episodes occur, Novartis had been asked by the FDA to update their existing LABA product (Aerolizer and Certihaler) labels with a new Boxed Warning and a Medication Guide to alert health care professionals and patients. Novartis' initial response was a refusal to include the warnings and Medication Guide. However, after negotiation of an appropriate label for the other marketed LABA, salmeterol, that included the Boxed Warning and Medication Guide, Novartis agreed to submit a revised label. The latest proposed labeling for the Certihaler dated March 30, 2006 still lacks a Medication Guide and is not reviewed in this document. The requirement for the Medication Guide was again conveyed to the Sponsor. Labeling negotiations are also underway for the Foradil Aerolizer, a single-dose DPI with the same active ingredient as the Certihaler (the LABA, formoterol). Labeling for the Certihaler will be much the same as that for the Aerolizer in order to ensure consistency of the label across Novartis' formoterol portfolio.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The risk management plan initially submitted was a plan for patient support upon approval and commercialization of the Certihaler that mimicked the patient support that was available in Study F2309, which is reviewed below. However, subsequent to the reports of inadvertent overdoses of formoterol with the marketed Certihaler device in Germany, Novartis stated they would submit a revised risk management plan to somehow deal with the overdose issue despite being informed by DPAP during a telephone conference on March 6, 2006 that the device needs to be modified in such a way that mishandling leading to inadvertent overdosing

could either no longer occur or if it is still possible, that it would not lead to overdosing and that revising the patient instructions for clarity would not be sufficient. On March 30, 2006, Novartis submitted a plan to redesign aspects of the Certihaler in order to prevent inadvertent overdosing.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

In the approvable letter of October 17, 2003, the Division recommended the applicant establish a more extensive database to further evaluate the Foradil Certihaler in adolescent and elderly populations.

b(4)

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This is the third 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,"

b(4)

Previously, on October 17, 2003, and December 14, 2004, the Division took Approvable actions on the application and noted requirements to address CMC and device malfunction issues (October, 2003 letter) including the fact that a substantial number of patients in the clinical program were not able to operate the Certihaler device successfully despite the finding on subsequent in vitro testing that the devices themselves were not malfunctioning (December, 2004 letter). To support approval, the Sponsor was required to develop improved mechanisms to instruct patients in the use of the device and demonstrate in a patient use study that these improved mechanisms were effective. Thus, the main components of the Sponsor's complete response dated October 10, 2005, and on which this review focuses, are revised instructions for the use of the device and the clinical study report for Study F2309, a 3-week multicenter study investigating patient use and functionality of the Foradil Certihaler device in patients with asthma. The evaluations of the safety and efficacy of the Foradil Certihaler (formoterol fumarate inhalation powder) by Richard Nicklas MD, other than the patient use issue addressed in this review, are contained in the initial NDA review and a subsequent review of a previous Complete Response that addressed device malfunction problems

submitted June 24, 2004 by the Sponsor and are dated October 7, 2003 and December 10, 2004, respectively. A brief summary of those findings follows.

NDA# 21-592 was originally submitted by Novartis on December 18, 2002. The NDA was submitted 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] b(4)

The drug substance, formoterol fumarate, is already approved in the US as a single dose dry powder inhaler called the Foradil Aerolizer (Novartis). The Foradil Aerolizer 12mcg BID was approved for asthma on February 16, 2001, (NDA 20-831) and for COPD on September 25, 2001 (NDA 21-279). This NDA is for the approval of the Foradil Certihaler inhalation powder device. The Certihaler is a multi-dose dry powder inhaler whereas the already approved Aerolizer is a single-dose delivery device.

A total of eight clinical studies were submitted with the original NDA, and one long-term safety study (603) was submitted in the 4-month safety update. The most important of these were the two dose-ranging studies (601 and 602), the two pivotal clinical studies in adults and adolescents (2302 and 2303), and the pivotal study in pediatric patients aged 5 to 12 years (604). Four additional studies were submitted in support of safety: 1) a 12-week multicenter trial intended to demonstrate non-inferiority of formoterol delivered by the MDDPI versus formoterol delivered by the Aerolizer device (605); 2) a small safety/tolerability study examining the effects of Foradil Aerolizer, 24mcg BID, on glucose control in 17 type 2 diabetic patients (2301); 3) a small active controlled safety/tolerability study examining the effects of Foradil Aerolizer 36mcg TID in 16 asthma patients (701); 4) a 12-month open-label safety study (603). As mentioned above, the clinical program is described in detail in the Medical Officer Reviews performed by Richard Nicklas, MD.

Two pivotal safety and efficacy studies were performed in adults and adolescents aged 13 years and older (Studies 2302 and 2303). These two studies supported the efficacy of Foradil Certihaler as a bronchodilator in asthmatic patients aged 13 years and older. In both studies, Foradil Certihaler was statistically superior to placebo on the primary endpoint, change from baseline FEV_1 $AUC_{0\text{-}12\ hours}$ after 12 weeks of treatment. The secondary endpoints generally served to support efficacy. One pivotal safety and efficacy study was performed in asthmatic children aged 5-12 years (Study 604). The results of this study support the safety and efficacy of Foradil Certihaler 10mcg BID as a bronchodilator in asthmatic patients aged 5-12 years, based on statistical superiority over placebo on the primary endpoint, FEV_1 $AUC_{0\text{-}12\ hours}$ ($p=0.01$).

The safety database provided with the application was sufficient to allow adequate estimation of the safety profile of this drug product. In addition, given that the systemic exposures using the Aerolizer and the Certihaler devices are not substantially different, the safety data used to support approval of the Aerolizer product can be used as additional support of the current application. The safety data did not suggest a specific safety concern with this product. The

incidence of certain adverse events that might be expected with a beta$_2$-agonist, such as tachycardia, palpitations, and tremor, were somewhat more frequent among patients treated with Foradil Certihaler than those treated with placebo. The most prominent of these was tremor, which occurred in 7% of patients treated with Foradil Certihaler and 1% of placebo patients. Of note, tremor was also less common in the Foradil Aerolizer (3%) and albuterol MDI (1%) groups.

On October 17, 2003, the Division took an Approvable action on the application. 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. The Applicant's responses to these deficiencies have been reviewed by the CMC Reviewer, Dr. Craig Bertha, and found to be acceptable. However, 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. For this reason, the October 17, 2003, action letter instructed the Applicant to provide evidence to demonstrate that design modifications [redacted] manufacturing) successfully corrected the problems. In order to address this issue, the Applicant performed and submitted the results of four studies in a Complete Response dated June 24, 2004. Two of these were "simulated patient use" studies (Studies 8521-19, and 8521-21), and two were patient use studies (Studies 2304, and 2306). While these studies addressed the device performance issues, important questions were raised in the patient use studies regarding the ability of patients to operate the device successfully. The fact that most of the devices that patients reported to be problematic were found to function normally in *in vitro* testing likely indicated that the devices themselves were not malfunctioning. Rather, the failure was in the ability of patients to understand the directions for use, and implement them effectively. Thus, in the Approvable action taken by the Division on December 14, 2004, in order to gain approval for this drug product, the Applicant was to develop a more effective patient education program about the use of the device, including instructions for use in the package insert, and then demonstrate that patient difficulty in using the Certihaler device can be minimized by use of this improved patient education about the use of the device. The revised patient instructions and patient use study 2309 are the subjects of this review.

Also, in the time since the last consideration of this NDA, the Agency has learned more concerning the safety of long-acting beta agonists (LABAs). In response to findings that LABAs may increase the chance of severe asthma episodes, and death when those episodes occur, the manufacturers of LABAs, including Novartis, have been asked to update their existing product labels with a new Boxed Warning and a Medication Guide to alert health care professionals and patients. This issue is further discussed in the Labeling Review, page 23.

1.3.2 Efficacy

The study reviewed as part of this Complete Response (Study F2309) did not assess efficacy. See the brief summary above and the initial review of NDA# 21-592 by Richard Nicklas, MD, dated October 7, 2003 for the full evaluation of efficacy.

1.3.3 Safety

Study F2309 was performed to address whether patient difficulty in using the Foradil Certihaler device observed in previous studies could be minimized by the use of improved patient education materials about how to use the device. The variables related to device use were the number and percentage of patients: (1) failing treatment due to inability to use the device, (2) who had one unscheduled visit and completed the study, (3) who contacted the study center by telephone at least once because of trouble taking dose from the device, (4) who contacted the study center by telephone at least once because of trouble taking dose from the device but did not need to go to the center, and (5) with at least one failed dose. In addition, a distribution of the patients with 1, 2, 3 or >3 failed doses was presented. In study F2309, the percentage of patients who felt that they did not receive a dose from the Certihaler was 3.9%. compared to 14-17% in previous patient use studies. While the Certihaler may be cumbersome to use for some select individuals, study F2309 did demonstrate that the difficulties encountered by patients in previous patient use studies could be mostly overcome with more effective instruction.

There were no deaths or serious adverse events recorded in the study. Thirty one patients (20%) experienced at least one AE during the study. The most common AEs were those typically seen with the use of sympathomimetic drugs such as B-2 agonists: headache (5 patients), dizziness, tremor and nausea (each of which were reported for 3 patients). One patient reported episodes of severe dizziness and shortness of breath, while all other patients had adverse events of mild or moderate severity.

Recently, in response to post-marketing reports from Germany of inadvertent overdoses of Foradil from the Certihaler, there was a voluntary recall of the Certihaler on 1/23/06. The Certihaler was launched in Germany and Switzerland in September, 2005. Novartis believes that patient misuse of the Certihaler was the cause of the overdoses and that a modification of the patient instruction leaflet similar to the revised patient instruction sheet submitted as a part of this submission, would resolve the overdose issue. The DPAP believes the device needs to be modified in such a way that mishandling leading to inadvertent overdosing could either no longer occur or if it is still possible, that it would not lead to overdosing. This issue is discussed further in the Safety Update, page 19.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Discussion of design of patient use study F2309
This study was designed to collect information on patient use of the Certihaler device in a real life environment. In real life, a patient who is first considered for treatment with the Certihaler will be given the instructions for use and trained by a health care provider. If the patient shows the ability to use the Certihaler, it will be dispensed for home use. In discussion of the design of the study with the Division, it was considered adequate to treat patients in an open-label fashion for a period close to the 'life' of the device, approximately 21 days in a situation that reflects the real-life post approval environment. The 21-day period was the same time period used in the previous Certihaler patient use studies CFOR258F2304 and CFOR258F2306.

Study F2309 Protocol summary
Study F2309 entitled, a 3-week multicenter study investigating patient use and functionality of the Foradil® Certihaler® device in patients with asthma, was conducted to address whether patient difficulty in using the Foradil Certihaler device observed in previous studies F2304 andF2306 could be minimized by the use of improved patient education and instruction materials. This was an open-label, single group study of 3 weeks treatment duration in approximately 150 patients aged > 5 years with a current diagnosis of asthma. At Visit 1 patients read the 'Certihaler Directions for Use' and were given a trainer (empty) inhaler to practice with. Patients were then observed while administering their first dose of drug from a functional Certihaler. Patients whose eligibility was confirmed by the successful use of at least one dose from the Certihaler entered the 3-week treatment period and received formoterol 10 µg bid delivered by the Certihaler device. Patient daily diary information and patient resource use information were collected during the 3-week treatment period. Devices suspected of having problems were subjected to functionality assessment.
Reviewer's Comment: There were no screening failures due to the inability to take a dose at screening visit (visit 1). A total of 24 devices were analyzed after the 3 week treatment period. No failure was observed in any of the devices. Actuation flow rate was between </= 35 liters/minute for 23 of the 24 and > 40 to 45 liters/minute for one device.

Patients were instructed that if they were unable to receive a dose at any time during the study as indicated by the air holes not opening and/or the dose counter not counting down when a regularly scheduled dose was to be taken, then they should try to take the dose again. If they were then unable to take the dose as indicated by the "air holes/dose counter" criterion above, then the patient was to review the 'Certihaler Directions for Use' and try to use the inhaler again. If they were still unable to take the dose then they should perform one or more of the following actions which utilize the resources available for patient use:

1. call a toll free number to receive instructions for patient use of the Certihaler,
2. access a web site which contains the instructional video on Certihaler use
3. play the instructional video on Certihaler use with a DVD or VCR player.

After using any or all of these resources, they should have tried to take the dose again. If they were still unable to take the dose then they were instructed to call the study center as soon as possible and speak with the study staff for advice. The coordinator would have assisted the patient in taking a dose. If this did not resolve the problem then the patient should immediately arrange a visit to the study center at the earliest time possible. Patients were only allowed to attend one unscheduled visit because of an inability to use the device. If a patient was unable to use the device after attending one unscheduled visit, the patient would have been discontinued from the study.

Patient resources
At Visit 1 patients were provided with an Inhaler Instructions Kit containing the 'Certihaler Directions for Use', information on a toll free number, information on a web site, and a Certihaler instructional video (in DVD and VCR format).

The Certihaler instructional video presented the Directions for Use in a short video format. Patients who watched the video because they were having difficulty using the device were asked to record this information in their patient diary.

The internet website provided access to the Certihaler instructional video, the Directions for Use and further information about Foradil. All of the information available on the website was identical to what was provided in the Inhaler Instructions Kit. To access the website a patient entered their center number, patient number and medication number. This information ensured that the website was being accessed by a patient in the study and also allowed data to be captured on individual utilization of the website. However if a patient did not enter the correct information, access would still be given.

Patients having difficulty using the Certihaler could also call a toll free number providing live help 24 hours a day during the study period. The operator assisted the patient in using the Certihaler to take the dose using the Directions for Use. Operators were provided with a script based on the Certihaler Directions for Use that they were to follow in order to assist patients in taking a dose from the inhaler.

Study population
Approximately 150 patients aged 5 years or older with asthma who were assigned to a single open-label treatment group (only patients who received study drug were included in the study population).

Inclusion Criteria

1. Cooperative male and female outpatients who were aged 5 years or older.
2. Patients with a current diagnosis of asthma, and who met the following criteria:
   a. received asthma treatment for at least the past 2 months
   b. whose FEV1 at Visit 1 was >40% of the predicted normal value for the patient when not medicated by long or short-acting bronchodilators. The criterion for FEV1 must have been demonstrated after a washout period during which:

- no short-acting B2-agonist was inhaled for at least 6 hours prior to the evaluation
- no long-acting B2-agonist was inhaled for at least 12 hours prior to the evaluation (including any formulation of Serevent, Foradil, or Advair/Seretide)
- no short-acting anticholinergic (i.e. ipratropium bromide or oxitropium) was inhaled for at least 8 hours prior to the evaluation
- no long-acting anticholinergic (i.e. tiotropium bromide) was inhaled for at least 48 hours prior to the evaluation
- no oral, parenteral or nebulized B2-agonist or oral anticholinergic was taken within 48 hours prior to Visit 1.
- no oral corticosteroids for the treatment of asthma deterioration/exacerbation within 3 months prior to Visit 1

c. had a documented FEV1 reversibility of at least 12% over baseline value following administration of a bronchodilator (or a > 12% increase in FEV1 over their baseline value within 30 minutes after inhalation of up to 360 µg (4 puffs) of albuterol at Visit 1).

d. were appropriately treated for their asthma condition (e.g. according to the step wise approach detailed in the GINA guidelines)

3. Patients who were not of adult age must have been able to give their assent to participate in the trial and must have had a parent or legal guardian capable of giving a full informed consent on their behalf. Adult patients must have been capable of giving a full informed consent.

4. Patients who must have been able to read and write in English. Pediatric patients must have had a caregiver who could read and write in English and who could assist them with completing the patient diary.

5. Patients who were capable of understanding the directions for device usage, evaluating device function and completing the patient diary.

6. Patients who demonstrated at Visit 1 the ability to use and activate an empty Certihaler training device and take a dose from a Certihaler containing study medication.

Exclusion Criteria

1. Pregnant women, nursing mothers, or females of childbearing potential, who did not use a reliable contraceptive method. Patients who became pregnant during the course of the trial must have been discontinued immediately from study therapy and the pregnancy followed as an adverse event.

2. Patients with a clinically significant condition which included, but was not limited to: hypokalemia, significant cardiovascular disease, uncontrolled hypertension, uncontrolled hyper - or hypothyroidism, hyperadrenergic states, and uncontrolled diabetes. Also patients with a history of noncompliance to medical regimens or who were considered potentially unreliable, including patients who were alcoholic or had a history of drug abuse or neurological disorders; or any condition that could compromise the patient's safety or compliance, or interfere with any protocol evaluations, or preclude completion of the trial.

3. QTc above 450 milliseconds for males or 470 milliseconds for females, or any findings on the screening ECG that in the opinion of the investigator presented a safety hazard for continuation in the study.
4. Patients with a history of malignancy and/or who received treatment for malignancy over the past 5 years (with the exception of basal cell carcinoma).
5. Patients who had a known history of untoward reactions to sympathomimetic amines or to inhaled medications or to any of the individual components in those therapies.
6. Patients who were hospitalized or had an emergency room treatment for an asthma exacerbation within six months prior to Visit 1.
7. Patients who received treatment with any investigational agent within 30 days prior to Visit 1.
8. Patients who took terfenadine, ebastine, or any anti-histamine labeled as potentially impacting QTc in the 4 days (96 hours) prior to Visit 1.
9. Patients treated with non-potassium sparing diuretics, beta-blocking agents, or cardiac anti-arrhythmics which may potentially prolong the QTc interval.
10. Patients treated with tricyclic anti-depressants, or monoamine oxidase inhibitors.
11. Patients who started treatment with or increased the dosage of an SSRI within one month prior to Visit 1, who received a dosage higher than that allowed in the package insert, or who had a significant cardiac disorder or QTc prolongation.
12. Patients who were enrolled in studies CFOR258F2304 or CFOR258F2306, or who had any experience using the Certihaler device.

Interruption or discontinuation of treatment

Patients who prematurely discontinued study medication attended a scheduled visit as soon after the last dose of study medication as possible, at which all assessments scheduled for the final visit were performed. At a minimum, all patients who prematurely discontinued study medication, including those who refused to return for a final visit, were to be contacted for safety evaluations during the 30 days following the last dose of study medication.

Patients could withdraw from the study or be withdrawn at the discretion of the investigator at any time. Patients could be withdrawn from the study prematurely for the following reasons: adverse events, abnormal laboratory values, abnormal test procedure results, unsatisfactory therapeutic effect, condition no longer required treatment, protocol violation, subject withdrew consent, lost to follow-up, administrative problems, death, or patient inability to use the device.

Drug treatment

All patients received open-label formoterol 10 ug (8.5 ug emitted dose) delivered by the Certihaler device, one inhalation twice daily (one inhalation in the morning and one inhalation in the evening approximately 12 hours apart). Patients took their first dose of study medication under observation

at the study center after training in use of the device. The last dose of study medication was taken on the evening prior to Visit 2. In addition, the investigator provided albuterol MDI (90 (μg per actuation) to the patient for use as rescue medication as required.

Concomitant therapy

The use of B-2 agonists other than those provided, or oral or inhaled anticholinergics were not allowed unless considered necessary by the investigator to treat an asthma deterioration/exacerbation. Inhaled combination products containing a corticosteroid and a long-acting B-2 agonist were not allowed during the trial. Patients using a fixed corticosteroid/ long-acting B-2 agonist combination at study entry were switched to an equivalent dose of inhaled corticosteroid.

Additionally, non-potassium sparing diuretics, beta-blockers, Class I and III cardiac anti-arrhythmics with known QTc prolongation potential, tricyclic anti-depressants and monoamine oxidase inhibitors were not permitted.

Anti-inflammatory medications for asthma, including inhaled and nasal corticosteroids, inhaled cromoglycate, and leukotriene antagonists were allowed during the study, but were not permitted to be discontinued while on study. Patients on theophylline were required to maintain the theophylline level within the therapeutic range. Use of anti-histamines, other than ebastine and terfenadine or those potentially impacting QTc, was permitted.

Selective serotonin re-uptake inhibitors could not be initiated during the study and those already being taken could not have their dose increased.

Criteria for evaluation

Device use: Failed doses were identified from daily records maintained by the patients in their diaries. Patients were instructed to record the number appearing in the dose counter window after their dose on the diary card. Failed doses were tabulated when this number was the same before and after dosing. Phone Contact Reports would have been recorded when patients telephoned the clinical centers, and Certihaler Patient Use Checklists would have been recorded when the patients returned to the clinical centers for unscheduled visits. Information on the numbers of patients using the website and toll-free numbers was collected electronically by a third party.

Safety: Adverse events (which included physical examination and vital signs abnormalities during the treatment period), FEV-1 measurement and screening ECG.

Statistical methods: No attempt was made to power the study for formal testing of a hypothesis and so the sample size was chosen following discussion with the Division.

No formal statistical analysis was conducted but the data were presented descriptively. The variables related to device use were the number and percentage of patients: (1) failing treatment due to

inability to use the device, (2) who had one unscheduled visit and completed the study, (3) who contacted the center by telephone at least once because of trouble taking dose from the device, (4) who contacted the center by telephone at least once because of trouble taking dose from the device but did not need to go to the center, and (5) with at least one failed dose. In addition, a distribution of the patients with 1, 2, 3 or >3 failed doses was presented.

Adverse events were summarized by system organ class and preferred term.

Data were summarized for the ITT population, which was defined as all patients who received at least one dose of Foradil delivered by the Certihaler. The safety population was identical to the ITT population.

Results

Demographics

There were 171 patients screened in the study with 155 patients actually enrolled. Fifty-four per cent were male and 46% female. The mean age in the study was 33.6 +/- 16.1 years (range 6-73 years). The mean duration of asthma for the group was 20 +/-13 years (range 1-63 yrs). All patients in the study had experience in using an MDI and 78% had used a DPI previously. The study population was relatively well educated with 99% of adult patients being high-school graduates and 51% of adults either graduating from college or doing post-graduate course work after college.

Reviewer's Comment: The educational level was similar to that of the other patient use studies, F2304 and F2306 but likely higher than the general population.

The mean drug exposure for patients in the 21 day study was 20.9 days (range 6-23 days).

Device Use

Unscheduled visits/telephone contacts/web site or instructional video use

None of the 155 patients treated during this study attended an unscheduled visit or made telephone contact with the study center. None of the patients prematurely discontinued the study due to an inability to use the device. No patients accessed the website or toll-free number for any reason. One patient reported watching the instructional video at home on the final day of treatment, but did not report any device issues and took each dose as expected.

Patients with failed doses

Failed doses were identified from the counter numbers recorded in the patient diary, where the dose counter did not decrease as expected. Of the 155 enrolled patients in this study, 2 patients (1.3%) had failed doses and reported in their diary card that they did not receive a dose from their device. A further 4 patients (2.6%) were identified with failed doses based on their reporting of the dose counter but answered "Yes" to the question in their diary of whether they had received their doses. Of these 6 patients (3.9%) with failed doses of study medication, 5 patients had one failed dose, while 1 patient missed five failed doses. The patient who had 5 failed doses experienced them

on 4 isolated days throughout the course of the 21-day study. Post-study technical device assessment did not reveal any problems with these devices.

Patients with failed doses based on the dose counter in the patient diary (ITT population)

	Formoterol 10 ug bid			
	Week 1 N=155	Week 2 N=153	Week 3 N=153	Total N=155
Patients (%) with at least one failed dose	3(1.9)	2(1.3)	2(1.3)	6(3.9)
Number of failed doses				
Patient 0503/00010	0	1*	0	1
Patient 0503/00012	1	0	0	1
Patient 0505/00016	2*	3*	0	5
Patient 0508/00001	1	0	0	1
Patient 0508/00010	0	0	1	1
Patient 0509/00001	0	0	1	1

Note the total column is number of patients with failed doses over the entire study duration.
* In response to a question on the diary card regarding the dose the patient selected the response "missed dose" i.e. that they tried to take the dose, but could not take the dose as instructed

None of the patients with failed doses contacted the study center, nor did they utilize any additional resources. Narratives for the two patients who acknowledged missing their doses are as follows:

Patient 0503/00010 (55 years old, female, Caucasian, high school graduate) recorded in her diary that she took her doses without any indication of a problem until the morning of Day 13 when she commented that she "tried 10 times". She succeeded in taking this dose, and the comment was probably associated with the evening dose on Day 13 when she marked the diary as "missed dose" and the dose counter number remained unchanged. The patient was able to take her next dose on the morning of Day 14 and all subsequent doses thereafter without problem, recording a total of 41 doses taken in the study. The investigator later clarified in a follow-up call with the patient that on Day 13 the patient "was able to get the Certihaler open, inhaled 10 times to try to get air holes open but they wouldn't open so she gave up trying to dose any further".

Patient 0505/00016 (36 years old, male, Caucasian, college graduate) recorded in the diary on the evening of Day 4 that he missed the dose, commenting that he was "unable to open" the device. On the morning of Day 5 he recorded that he took the dose and the dose counter decreased as expected. The patient experienced further missed doses on the evening of Day 7, the morning of Day 9 and the morning and evening of Day 12, while managing to take the dose at the intervening time points. From the morning of Day 13 onwards the patient recorded no further problems in taking his doses and recorded a total of 39 doses taken in the study. The investigator recorded that "the patient reported that he completed the diary the night before Visit 2 and forgot to write down some doses". Regarding the missed doses, the investigator recorded that "on days when he [the patient] was unable to open device, he was unable to pull the cap out. Patient tried a couple of times unsuccessfully. Patient reported that he did not lay the device level on a table or counter before trying to open it. Patient reported that he did not call the site for help or use the patient resources (DVD/VHS, instructions or website) because he was at work and was too busy."

Reviewer's comment: After the instruction at the screening visit there was minimal use of any of the resources (web site, phone contact center, video use) available to patients. The above 2 patients, however, are examples of real-life situations where individuals had difficulty using the Certihaler and may have missed a dose; patient 0503/00010 gave up trying to take a dose after the air holes would not open and patient 0505/00016, although the diary may be suspect because he reported completing it the night before the second study visit, did have problems opening the

Certihaler likely due to his own impatience. These 2 individuals represent 1.3% of patients in the study

The other four patients who missed a dose according to the dose counter, but answered 'Yes' when queried as to whether they received their dose, were as follows:

Patient 0503/00012 (52 years old, male, Caucasian, some college education) recorded in the diary that he took doses normally until the evening of Day 4 when the dose counter did not decrease by one as expected. The patient commented that he "took the dose but the counter did not advance". The investigator further commented that the "airholes opened, patient feels he got the dose". The counter did decrease after the morning dose on Day 5 and decreased as expected for all subsequent doses. The patient recorded a total of 40 doses taken during the study.

Patient 0508/00001 (14 years old, male, Caucasian, current education to 8th grade or less) recorded in the diary on the evening of Day 2 that he forgot to take the dose but the dose counter was recorded as having decreased from 58 to 57 doses. The patient took all following doses normally until the morning of Day 6, when after taking the dose the dose counter was not recorded as decreasing by one, although the patient had answered that he did take the dose. The dose counter decreased as expected for all subsequent doses until the morning dose on Day 16, after which it was recorded as having decreased from 32 to 30 doses. The patient made no comment. The dose counter then decreased as expected for the patient's remaining doses and the patient recorded a total of 36 doses taken during the study.

Patient 0508/00010 (44 years old, female, Caucasian, some college education) recorded in the diary that she took all doses normally through the course of the study. However, after taking the dose on the morning of Day 16 the recorded dose counter number was the same as that before the dose was taken. The patient indicated that she had taken the dose and did not provide any further comment. The dose counter did decrease by one following the dose on the evening of Day 16 and continued to decrease as expected after all subsequent doses. The patient recorded a total of 38 doses taken during the study.

Patient 0509/00001 (52 years old, female, Caucasian, college graduate) recorded in the diary that she took all doses normally through the course of the study. However, after taking the dose on the morning of Day 21 the recorded dose counter number was the same as that before the dose was taken. The patient indicated that she had taken the dose and did not provide any further comment. The dose counter did decrease by one following the dose on the evening of Day 21, which was her last dose in the study. The investigator recorded at the end of the study the number of doses left on the device was one less than recorded in the patient diary, and commented that the patient "probably made a recording error on the diary". The patient recorded a total of 41 doses taken during the study.

Reviewer's comment: The above "failed doses" as not likely true device failures or inability to use the Certihaler but more likely the comments are the result of human error or forgetfulness.

Fifty-five of the 155 patients enrolled (35.5%) forgot to take 1 or more doses of study medication over the course of the 21-day trial. This was thought to reflect the real-life usage of the product.

Seventeen of the 155 enrolled patients (11%) reported comments in their diaries related to device use. This included 3 of the patients with failed doses, 1 patient who had a dose counter record issue and 13 patients who only made comments in the patient diary. All comments occurred at isolated time points with no indications of problems before or afterwards.

Six patients recorded the dose counter decreasing by more than one count following an inhalation. For 5 of these patients this was recorded at one time point and for 1 patient this occurred at three isolated time points. Post-study technical device assessment did not reveal any problems with these devices. A comparison of study F2309 patient use outcomes with those of the 2 previous patient use studies is shown below.

Comparison with other patient use studies

Study	F2304 N=157	F2306 N=154	F2309 N=155
• Discontinued*	2	6	0
(%)	3.2	4.5	
• Did not get all doses*	22	26	6
(%)	14.0	16.9	3.9
• Missed >1 dose*	15	18	1
(%)	9.6	11.7	0.7

* due to device issues

7.1.1 Deaths

There were no deaths that occurred in study 2309.

7.1.2 Other Serious Adverse Events

There were no serious adverse events reported in study 2309.

7.1.3 Dropouts and Other Significant Adverse Events

There were 2 patients that discontinued the study prematurely; patient 0505/00001 who dropped out on study day 6 and patient 0509/00008 who discontinued on study day 7.

7.1.3.1 Overall profile of dropouts

Patient 0505/00001 was a 41 year old male who was withdrawn from the study due to a protocol violation. The subject's ECG performed at visit 1 (screening visit) demonstrated a QTc interval > 450 milliseconds but the patient continued in the study in error. Patient 0509/00008 was a 27 year old female who withdrew from the study due to a combination of adverse events that included shortness of breath, headache, nausea, dizziness, and dry mouth.

7.1.3.2 Adverse events associated with dropouts

Patient 0509/00008 experienced a series of adverse events from July 30-31, 2005 that lead her to withdrawal from the study. These included 3 episodes of shortness of breath (1 severe, 1 moderate, 1 mild severity), 2 episodes of dry mouth (both moderate severity), 2 episodes of headache (both mild severity), 2 episodes of nausea (both moderate severity), and 1 episode of dizziness (felt to be severe). These episodes were felt to be possibly related to the study drug. She did not report any AEs prior to July 30 despite taking 12 out of a possible 13 doses of formoterol (missed the AM dose on study day 3). All AEs resolved within 8 hours after their onset without specific treatment except one episode of shortness of breath judged to be mild that began on July 31, 2005 and resolved on August 3, 2005, again without specific therapy. Significant past medical problems that were active at the start of the study were seasonal and perennial allergic rhinitis, occasional headache, intermittent body aches, and depression.

7.1.5 Common Adverse Events

7.1.5.1 Incidence of common adverse events

Thirty one patients (20%) experienced at least one AE during the study. As might be expected for this patient population, infections, nervous system disorders and respiratory events were the most frequently reported AEs during the study. The most common AEs were headache (5 patients), dizziness, tremor and nausea (each of which were reported for 3 patients). One patient reported episodes of severe dizziness and shortness of breath, while all other patients had adverse events of mild or moderate severity.

Adverse events suspected to be study drug related were reported for 7 (4.5%) patients. This included one patient (0509/00008) with nausea, dry mouth, dizziness headache and dyspnea which led to discontinuation of study medication. All of these symptoms resolved except for the dyspnea and dry mouth, which were recorded as resolved on August 3, 2005. This patient did not record any difficulties taking study medication in the patient diary.

A further patient (0501/00004) had mild insomnia suspected to be study drug related which was ongoing at the end of the study. Other AEs suspected to be study drug related resolved without treatment. These included one patient (0501/00009) with mild dysgeusia and nervousness, one patient (0503/00011) with moderate tremor, one patient (0505/00002) with mild agitation, dizziness and tremor, one patient (0505/00013) with mild nausea, muscle spasms (hand and leg cramps) headache, tremor and dizziness, and one patient (0505/00015) with mild palpitations. None of the suspected AEs were serious adverse events. The patient diary did not indicate that these patients exceeded their doses of study medication.

Reviewer's comment: Study 2309 was an open-label study so no comparison of adverse events with placebo is possible. The more common adverse events (headache, dizziness, tremor) are those generally seen in the sympathomimetic class of drugs to which Foradil belongs.

One patient had bacterial pneumonia and three patients had upper respiratory tract infections during the study. One of the patients with a respiratory tract infection recorded that she had to inhale twice to get the dose of study medication in the diary on the day before the start date of the infection, but otherwise these respiratory events did not affect the patient's ability to take their doses of study medication. FEV_1 was recorded for each patient at Day 1 and treatment endpoint and did not show a decrease suggestive of worsening lung function.

The table below lists adverse events for patients enrolled in Study 2309 according to MEDRA preferred term.

Number (%) of patients with adverse events by preferred term (Safety population)

Preferred term	Formoterol 10 ug bid (N=155) n (%)
Total number of patients with any AE	31 (20.0)
Headache	5 (3.2)
Dizziness	3(1.9)
Tremor	3(1.9)
Nausea	3(1.9)
Nasal congestion	2(1.3)
Pharyngolaryngeal pain	2(1.3)
Myalgia	2(1.3)
Nasopharyngitis	2(1.3)
Upper respiratory tract infection	2 (1.3)
Agitation	1 (0.6)
Arthralgia	1 (0.6)
Arthritis	1 (0.6)
Asthenopia	1 (0.6)
Asthma	1 (0.6)
Blood pressure increased	1 (0.6)
Dermatitis contact	1 (0.6)
Diarrhoea	1 (0.6)
Dry mouth	1 (0.6)
Dysgeusia	1 (0.6)
Dyspnoea	1 (0.6)
Excoriation	1 (0.6)
Eye haemorrhage	1 (0.6)
Folliculitis	1 (0.6)
Insomnia	1 (0.6)
Muscle spasms	1 (0.6)
Nervousness	1 (0.6)
Pain	1 (0.6)
Pain in extremity	1 (0.6)
Palpitations	1 (0.6)
Pneumonia bacterial	1 (0.6)
Postnasal drip	1 (0.6)
Postoperative infection	1 (0.6)
Post procedural pain	1 (0.6)
Vaginal mycosis	1 (0.6)
Viral upper respiratory tract infection	1 (0.6)
Vomiting	1 (0.6)

Source: Post-text table 10.1-1

7.1.7 Laboratory Findings

No laboratory evaluations were performed in study 2309

7.1.8 Vital Signs

Vital signs were taken at the screening visit (visit 1) and study completion visit (visit 2). No abnormalities in vital signs were reported as adverse events in study 2309.

7.1.9 Electrocardiograms (ECGs)

ECGs were performed once during screening in order to screen out individuals who did not meet ECG study inclusion criteria. One patient, 0505/00001, was noted to have a prolonged QTc interval and should have been excluded from the study for 6 out of the 21 days until the protocol violation was noted. The patient did not have any AEs during his tenure in the trial.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.9 Safety Update

A safety update has been submitted that includes a summary of safety data that has become available since the June 24, 2004 complete response. The update includes information from study F2309 which is reviewed in detail above and information regarding adverse events, including serious adverse events, and discontinuations due to adverse events for ongoing Foradil Certihaler studies. The cutoff date for inclusion of data is July 31, 2005.

Ongoing trials include study F2308, a randomized, multi-center, double-blind, single-dose cross-over study in 51 adult patients with asthma to evaluate the efficacy of formoterol administered via Certihaler X and Certihaler Z and via the Aerolizer device. This study has been completed. There were no deaths, serious adverse events and no discontinuations in the study. There were 11 adverse events, 10 mild, 1 moderate (dizziness).

The second ongoing trial is a randomized, multi-center, placebo-controlled study in 844 adults with COPD to compare the efficacy and safety of formoterol via the Certihaler, tiotropium via the HandiHaler, and tiotropium via the HandiHaler in combination with formoterol via the Certihaler administered to patients with stable COPD for 24 weeks. This trial is ongoing and remains blinded. There has been 1 death in the trial. This patient (0117/00009, Netherlands) was discontinued from the study after 1 month of treatment due to dyspnea attributed to a COPD exacerbation. However, the patient was subsequently diagnosed with bronchial carcinoma localized to the mediastinum and right bronchus and died approximately 4 weeks after discontinuing from the study.

There have been 28 non-fatal SAEs in the study, including 12 COPD exacerbations. Other SAEs are consistent with an older population with concomitant illnesses and include angina/chest pain (3), AV block or atrial fibrillation (2), CVA (2), coronary artery disease/syndrome (3), and pulmonary embolism (1).

There was 1 report of a device failure that may have caused a patient to receive an excess of study drug. A 52 year old male was unable to operate the device (no medication felt to be dispensed). On the third try, the patient felt that a lot of powder was dispensed. His hands trembled for about half an hour with subsequent complete recovery. An assessment of the device demonstrated a misaligned dosing bar. This type of failure causes the device to stop working and previous failures of this type did not allow powder leakage or increased dose. The reservoir was refilled with powder, the dosing bar misaligned and upon testing there was no loss of powder from the reservoir. When the device was assembled correctly, it functioned normally. Further investigations are ongoing at the device manufacturer.

Correspondences from Novartis on February 2 and March 1, 2006 notified the FDA that in January and February, 2006 there were 5 post-marketing CIOMS adverse reaction reports from Germany in which patients had inadvertently received overdoses of Foradil from the Certihaler. Adverse reactions to the overdoses were severe in several of the cases with tachycardia to a heart rate of 150, hypertension to 200 mmHg (systolic), and tremor and insomnia lasting up to several days. After discussion with the German and Swiss health authorities, there was a voluntary recall of the Certihaler on 1/23/06. The Certihaler was launched in Germany and Switzerland in September, 2005. At the launch, the patient instruction leaflet was similar to the instruction sheet submitted to the FDA in Novartis' Complete Response on June 24, 2004 that DPAP felt was inadequate. Novartis believes that patient misuse of the Certihaler was the cause of the overdoses and that a modification of the patient instruction leaflet provided with the German and Swiss drug products, similar to the revised patient instruction sheet submitted as a part of this submission, would resolve the overdose issue. A subsequent letter to German and Swiss wholesalers, pharmacies, and physicians communicated the recall and stated that the package leaflet would be updated to clearly explain the correct use of the Certihaler before the product would become available again.

In a telecom between DPAP and representatives from Novartis on March 6, 2006, Novartis stated that they have not made plans to make any additional modifications to the device as they felt that the problems with the device could be addressed through the label. They indicated that they planned to add two additional steps to the label regarding how to open and close the device. The Division noted that this type of overdose was not observed during clinical development and the problem would not be addressed by improved labeling instructions. Subsequently, on March 30, 2006, Novartis submitted a plan in which they would redesign parts of the Certihaler in an attempt to prevent inadvertent overdosing.

Evaluation of the overdoses by Novartis included interviews with patients, reviews of manufacturing records, inspection of devices from 2 (out of 5) overdoses, and attempts to simulate the reported events in the laboratory. Inspection of the 2 devices revealed "distorsion damage" that deformed the sliding shelter of the device. This type of damage could be reproduced by forcibly pushing down on the cap prior to it being extended fully. Please see CMC review # 5 by Craig M. Bertha Ph.D. for a more complete description and discussion of the device failures.

In addition to the overdoses, there have been 389 complaints from the German and Swiss commercial markets since the Certihaler became available. For 75 of the devices there were problems with device failure; an increase in actuation flow rate above the specification limit of 40 LPM (14), dose counter failures (3), misaligned dosing bars (27), externally-cause damage to the device (27), and 4 other not yet classified failures.
Reviewer's Comment: While inadequate instruction is a likely issue in the use of this device, I have great concern that mishandling of the device by a patient could result in a potentially fatal overdose of formoterol. In the clinical development program reviewed previously, mishandling generally resulted in being unable to receive a dose of medication rather than the occurrence of serious overdoses. In addition, after review of the CIOMS reports, 2 of the 5 patients had substantial experience in using the Certihaler, one with 3 months usage with 3 prescription devices and another with approximately 2 months of usage with 3 sample devices and 1 prescription device, prior to the overdoses. This leads one to think that, at least in these 2 patients, the overdoses may not have been due to misuse alone or that overdose may occur despite appropriate use. On the basis that mishandling of the device could result in serious or even fatal overdoses of formoterol in a population (elderly COPD) particularly sensitive to adverse events such as arrhythmias or stroke as a result of excess beta receptor stimulation, I agree with the conclusion of CMC reviewer Craig M. Bertha, Ph.D. that the applicant take steps to redesign the internal components of the device in such a way that such mishandling could either no longer occur or if it is still possible, that it would not lead to the events that could cause overdosing.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable as this review is of a single study to assess the ability of patients with asthma to properly use a new MDDPI device, the Foradil Certihaler over a 3 week period in a context reflecting the real life situation.

7.4.2 Explorations for Predictive Factors

Not applicable as this review is of a single study to assess the ability of patients with asthma to properly use a new MDDPI device, the Foradil Certihaler over a 3 week period in a context reflecting the real life situation.

9 OVERALL ASSESSMENT

9.2 Recommendation on Regulatory Action

The recommendation is for an approvable action for the Foradil Certihaler MDDPI. There are 2 outstanding clinical issues detailed below that preclude approval, the issue of inadvertent

overdosing of patients in Germany and the lack of an adequate label. While the patient instructions for use, including figures, have been extensively revised in order to improve patient comprehension and a patient use study (F2309) has been conducted which demonstrated improved ability of patients to use the Certihaler, recent post-marketing reports from Germany of serious overdoses of formoterol due to device failures raise serious safety concerns regarding both the proper use of the device and the device itself. On the basis that mishandling of the device could result in serious or even fatal overdoses of formoterol in a population (elderly COPD) particularly sensitive to adverse events such as arrhythmias or stroke as a result of excess beta receptor stimulation, the applicant must take steps to redesign the internal components of the device in such a way that such mishandling could either no longer occur or if it is still possible, that it would not cause overdosing. The device cannot be approved until such device failures are resolved.

In addition, in response to recent findings that LABAs may increase the chance of severe asthma episodes, and death when those episodes occur, Novartis had been asked by the FDA to update their existing LABA product (Aerolizer and Certihaler) labels with a new Boxed Warning and a Medication Guide to alert health care professionals and patients. Novartis initially refused to include the Boxed Warning and Medication Guide. However, after negotiation of an appropriate label for the other marketed LABA, salmeterol, that included the Boxed Warning and Medication Guide, Novartis agreed to submit a revised label. The latest proposed labeling for the Certihaler dated March 30, 2006 still lacks a Medication Guide and is not reviewed in this document. Labeling negotiations are also underway for the Foradil Aerolizer, a single-dose DPI with the same active ingredient as the Certihaler (the LABA, formoterol). Labeling for the Certihaler will be much the same as that for the Aerolizer in order to ensure consistency of the label across Novartis' formoterol portfolio.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The plan initially submitted for patient support upon approval and commercialization of the Certihaler mimicked the patient support that was available in Study F2309 and was felt to be adequate. It included 'Certihaler Directions for Use', instructions, the ability to watch a Certihaler instructional video information, a toll free number to call with questions/problems, and a web site where Certihaler instructions, including the video, would be available.

However, subsequent to the reports of inadvertent overdoses of formoterol with the marketed Certihaler device in Germany, Novartis stated they would submit a revised risk management plan in an attempt to deal with the overdose issue.

Reviewer's Comment: The applicant was informed by the Agency during a telephone conference on March 6, 2006 that simply revising the patient instructions for clarity is not sufficient and that the devices should be modified in such a way that such mishandling could either no longer occur or if it is still possible, that it would not lead to overdosing.

The applicant was reluctant to pursue such a course of action and stated that they were going to submit a plan that would mitigate the risk that such overdosing would occur if the product were marketed in the US. Such a plan, while necessary, will not be sufficient to ensure against unintended overdoses and, by itself, not sufficient for approval of the Certihaler device. Novartis subsequently submitted a plan on March 30, 2006 to re-design the device in order to prevent overdosing due to misuse.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments

9.3.3 Other Phase 4 Requests

In the approvable letter of October 17, 2003, the Division recommended the applicant establish a more extensive database further evaluate for the Foradil Certihaler in adolescent and elderly populations. [redacted] b(4)

9.4 Labeling Review

Much of the labeling for the Foradil Certihaler had been previously agreed upon. However, in the time since the last consideration of this NDA, the Agency has learned more concerning the safety of long-acting beta agonists (LABAs). In response to findings that LABAs may increase the chance of severe asthma episodes, and death when those episodes occur, the manufacturers of LABAs have been asked to update their existing product labels with a new Boxed Warning and a Medication Guide to alert health care professionals and patients. Novartis initial response was a refusal to include the Boxed Warning and Medication Guide. However, after negotiation of an appropriate label for the other marketed LABA, salmeterol, that included the Boxed Warning and Medication Guide, Novartis has agreed to submit a revised label. The latest proposed labeling for the Certihaler dated March 30, 2006 still lacks a Medication Guide and is not reviewed in this document. Labeling negotiations are also underway for the Foradil Aerolizer, a single-dose DPI with the same active ingredient as the Certihaler (the LABA, formoterol). Labeling for the Certihaler will be much the same as that for the Aerolizer in order to ensure consistency of the label across Novartis' formoterol portfolio.

The Division of Surveillance, Research, and Communication Support has developed a proposed Medication Guide for the Certihaler utilizing the product patient instruction sheet and incorporating the added warnings required for LABAs with an indication to treat asthma (Consult dated January 30, 2006 by Jeanine Best).

The Division of Medical Errors and Technical Support was also consulted to review the label and had both specific and general comments, including more detailed explanations on device use and. possibly, the need for a device redesign if confusion still exists after more detailed label

changes are made (review by Kimberly Petersen, December 15, 2005). In light of both the inadvertent overdosing of some patients in Germany that Novartis hopes to address with added instructions and the requirement to include added safety warnings concerning the use of LABAs, the specific suggestions by DMETS have not yet been incorporated into the label Novartis initially proposed.

9.5 Comments for the Action Letter

1. The inadvertent overdosing of patients who used the Certihaler marketed in Germany is a serious safety concern that needs to be resolved to support approval of the drug product. Simply revising the patient instructions will not be sufficient. For approval, the device should be modified in such a way that any mishandling of the device will not result in an overdose. To ensure this beyond a reasonable doubt, the revised device will need to undergo extensive in vitro testing and may require clinical use studies. In addition, based on the impact the revisions of the device have on drug flow characteristics, additional clinical efficacy and safety studies may be required.

2. Adequate labeling to address the recently found heightened risk of severe asthma episodes and death in patients with asthma who use LABAs, including formoterol, is required for approval of the Certihaler. These changes will need to include both a Boxed Warning and creation of a Medication Guide for the product. The most recent proposed label submitted on March 30, 2006, remains deficient.

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

/s/

Anthony Durmowicz
4/10/2006 11:30:23 AM
MEDICAL OFFICER

Badrul Chowdhury
4/10/2006 11:49:14 AM
MEDICAL OFFICER
I concur

CLINICAL REVIEW

Application Type	NDA 21-592
Submission Number	N000
Submission Code	BZ
Letter Date	24 June 2004
Stamp Date	29 June 2004
PDUFA Goal Date	25 December 2004
Reviewer Name	Richard Nicklas MD
Review Completion Date	10 December 2004
Established Name	formoterol fumarate
(Proposed) Trade Name	Foradil Certihaler
Therapeutic Class	beta agonist bronchodilator
Applicant	Novartis
Priority Designation	standard
Formulation	Certihaler (inhalation powder)
Dosing Regimen	10 mcg bid
Indication	maintenance treatment of asthma and the prevention of bronchospasm
Intended Population	adults and children 5 years and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Foradil Certihaler remains approvable. This drug product can not be approved until it has been clearly shown that patients can reliably and consistently use the Certihaler device. In order to do that, patients must be more effectively instructed in the use of the device. In patient use studies, despite what appeared to be adequate instruction in the use of the device, an unacceptably high percentage of patients found the device difficult to use and could not use the device properly. Specifically, 14-18% did not feel that the dose counter decreased by one with use of the device at some point, 10-13% felt that they did not get the dose at some point, 52% indicated that they noticed a difference in triggering the device and 41% had to breathe harder to make the device work. The applicant will need to perform a patient use study with new and more comprehensive instructions for use of the device. This study will need to demonstrate that the difficulties encountered by patients in the patient use studies submitted with the Complete Response of 24 June 2004 can be overcome with more effective instruction and should be performed in a representative sample of patients with the intensity of instruction that could be expected in a clinical setting.

Although not a deficiency, in regard to educational activities to avoid confusion between the use of Foradil Aerolizer and Foradil Certihaler, the plan submitted for differentiation in use of these two products is unacceptable. In the promotional material for this drug product, educational activities should compare the Certihaler and the Aerolizer and indicate that the Certihaler should only be used for the treatment of asthma in order to address the comment cited in the approvable letter.

1.2 Recommendation on Postmarketing Actions

1.2.1. Risk Management Activity

The applicant, in order to gain approval for this drug product, will need to develop a more effective patient education program about the use of the device, including instructions for use in the package insert, and then demonstrate that patient difficulty in using the Certihaler device can be minimized by use of this improved patient education about the use of the device.

1.2.2. Required Phase 4 Commitments

There are no phase 4 commitments.

1.2.3. Other Phase 4 Requests

In regard to further evaluation in adolescent and elderly patients, the applicant has proposed studies which are appropriate to meet the recommendation in the approvable letter of 17 October

2003 to establish a more extensive database for administration of Foradil Certihaler to adolescent and elderly patients.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

An indication is sought for the use of Foradil Certihaler in the long-term maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airway disease.

The applicant performed *2 simulated in-use studies* and *2 patient use clinical studies* in 300 patients with asthma evaluating the function of the Foradil (formoterol fumarate) Certihaler.

The 2 simulated patient use studies were addressed in report ADR 8521-19 entitled "Evaluation of functionality of dose counter and actuation air flow rate for the Foradil Certihaler as a function of simulated patient use" and ADR 8521-21, entitled "Extended study on functionality of dose counter and actuation air flow rate for the Foradil Certihaler as a function of simulated patient use". The purpose of these simulated studies was to investigate any change in actuation air flow rate and overall function of the device (commercial production line device) during simulated patient use.

The *two patient use studies* were performed to evaluate the function of the device in patients by collecting patient observation data on potential device failures and conducting an in-vitro technical assessment of the devices after three weeks of use. These were open label uncontrolled multi-center studies in patients with asthma who received 10 mcg (1 inhalation) of formoterol delivered by Certihaler bid approximately 12 hours apart.

1.3.2 Efficacy

1.3.2.1. Study Design:

Simulated Use study 1 was initiated because of a variety of complaints in regard to devices returned from clinical phase 3 studies after patient use. There were 174 devices returned with complaints. Of these, 111 device failures were confirmed by the applicant, including an increase in actuation flow rate in about 2/3 of the returned devices. The purpose of this simulated study was to investigate any change in actuation air flow rate and overall function of the device (that would be used on the commercial production line) during simulated patient use.

SkyePharma and Novartis personnel were assigned to carry Foradil Certihaler devices during their daily personal routines. There were 10 individuals who carried a total of 60 Certihaler units with each individual carrying 6 inhalers during the test period of 5 weeks. There are 60 doses in each device with the counter counting down from 60 to 0 after each correct inhalation by the patient. The devices were brought twice a day to the laboratory for in-vitro actuation which simulated dose inhalation using a dosage unit sampling apparatus at 60 L/min. Daily handling

and storage of the inhalers was recorded by each individual. There were 15 reference inhalers that were stored in the laboratory under ambient conditions and served as control samples. These reference samples underwent the same testing sequence as the samples carried by personnel. The actuation flow rate was measured and recorded once a week with every 10th actuation (patients only carried the device during weekdays). Dose counter functionality was assessed by recording the number after each actuation. After the last dose (counter display 00) an additional waste shot was taken and recorded to confirm that the counter display changed to the final 999 reading and device lockout occurred.

Actuation air flow rate (AFR) was measured by determining two consecutive actuations at 60/59, 31/30, and 01/00 dose counter readings. Four "Flow Control Modules" were equipped with a 'Drager Volumeter', an 'Inhalation Test Box' and a 'Dosage Unite sampling Apparatus'. An air flow rate of 30 L/min, 35 L/min, 40 L/min and 45 L/min was pre-adjusted to each individual test set up. Each device was shaken, opened and inserted in the first test set-up having the air flow rate adjusted to 30 L/min. The simulated inhalation was activated for 8 seconds to reach a total simulated inspiration volume of 4 liters. If the actuation and release of the dose was observed, the device was removed from the apparatus. During closing of the protective cap, the function of the counter was checked. Both successful actuation and counting were noted at the specific AFR in the work sheet. If a device failed to activate, the procedure was repeated. If the device failed to actuate a second time at 30 L/min, the device actuation was attempted at 35 L/min, using the next test setup with the increased pre-set flow rate. The test was repeated continuously, increasing the flow rate in steps of 5 L/min until actuation occurred and the observation was noted. The duration of the airflow was decreased relative to the AFR to reach a volume of 4 liters.

Air flow rate	Actuation time
30 L/min	8 seconds
35 L/min	6.9 seconds
40 L/min	6 seconds
45 L/min	5.3 seconds
50 L/min	4.8 seconds
60 L/min	4 seconds

Simulated study 2 was a simulated use study with 200 Foradil Certihalers and 10 reference inhalers, performed in order to evaluate counter functionality and actuation flow rate. Instead of personnel carrying the device, mechanical agitation by a laboratory shaker for one hour between actuations with not more than 6 actuations per day was chosen to simulate daily patient use. *(NOTE: 6 actuations per day did not simulate the recommended daily dose of 2 actuations; overuse of the device is unlikely to have changed the conclusions obtained from this study).*

Actuation flow rate was measured at actuations corresponding to dose counter readings of 60/59, 31/30 and 01/00 for 2 consecutive actuations using the same test setup as in simulated study 1. The reference (control) inhalers were not agitated on the shaker and were kept under standard conditions.

Two identical *patient use studies* were performed (*studies 2304 and 2306*). The objective of these studies was to evaluate the function of the Cerihaler device during and after patient use by collecting patient observation data on potential device failure and conducting an in-vitro technical assessment of the devices at the conclusion of the study, i.e. after three weeks of use. Analysis was descriptive for device functionality and safety (adverse events) only. No formal statistical analysis was done. *(NOTE: Study 2306 was performed subsequent to study 2304. In study 2304, there were 3 devices that had confirmed device malfunction based on in-vitro studies. Specifically, there was misalignment of the dosing bar and the sliding shelter of the device which led to failure of the dosing mechanism to move so that the dose could not be delivered. This defect had not been observed prior to that time, was not reproducible in the laboratory and was attributed by the applicant to the fact that study 2304 was performed with devices manufactured in 2002 without studs on the guiding rail. Study 2306 was performed using devices that included studs on the guiding rail.)*

Studies 2304 and 2306 were 3 week, open label, uncontrolled, multi-center studies in patients with asthma (FEV-1 40% or greater) who were 5-74 years of age. Patients received 10 mcg (1 inhalation) of formoterol delivered by Certihaler twice a day approximately 12 hours apart. Albuterol was used as rescue medication. Patients kept a diary that recorded counter number after each use and responded to specific questions about the function of the device. The devices were collected, sent back to Novartis and then shipped to SkyePharma for technical in-vitro assessment. The expected number of actuations by patients was 42 (twice a day for 21 days). Since 60 actuations are delivered by the Certihaler, there were doses left in returned devices. Devices from patients who discontinued the study prior to completion of the three week treatment period were collected and sent to SkyePharma and all unused devices were also collected and returned to Novartis. If the patient considered that the device was not functioning correctly, the patient contacted the study site. If it was determined that the device was malfunctioning, the patient was to be withdrawn from the study. The dataset obtained from the in-vitro technical assessment at the conclusion of the study was considered the primary data for the identification of device function but the results of the in-vitro assessment were to be considered in conjunction with the data recorded daily by the patient in the patient diary.

All Certihaler devices were assessed after the patient treatment period by SkyePharma and given a rating of 0 = device functioning or 1 = device failure. Device assessment included: 1) visible appearance and weight of the returned MDDPI; 2) counter position function; 3) digital photography; 4) functionality of the protective cap and mouthpiece, as reflected in any inconsistencies during opening or bending movements of the protective cap and during removal of the mouthpiece; 5) actuation flow rate (flow rate required to trigger the valve shield); 6) dose counter function test; and 7) lock-out mechanism.

Assessment of AFR was initiated at 30 L/min with increases of 5 L/min if the valve shield failed to move (flow rate was not adequate to trigger the valve shield). Any AFR above 50 L/min was rated a device failure. If the dose counter was not functioning correctly in any way, it was considered a device failure. After the AFR testing, waste shots were made at a flow rate of 60 L/min. After the last dose (counter display 00) an additional waste shot was performed and

recorded to confirm that the counter display changed to the final '999' reading and the device lock out mechanism engaged. If the lock-out failed it was considered a device failure

The initial technical assessment of the devices was conducted without reference to the information recorded in the patient diaries. However, at the final evaluation, the technical results were considered in conjunction with the data recorded daily by the patient in the diary so that any device identified as a problem device either from the technical assessment or by the patient was assessed and a narrative prepared discussing functionality of the given device.

1.3.2.2 Study Results

In *simulated study 1*, there was an increase of 5 L/min in *actuation flow rate* throughout the patient use period with 37 devices (50%), an increase of 10 L/min with 22 devices (30%), an increase of 15 L/min with 9 devices (12%) and no increase with 6 devices (8%) (v1, a1, p23, t7.2). One device was removed from the study before the actuation flow rate could be measured because of double counting after the first dose. The applicant states that an increase in AFR of 5 L/min is "inherent" in the specific device design and caused by a "very" small amount of powder deposition in the device. *Comment: Clearly a number of devices had an even greater increase in AFR than could be accounted for on this basis.* There was no significant difference in actuation flow rate reported when devices that were carried by personnel at daily temperatures above 30 degrees C were compared with reference devices stored in the lab at stable conditions of 22 degrees C and 50-65% relative humidity.

Four *dose counter* malfunctions were observed with four different devices out of the 75 devices evaluated, including one reference device (6%) and 3 devices that were carried by personnel (5%). The dose counter malfunctions were: 1) on 2 devices, the counter counted down two units on closure of the protective cap (double counting); and 2) on 2 devices, the counter did not count down the delivered dose after closing the protective cap.

Extensive testing in the laboratory could not reproduce the *double counting*. The applicant therefore classified this defect as "unknown" and most likely due to "operator failure" i.e. "wrong observation". *Comment: It should be recognized that those individuals who were carrying the devices were employed by the applicant and had been adequately trained in the use of the device.*

The failure of two devices to *count down* was reproduced under experimental conditions. The failure of the device to count down could be reproduced by two types of manipulation: 1) the protective cap was forcefully pushed inward while closing it after inhalation; and 2) the protective cap was closed halfway and stopped just as the counter begins to re-register so that when the cap was re-opened and closed, the dose counter did not count. Dosing without counting is not possible for a correctly working device. In the case where the counter did not work when actuated at 30 L/min, this failure was attributed to the "artificial laboratory test set up" where the low flow rate drawn through the device caused only partial movement of the valve shield resulting in failure to trigger the counter mechanism on closure of the protective cap. In all cases, the next immediate actuation counted correctly. Since the failure of the two devices to

count down was considered due to "operator failure" and an "artifact of the test system" the applicant considers that the dose counter has been shown to be reliable. *Since "operator failure" was a failure by individuals adequately trained in the use of the device and there was failure of the device to count down when manipulated in the laboratory, the data from this study indicate that counter malfunction does occur, although infrequently after use of the Certihaler device.* As a result of the double counting effect seen in this simulated study, Riwisa, the device manufacturer, started an internal study focused on counter problems with 500 empty devices. The testing was done with an automated system that automatically opens the protective cap and rotates the cap 90 degrees down. An aspiration port, connected to a vacuum pump, is then adapted to the mouthpiece. The preset vacuum aspirates the valve shield of the inhaler. After release, this mechanism rotates the protective cap back and closes the inhaler. At the end of the test, the effective counter display is compared with the present number of actuations. No counter failure was observed (v1, a1, p17, s6.8).

In *simulated study 2*, there was no significant difference in average actuation flow rate when Certihalers were shaken compared to when they were not (reference inhalers) (v1, a2, p12. f6-2, 6-3). For the shaken inhalers, by the end of the device life, approximately 10% were actuated by 40 L/min and approximately 10% were actuated by 45 L/min. There were a few devices that required an AFR of 50 L/min to be actuated. In comparison, for the reference inhalers, by the end of the device life, 10-30% required 35 L/min AFR to be actuated and 30-40% required 40 L/min AFR to be actuated. About 40-50% of both the shaken inhalers and the reference inhalers required 30 L/min to be actuated when the counter display was 1/0. An increase of 5 L/min in AFR is attributed by the applicant to small quantities of powder within the internal mechanism of the device resulting in increased friction of the sliding parts during actuation of the device. There were 5 devices (3% of devices) which had intermittent counter "problems", i.e. the counter did not work for one or two attempts but functioned correctly thereafter until lockout, attributed by the applicant to "mishandling". (NOTE: It is less likely that the device would have been mishandled by the laboratory personnel than by patients using the device and the applicant does not explain further how the devices could have been mishandled). No permanent dose-counter failure occurred.

In *patient use study 2304*, 157 patients entered the study and 150 patients completed the study. There were 2 patients who discontinued because of adverse events and 5 patients who discontinued because of device malfunction or failure (confirmed in 3 patients; see below). In the patient diary, the patient was asked to respond to 3 specific questions: 1) "Did the dose counter decrease by one?"; 2) "Did you get the dose?"; and 3) "Did you notice any difference in triggering the device?". A difference in device triggering was the major complaint by patients. Of the 81 patients (52%) who noted a difference in triggering the device, 17 (21%) of these patients also reported that the dose counter did not decrease and 17 (21%) reported that they did not get a dose of study medication. There were 8 patients who noted both that the dose counter did not decrease and that they did not get a dose of study medication. The remainder of the patients who gave a positive response, EITHER noted that the dose counter did not decrease OR that they did not get the dose. In-vitro data at the end of the study showed that most of the devices perceived by patients to be malfunctioning in some way were functioning normally without an increase in actuation flow rate or dose counter malfunction. Of 157 assessed devices,

153 worked without malfunction during in-vitro assessment, i.e. the dose counter functioned, the lock-out worked, and the actuation flow rates were expected given a 5 L/min increase with the use of the device. Of the 4 devices that malfunctioned during in-vitro testing, 3 were devices used by patients who discontinued because of device malfunction. These devices were found to have misalignment of the dosing bar and the sliding shelter of the device resulting in failure of the dosing mechanism to move so that the dose could not be delivered. This defect was attributed by the applicant to the fact that the devices were manufactured in 2002 without studs on the guiding rail. One device was accidentally damaged in the lab and removed from the testing program while all of the other 153 returned devices functioned normally without mechanical failure.

In vitro device assessment that was done at the completion of the study confirmed that there was a mechanical failure in 3 of the 5 devices (2%) used by patients who discontinued because of device problems. The device functioned normally in the other 2 patients. There was a misalignment of the dosing bar and the sliding shelter of the device in the 3 malfunctioning devices that resulted in failure of the dosing mechanism to move so that the dose could not be delivered. This was a device failure that had not been observed in any of the previous clinical studies or during technical testing. This jamming of the sliding shelter and dosing bar could not be reproduced in the laboratory and was not a result of permanent deformation of the Certihaler.

Potential inconsistencies during the manufacturing process were retrospectively re-checked and no deviations for the production process of the sliding shelter, dosing bar and guiding rail were observed. All Certihalers showing misaligned position of the dosing bar and sliding shelter were from the same manufacturing period on the assembly line.

There were another 9 devices that did not actuate at 40 L/min or less but did actuate at 45 L/min and one device actuated at 50 L/min after failing to actuate at 40 and 45 L/min. Of these, 4 patients did not comment on any problem in their diary, 4 patients commented about device function at some point during the study but did not indicate a problem at the last recorded visit and one patient indicated in the diary on the morning of the last day that it was hard to get a dose. At all visits, the dose counter had decreased as expected. There were no dose counter failures, or failure in lock-out.

In *Patient Use Study 2306*, 154 patients entered into the study and 145 patients completed the study. There were 9 patients who discontinued prematurely: one due to an adverse event, five because of malfunction of the device, one because the device was destroyed by a dog, one because of problems using the device missed multiple doses and one because the patient broke the device.

There were 73 patients (47%) who noted some sort of device malfunction at least once during the study. Of these patients, 28 (18%) indicated that the dose counter did not decrease by one. There were 16 patients (10%) who indicated that they did not get the dose. There were 14 of these 16 patients (86%) who indicated that they had to breathe in harder to make the device work. There were 63 patients in all (41%) who indicated that they had to breathe in harder to make the device

work. There were 19 of these patients (30%) who also indicated that the dose counter did not decrease and 14 (22%) who indicated that they did not get the dose.

In-vitro device assessment of the device at the end of the study found only one device with a mechanical failure, while all other devices functioned normally. The one malfunctioning device had a dose counter that failed to count the dose. The patient who had this device recorded that the dose counter did not decrease by one on several occasions and that he did not get the dose of study medication. The device was still actuating and providing medication yet the dose counter had stopped counting at counter display '43' due to the damaged counter mechanism.

1.3.2.3. Conclusions:

There were a small number of devices in which an actuation flow rate of up to 50 L/min was needed to actuate the device. In addition, there were 30% who had an increase in AFR of 10 L/min and 12% who had an increase in AFR of 15 L/min throughout the use of the device. Since the range of AFR noted in these studies is within the range easily generated by patients with asthma, these increases in AFR are unlikely to be clinically significant. Therefore, while these data indicate that the increase in AFR seen in these studies was due to more than just a small amount of powder within the device, no further evaluation by the applicant is necessary.

The dose counter failed in 5% of the devices in simulated use study 1 and there were 2% of devices whose dose counter did not work properly in simulated use study 2. In studies 2304 and 2306 there were 21% and 18% of the patients in those studies, respectively, who indicated that the dose counter did not decrease by one at some point in the study. In-vitro assessment at the conclusion of these studies showed that there was dose counter malfunction in only one device used by a patient who had noted dose counter malfunction during the study (study 2306). During the study, the devices on which the dose counter failed did not have a dose counter failure for the remaining actuations of the device. Since most patients who noted that the dose counter did not count down at one point during the study, did not note this effect subsequent to that point in the study, it is not surprising that in-vitro assessment that was done at the end of the study does not confirm what patients noted during the study . Failure to count down one dose during the life of the device, if this was an accurate observation by the patient, does not raise safety concerns about the use of this device.

There were 13% and 10% of patients in studies 2304 and 2306, respectively, who did not feel that they got a dose at some time point throughout the use of the device. Patients who failed to get a dose at some point in the study indicated that they did get a dose with subsequent actuations. The majority of these patients did not notice any malfunction of the dose counter. The reason why some patients felt that they did not get a dose is unclear, although lack of malfunction of the devices on in-vitro testing, the ability to get a dose through the rest of the device use, and normal functioning of the dose counter, suggest that this may have been due in at least some cases to misperception on the part of the patient.

In patient use study 2304, there was a failure rate of 2% of the Certihaler devices characterized by a failure of the dose being delivered. In patient use study 2306, using devices with studs, the

absence of which was felt by the applicant to be the cause for device malfunctioning in study 2304, there was only one device (0.6%) and this was a device that had a malfunctioning dose counter. This incidence of malfunction is clinically acceptable for a drug product that is intended for the maintenance treatment of asthma.

The performance of in-vitro testing at the end of the study helps to distinguish between accurate and inaccurate conclusions by patients on the function of device. Nevertheless, there is a strong indication that patients had significant difficulty understanding how to use the device effectively, despite what should have been adequate education about its use. This is a serious deficiency for any drug product and must be corrected before Foradil Certihaler can be approved.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Foradil (formoterol fumarate) is a formylamino-substituted catecholamine derivative that exerts a preferential effect on beta-2 adrenergic receptors of bronchial smooth muscle. Foradil has a relatively rapid onset of action and a long duration of action (at least 12 hours). Foradil Aerolizer which is a single dose dry powder capsule inhaler is approved in the United States for the maintenance treatment of asthma and COPD and the prevention of exercise-induced bronchospasm in adults and children 5 years of age and older. With this submission, the applicant has submitted an NDA for a new delivery device for Foradil, a multi-dose dry powder inhaler, the Certihaler, developed by SkyePharma. The device used in the clinical development program was manufactured as a [redacted] tooled device and the marketed device will be manufactured as a [redacted] tooled device. b(4)

2.2 Currently Available Treatment for Indications

Foradil (formoterol fumarate) is available for the treatment of asthma as the Aerolizer, a metered dose inhaler. Long-acting beta adrenergic agonists such as formoterol and salmeterol have become widely used for the treatment of asthma. In addition, inhaled corticosteroids, e.g Flovent, Azmacort, are currently available to treat asthma.

2.5 Presubmission Regulatory Activity

This submission by the applicant provides data from simulated use and patient use studies to address the device problems identified in phase 3 studies i.e. actuation flow rate and dose counter malfunction. At the Division's request, the applicant has performed simulated in-use studies and 2 patient use clinical studies in 300 patients with asthma in order to demonstrate that the actuation flow rate and dose counter problems found in phase 3 studies with the deice that will be manufactured for commercial use.

An Approvable letter was sent to the applicant on 17 October 2003. The sponsor has submitted a Complete Response to that Approvable letter in this submission, which supersedes amendments made to the NDA on 15 July 2003 and 29 August 2003. In the Approvable letter of 17 October 2003, there were a number of CMC deficiencies that included concern about whether the drug product prepared for commercial use would have the same counter and actuation flow rate problems described by the applicant for devices used in phase 3 studies. The applicant was asked in this regard (1a of Approvable letter) to, "Provide a summary of the efforts that have been taken to assure that the drug product prepared with _____ tooled devices will have acceptable performance and will not display the same counter and actuation flow rate (or other) problems outlined in your included report in attachment 11 of section 3.2.P.2 and attachment 2 of this section in the March 17, 2003 amendment. Provide supporting data demonstrating the decrease in the percentage of complaints. A preliminary review of your response to the this comment suggest that in vitro data alone, even with a larger sample size, may be insufficient to address our concerns regarding device failure which may require the submission of additional clinical data." b(4)

In addition, the following clinical comments (not deficiencies) were conveyed to the sponsor: 1) comment 13. "You should consider studies to establish a more extensive database for administration of Foradil Certihaler to adolescent and elderly patients.", and 2) comment 14. "Provide your 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 addition, the following clinical comments on the draft labeling were included: b(4)

b(4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Background:

The Foradil Certihaler is a dry powder inhaler (DPI) designed to release the metered dose of dry powder only after the inspiratory flow rate of the patient overcomes an actuation air flow threshold. This actuation based on an air flow threshold results in more consistent delivery of the active therapeutic agent in the aerodynamic fine particle range.

An Approvable letter was sent to the sponsor on 17 October 2003. In the Approvable letter of 17 October 2003, there were a number of CMC deficiencies, that included concern about whether the drug product prepared with the ——— tooled devices would display the same counter and actuation flow rate problems outlined be the sponsor previously. b(4)

The most frequent comments by patients in phase 3 studies utilizing devices produced from ——— tools and a ——— assembly process concerned possible malfunction related to actuation flow rate and functioning of the dose counter. Of the inhalers returned with complaints, 101 were because of an increase in the actuation flow rate > 40 L/min and 15 because of malfunction of the dose counter. The sponsor calculated a complaint rate of 1.5% based on phase 3 studies in which at least 5308 Foradil and 1960 placebo inhalers were used (total 7268 inhalers used)(111/7268 = 0.015 or 1.5%). This assumes that there was complete use of a 60 dose inhaler and bid administration. If devices were only partly used, the applicant points out that a much larger number of inhalers would have been used during phase 3 studies, which was almost certainly the case. b(4)

The CMC reviewer has recommended approval provided the sponsor can meet the recommended specifications for magnesium stearate and agrees to the phase IV commitments being requested.

6. INTEGRATED REVIEW OF EFFICACY

6.1. Indication

The applicant is seeking an indication for Foradil Certihaler for the 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 with reversible obstructive airway disease.

6.2. Specific Studies

The applicant performed *2 simulated in-use studies* and *2 patient use clinical studies* in 300 patients with asthma evaluating the function of the Foradil (formoterol fumarate) Certihaler. The *2 simulated patient use studies* were addressed in report ADR 8521-19 entitled "Evaluation of functionality of dose counter and actuation air flow rate for the Foradil Certihaler as a function of simulated patient use" and ADR 8521-21, entitled "Extended study on functionality of dose counter and actuation air flow rate for the Foradil Certihaler as a function of simulated patient use".

The applicant performed *two patient use studies* to evaluate the function of the device in patients by collecting patient observation data on potential device failures and conducting an in vitro technical assessment of the devices after three weeks of use. These were open label uncontrolled multi-center studies in patients with asthma who received 10 mcg (1 inhalation) of formoterol delivered by Certihaler bid approximately 12 hours apart.

6.2.1. Report ADR 8521-19 for *simulated study 1* (v1, p3-6)

6.2.1.1. Objectives and design:

Simulated Use study 1 was initiated because of a variety of complaints in regard to devices returned from clinical phase 3 studies after patient use. There were 174 devices returned with complaints. Of these, 111 device failures were confirmed by the applicant, including an increase in actuation flow rate in about 2/3 of the returned devices. The purpose of this simulated study was to investigate any change in actuation air flow rate and overall function of the device (that would be used on the commercial production line) during simulated patient use.

SkyePharma and Novartis personnel were assigned to carry Foradil Certihaler devices during their daily personal routines. There were 10 individuals who carried a total of 60 Certihaler units with each individual carrying 6 inhalers during the test period of 5 weeks. There are 60 doses in each device with the counter counting down from 60 to 0 after each correct inhalation by the patient. The devices were brought twice a day to the laboratory for in-vitro actuation which simulated dose inhalation using a dosage unit sampling apparatus at 60 L/min. Daily handling and storage of the inhalers was recorded by each individual. There were 15 reference inhalers that were stored in the laboratory under ambient conditions and served as control samples. These reference samples underwent the same testing sequence as the samples carried by personnel. The actuation flow rate was measured and recorded once a week with every 10^{th} actuation (patients only carried the device during weekdays). Dose counter functionality was assessed by recording the number after each actuation. After the last dose (counter display 00) an additional waste shot was taken and recorded to confirm that the counter display changed to the final 999 reading and device lockout occurred.

Actuation air flow rate (AFR) was measured by determining two consecutive actuations at 60/59, 31/30, and 01/00 dose counter readings. Four "Flow Control Modules" were equipped with a

'Drager Volumeter', an 'Inhalation Test Box' and a 'Dosage Unite sampling Apparatus'. An air flow rate of 30 L/min, 35 L/min, 40 L/min and 45 L/min was pre-adjusted to each individual test set up. Each device was shaken, opened and inserted in the first test set-up having the air flow rate adjusted to 30 L/min. The simulated inhalation was activated for 8 seconds to reach a total simulated inspiration volume of 4 liters. If the actuation and release of the dose was observed, the device was removed from the apparatus. During closing of the protective cap, the function of the counter was checked. Both successful actuation and counting were noted at the specific AFR in the work sheet. If a device failed to activate, the procedure was repeated. If the device failed to actuate a second time at 30 L/min, the device actuation was attempted at 35 L/min, using the next test setup with the increased pre-set flow rate. The test was repeated continuously, increasing the flow rate in steps of 5 L/min until actuation occurred and the observation was noted. The duration of the airflow was decreased relative to the AFR to reach a volume of 4 liters.

Air flow rate	Actuation time
30 L/min	8 seconds
35 L/min	6.9 seconds
40 L/min	6 seconds
45 L/min	5.3 seconds
50 L/min	4.8 seconds
60 L/min	4 seconds

6.2.1.2. Study results:

In *simulated study 1*, there was an increase of 5 L/min in *actuation flow rate* throughout the patient use period with 37 devices (50%), an increase of 10 L/min with 22 devices (30%), an increase of 15 L/min with 9 devices (12%) and no increase with 6 devices (8%) (v1, a1, p23, t7.2). One device was removed from the study before the actuation flow rate could be measured because of double counting after the first dose. The applicant states that an increase in AFR of 5 L/min is "inherent" in the specific device design and caused by a "very" small amount of powder deposition in the device. There was no significant difference in actuation flow rate reported when devices that were carried by personnel at daily temperatures above 30 degrees C were compared with reference devices stored in the lab at stable conditions of 22 degrees C and 50-65% relative humidity.

Four *dose counter* malfunctions were observed with four different devices out of the 75 devices evaluated, including one reference device (6%) and 3 devices that were carried by personnel (5%). No batch correlation was found. The dose counter malfunctions were: 1) on 2 devices, the counter counted down two units on closure of the protective cap (double counting); and 2) on 2 devices, the counter did not count down the delivered dose after closing the protective cap.

Extensive testing in the laboratory could not reproduce the *double counting*. The applicant therefore classified this defect as "unknown" and most likely due to "operator failure" i.e. "wrong observation". *(NOTE: It should be recognized that those individuals who were carrying*

the devices were employed by the applicant and had been adequately trained in the use of the device).

The failure of two devices to *count down* was reproduced under experimental conditions. The failure of the device to count down could be reproduced by two types of manipulation: 1) the protective cap was forcefully pushed inward while closing it after inhalation; and 2) the protective cap was closed halfway and stopped just as the counter begins to re-register so that when the cap is re-opened and closed, the counter dose not count. Dosing without counting is not possible for a correctly working device. In the case where the counter did not work when actuated at 30 L/min, this failure was attributed by the applicant to the "artificial laboratory test set up" where the low flow rate drawn through the device caused only partial movement of the valve shield resulting in failure to trigger the counter mechanism on closure of the protective cap. In all cases, the next immediate actuation counted correctly. Since the failure of the two devices to count down was considered due to "operator failure" and an "artifact of the test system" the applicant considers that the dose counter has been shown to be reliable. *Since "operator failure" was a failure by individuals adequately trained in the use of the device and there was failure of the device to count down when manipulated in the laboratory, this reviewer believes that the data from this study indicates that counter malfunction does occur, although infrequently after use of the Certihaler device.* The devices which had dose counter failure were returned to the manufacturer (Riwisa) for further investigation and the manufacturer did automated testing of dose counter function with 500 inhalers actuated 61 times each and found no dose counter failures (v1, a1, p17, s6.8). As a result of the double counting effect seen in this simulated study, RIWISA started an internal study focused on counter problems with 500 empty devices. The testing was done with an automated system that automatically opens the protective cap and rotates the cap 90 degrees down. An aspiration port, connected to a vacuum pump, is then adapted to the mouthpiece. The preset vacuum aspirates the valve shield of the inhaler. After release, this mechanism rotates the protective cap back and closes the inhaler. At the end of the test, the effective counter display is compared with the present number of actuations. No counter failure was observed.

6.2.2. Report ADR-8521-21 for *simulated study 2* (v1, p7-8)

Simulated study 2 was a simulated use study with 200 Foradil Certihalers and 10 reference inhalers, performed in order to evaluate counter functionality and actuation flow rate. Instead of personnel carrying the device, mechanical agitation by a laboratory shaker for one hour between actuations with not more than 6 actuations per day was chosen to simulate daily patient use. *(NOTE: 6 actuations per day did not simulate the recommended daily dose of 2 actuations; overuse of the device is unlikely to have changed the conclusions obtained from this study).*

Actuation flow rate was measured at actuations corresponding to dose counter readings of 60/59, 31/30 and 01/00 for 2 consecutive actuations using the same test setup as in simulated study 1. The reference (control) inhalers were not agitated on the shaker and were kept under standard conditions.

Study results:

In *simulated study 2*, there was no significant difference in average actuation flow rate when Certihalers were shaken compared to when they were not (reference inhalers) (v1, a2, p12. f6-2, 6-3). For the shaken inhalers, by the end of the device life, approximately 10% were actuated by 40 L/min and approximately 10% were actuated by 45 L/min. There were a few devices that required an AFR of 50 L/min to be actuated. In comparison, for the reference inhalers, by the end of the device life, 30-40% required 40 L/min AFR to be actuated, and 10-30% required 35 L/min AFR to be actuated. About 40-50% of both the shaken inhalers and the reference inhalers required 30 L/min to be actuated when the counter display was 1/0. An increase of 5 L/min is attributed by the applicant to small quantities of powder within the internal mechanism of the device resulting in increased friction of the sliding parts during actuation of the device. There were 5 devices (3% of devices) which had intermittent counter "problems", i.e. the counter did not work for one or two attempts but functioned correctly thereafter until lockout, attributed by the applicant to "mishandling". *Comment: It is less likely that the device would have been mishandled by the laboratory personnel than by patients using the device and the applicant does not explain further how the devices could have been mishandled.* No permanent dose-counter failure occurred.

6.2.3. *Patient Use Study CFOR258F2304* (v1, pgs9-13, a4, a5):

6.2.3.1. Study Objective:

Two identical *patient use studies* were performed (*studies 2304 and 2306*). The objective of these studies was to evaluate the function of the Cerihaler device during and after patient use by collecting patient observation data on potential device failure and conducting an in-vitro technical assessment of the devices at the conclusion of the study, i.e. after three weeks of use. Analysis was descriptive for device functionality and safety (adverse events) only. No formal statistical analysis was done. *Comment: Study 2306 was performed subsequent to study 2304. In study 2304, there were 3 devices that had confirmed device malfunction based on in-vitro studies. Specifically, there was misalignment of the dosing bar and the sliding shelter of the device which led to failure of the dosing mechanism to move so that the dose could not be delivered. This defect had not been observed prior to that time, was not reproducible in the laboratory and was attributed by the applicant to the fact that study 2304 was performed with devices manufactured in 2002 without studs on the guiding rail. Study 2306 was performed using devices that included studs on the guiding rail.*

6.2.3.2. Study Design:

Studies 2304 and 2306 were 3 week, open label, uncontrolled, multi-center studies in patients with asthma (FEV-1 40% or greater) who were 5-74 years of age. Patients received 10 mcg (1 inhalation) of formoterol delivered by Certihaler twice a day approximately 12 hours apart. Albuterol was used as rescue medication. Patients kept a diary that recorded counter number after each use and responded to specific questions about the function of the device. The devices were collected, send back to Novartis and then shipped to SkyePharma for technical in-vitro assessment. The expected number of actuations by patients was 42 (twice a day for 21 days).

Since 60 actuations are delivered by the Certihaler, there were doses left in returned devices. Devices from patients who discontinued the study prior to completion of the three week treatment period were collected and sent to SkyePharma and all unused devices were also collected and returned to Novartis. If the patient considered that the device was not functioning correctly, the patient contacted the study site. If it was determined that the device was malfunctioning, the patient was to be withdrawn from the study. The dataset obtained from the in-vitro technical assessment at the conclusion of the study was considered the primary data for the identification of device function but the results of the in-vitro assessment were to be considered in conjunction with the data recorded daily by the patient in the patient diary.

All Certihaler devices were assessed after the patient treatment period by SkyePharma and given a rating of 0 = device functioning or 1 = device failure. Device assessment included: 1) visible appearance and weight of the returned MDDPI; 2) counter position function; 3) digital photography; 4) functionality of the protective cap and mouthpiece, as reflected in any inconsistencies during opening or bending movements of the protective cap and during removal of the mouthpiece; 5) actuation flow rate (flow rate required to trigger the valve shield); 6) dose counter function test; and 7) lock-out mechanism.

Assessment of AFR was initiated at 30 L/min with increases of 5 L/min if the valve shield failed to move (flow rate was not adequate to trigger the valve shield). Any AFR above 50 L/min was rated a device failure. If the dose counter was not functioning correctly in any way, it was considered a device failure. After the AFR testing, waste shots were made at a flow rate of 60 L/min. After the last dose (counter display 00) an additional waste shot was performed and recorded to confirm that the counter display changed to the final '999' reading and the device lock out mechanism engaged. If the lock-out failed it was considered a device failure

The initial technical assessment of the devices was conducted without reference to the information recorded in the patient diaries. However, at the final evaluation, the technical results were considered in conjunction with the data recorded daily by the patient in the diary so that any device identified as a problem device either from the technical assessment or by the patient was assessed and a narrative prepared discussing functionality of the given device.

Study 2304 was a 3 week open label uncontrolled multi-center study in 157 patients with asthma (FEV-1 40% or greater) who were 5-74 years of age. Patients received 10 mcg (1 inhalation) of formoterol delivered by Certihaler twice a day approximately 12 hours apart with albuterol as rescue medication.

Patient Diary: Patients kept a diary that recorded counter number after each use and patients responded to the following questions: "Did the dose counter decrease by one?"; "Did you get the dose?; and "Did you notice any difference in triggering the device?" "If yes, please comment." At the end of the treatment period, at least 14 doses were required to be left in the Certihaler. The devices were collected, send back to Novartis and then shipped to SkyePharma for technical assessment. Devices from patients who discontinued the study prior to completion of the three week treatment period were collected and sent to SkyePharma and all unused devices were also collected and returned to Novartis. If the patient considered that the device was not functioning

correctly, the patient contacted the site. If it was determined that the device was malfunctioning, the patient was to be withdrawn from the study.

Post Treatment Assessment: All Certihaler devices were assessed after the patient treatment period by SkyePharma and given a rating of 0 = device functioning or 1 = device failure. Device assessment included: 1) visible appearance and weight of the returned MDDPI; 2) counter position (number); 3) digital photography; 4) functionality of the protective cap and mouthpiece, as reflected in any inconsistencies during opening or bending movements of the protective cap and during removal of the mouthpiece; 5) actuation flow rate (flow rate required to trigger the valve shield); 6) dose counter function test; and 7) lock-out mechanism.

Visible properties and weight of returned inhaler: The inhaler was inspected for visual appearance and the weight of the inhaler was recorded to determine the approximate amount of powder released during the in vitro tests of device functioning.

Counter position: The counter position was noted as an indicator of the number of inhalations remaining and whether the counter was functioning and the alignment of the counter figures was checked.

Function of the protective cap and mouthpiece: The moving parts of the inhaler were tested. Any inconsistencies during the opening or bending downward movements of the protective cap and during the removal of the mouthpiece were noted.

Actuation Flow Rate: The flow rate required to trigger the value shield was performed in incremental steps of 5 L/min up to the actuation point beginning at an actuation flow rate of 30 L/min. The minimum flow rate needed to actuate an inhaler was recorded as the average of three consecutive actuations. If the valve shield failed to move during three attempts, the flow rate was increased by 5 L/min and the test repeated. Actuation flow rates above the release specification of 50 L/min were rated as a "failure" and devices were identified where actuation occurred at 40, 45, 50, and 55 L/min. The simulated inhalation was actuated for a duration of 8 seconds to reach a total simulated inspiration volume of 4 liters.

Dose Counter Function: The counter number noted during the initial identification of the returned device was compared to the counter number after actuating each number of doses in the determination of the actuated flow rate. The counter display should have been the same as the calculated difference of the initial counter reading minus the number of effective actuations. After the last dose (counter display 00) an additional waste shot was recorded to confirm that the counter display changed to the final "999" reading and the device lockout mechanism functioned.

The initial technical assessment of the devices was conducted without reference to the information recorded in the patient diaries. However, at the final evaluation, the technical results were considered in conjunction with the data recorded daily by the patient in the diary so that any device identified as a problem device either from the technical assessment or by the patient was assessed and a narrative prepared discussing functionality of the given device.

Safety Monitoring: adverse events were monitored.

6.2.3.3. Study Results (v2, a6, pgs12-32):

In *patient use study 2304*, 157 patients entered the study and 150 patients completed the study. There were 2 patients who discontinued because of adverse events and 5 patients who discontinued because of device malfunction or failure (confirmed in 3 patients; see below) (v6, p58-59). In the patient diary, the patient was asked to respond to 3 specific questions: 1) "Did the dose counter decrease by one?"; 2) "Did you get the dose?"; and 3) "Did you notice any difference in triggering the device?". A difference in device triggering was the major complaint by patients. Of the 81 patients (52%) who noted a difference in triggering the device, 17 (21%) of these patients also reported that the dose counter did not decrease and 17 (21%) reported that they did not get a dose of study medication. There were 8 patients who noted both that the dose counter did not decrease and that they did not get a dose of study medication. The remainder of the patients who gave a positive response, EITHER noted that the dose counter did not decrease OR that they did not get the dose. In-vitro data at the end of the study showed that most of the devices perceived by patients to be malfunctioning in some way were functioning normally without an increase in actuation flow rate or dose counter malfunction. Of 157 assessed devices, 153 worked without malfunction during in-vitro assessment, i.e. the dose counter functioned, the lock-out worked, and the actuation flow rates were expected given a 5 L/min increase with the use of the device. Of the 4 devices that malfunctioned during in-vitro testing, 3 were devices used by patients who discontinued because of device malfunction. These devices were found to have misalignment of the dosing bar and the sliding shelter of the device resulting in failure of the dosing mechanism to move so that the dose could not be delivered. This defect was attributed by the applicant to the fact that the devices were manufactured in 2002 without studs on the guiding rail. One device was accidentally damaged in the lab and removed from the testing program while all of the other 153 returned devices functioned normally without mechanical failure.

In vitro device assessment that was done at the completion of the study confirmed that there was a mechanical failure in 3 of the 5 devices (2%) used by patients who discontinued because of device problems. The device functioned normally in the other 2 patients. There was a misalignment of the dosing bar and the sliding shelter of the device in the 3 malfunctioning devices that resulted in failure of the dosing mechanism to move so that the dose could not be delivered. This was a device failure that had not been observed in any of the previous clinical studies or during technical testing. This jamming of the sliding shelter and dosing bar could not be reproduced in the laboratory and was not a result of permanent deformation of the Certihaler.

Potential inconsistencies during the manufacturing process were retrospectively re-checked and no deviations for the production process of the sliding shelter, dosing bar and guiding rail were observed. All Certihalers showing misaligned position of the dosing bar and sliding shelter were from the same manufacturing period on the assembly line. The applicant attributes this particular device failure to the fact that the study was performed with devices manufactured in 2002 without studs on the guiding rail. The applicant repeated the study (study 2306; see below) with

devices that contained the studs. One device was accidentally damaged in the lab and removed from the testing program while all of the other 153 returned devices functioned normally without mechanical failure.

There were another 9 devices that did not actuate at 40 L/min or less but did actuate at 45 L/min and one device actuated at 50 L/min after failing to actuate at 40 and 45 L/min. Of these, 4 patients did not comment on any problem in their diary, 4 patients commented about device function at some point during the study but did not indicate a problem at the last recorded visit and one patient indicated in the diary on the morning of the last day that it was hard to get a dose. At all visits, the dose counter had decreased as expected. There were no dose counter failures, or failure in lock-out.

There were 22 patients (14%) who responded negatively to the question "Did the dose counter decrease by one?", 21 patients (13%) who responded negatively to the question "Did you get the dose?", and 76 patients (48%) who responded negatively to the question "Did you notice any difference in triggering the device?"(v6, p61).

There were another 8 devices that did not actuate at 40 L/min or less but did actuate at 45 L/min and one device actuated at 50 L/min after failing to actuate at 40 and 45 L/min. Of these, 4 patients did not comment on any problem in their diary, 4 patients commented about device function at some point during the study but did not indicate a problem at the last recorded visit and one patient indicated in the diary on the morning of the last day that it was hard to get a dose. At all visits, the dose counter had decreased as expected. There were no dose counter failures, or failure in lock-out (v2, pgs 13-17).

There were 26 patients (16.6%) in study 2304 who reported an adverse event. There were 2 patients who had severe adverse events suspected of being related to Foradil administration – insomnia and feeling jittery. In general, the adverse events were consistent with administration of an inhaled beta agonist or asthma and no unexpected or unusual adverse events were reported. There were 2 patients who were discontinued from the study; one developed moderate tremor which went away when Foradil was discontinued; the other patient developed exacerbation of asthma not suspected of being related to the study medication. There were no serious adverse events reported. *In general, the adverse events that were reported were those frequently seen after administration of an inhaled beta agonist and were not serious or unexpected. No safety issues are raised from the data in this study.*

6.2.3.4. *Comments: There was a failure rate of 2% of the Certihaler devices characterized by a failure of the dose being delivered. This was recognized by the patient and is clinically acceptable for a drug product proposed for maintenance administration in the treatment of asthma. However, there was a significant incidence of patient inability to use the device correctly associated either with real or perceived malfunction of the device. This is a serious deficiency for this drug product and must be addressed by the applicant before Foradil Certihaler can be approved (see comments to applicant). There was no safety signal from the adverse events reported in this study.*

6.2.4. *Patient Use Study CFOR258F2306* (v1, p13-15)(v2, a7)

Two identical *patient use studies* were performed (*studies 2304 and 2306*). The objective of these studies was to evaluate the function of the Cerihaler device during and after patient use by collecting patient observation data on potential device failure and conducting an in-vitro technical assessment of the devices at the conclusion of the study, i.e. after three weeks of use. Analysis was descriptive for device functionality and safety (adverse events) only. No formal statistical analysis was done. *(NOTE: Study 2306 was performed subsequent to study 2304. In study 2304, there were 3 devices that had confirmed device malfunction based on in-vitro studies. Specifically, there was misalignment of the dosing bar and the sliding shelter of the device which led to failure of the dosing mechanism to move so that the dose could not be delivered. This defect had not been observed prior to that time, was not reproducible in the laboratory and was attributed by the applicant to the fact that study 2304 was performed with devices manufactured in 2002 without studs on the guiding rail. Study 2306 was performed using devices that included studs on the guiding rail.)*

6.2.4.1. Study Design: identical to study 2304 except that the patient diary card was revised by changing the third question in the patient diary from "Did you notice any difference in triggering the device?" to "Did you have to breathe in any harder to make the device work? If yes, please comment.". The rationale for this change is not given by the applicant. In addition, patients were asked to write in the diary when and how they cleaned the device to assess any unusual handling of the device and drawings in the patient instructions in this regard were improved.

6.2.4.2. Study Results (v2, a9, pgs7-30)

There were 154 patients entered into the study 5-74 years of age and 145 patients completed the study. There were 9 patients who discontinued prematurely: one due to an adverse event (headache), five because of malfunction of the device, one because the device was destroyed by a dog, one because the patient missed multiple doses because of device and counter malfunction (described by the applicant as "administrative") and one because the patient broke the device.

There were 73 patients (47%) who had some type device malfunction at least once during the study. Of these patients, 28 (18%) indicated that the dose counter did not decrease by one. There were 16 patients (10%) who indicated that they did not get the dose. There were 14 of these 16 patients (86%) who indicated that they had to breathe in harder to make the device work. There were 63 patients in all (41%) who indicated that they had to breathe in harder to make the device work. There were 19 of these patients (30%) who also indicated that the dose counter did not decrease and 14 (22%) who indicated that they did not get the dose.

In-vitro device assessment at the end of the study found only one device with a mechanical failure, while all other devices functioned normally. The one malfunctioning device had a malfunctioning dose counter where the dose counter failed to count the dose. The patient who had this device recorded that the dose counter did not decrease by one on several occasions and that he did not get the dose of study medication. The device was still actuating and providing medication yet the dose counter had stopped counting which was due to a damaged counter

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mechanism. A hole was drilled into the top shell of the device, an endoscope was inserted and it was noted that a [redacted]

There were 19 adverse events (12%) reported from this study. One patient developed a severe headache requiring discontinuation from the study that was suspected of being related to Foradil administration. There were no serious adverse events reported. *In general, the adverse events that were reported were those frequently seen after administration of an inhaled beta agonist and were not serious or unexpected. No safety issues are raised from the data in this study*

COMMENT: *Using devices with studs, the absence of which was felt by the applicant to be the cause for device malfunctioning in study 2304, there was only one device (0.6%) that had a malfunctioning dose counter. This incidence of malfunction is clinically acceptable for a drug product that is intended for the maintenance treatment of asthma. However, there was a significant incidence of patient inability to use the device correctly associated either with real or perceived malfunction of the device. This is a serious deficiency for this drug product and must be addressed by the applicant before Foradil Certihaler can be approved (see comments to applicant). No safety signals were apparent from the data in this study.*

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The only safety parameter that was assessed by the applicant was adverse events in patient use studies 2304 and 2306.

7.1.1. Deaths

There were no deaths in the studies performed by the applicant that were included in this submission.

7.1.2. Other Serious Adverse Events

There were no serious adverse events reported from the studies included in this submission.

7.1.3. Dropouts and Other Significant Adverse Events

There were 2 patients discontinued from study 2304. Adverse events were moderate tremor "suspected" by the investigator of being related to the study drug and moderate asthma exacerbation not "suspected" of being related to the study drug. One patient was discontinued from study 2306 because of a moderately severe headache "suspected" by the investigator of being related to the study drug. *Tremor is a recognized adverse effect from beta2 adrenergic bronchodilators. Asthma exacerbations occur in patients with asthma during study of*

medications and headache is a common adverse event noted in studies of medications. None of these adverse events sends a signal about the safety of Foradil Certihaler.

7.1.3.1. Overall Profile of dropouts

In study 2304, there were 7 patients discontinued from the study. Of these, 2 were discontinued because of adverse events and 5 were discontinued because of device malfunction. In study 2306, 9 patients were discontinued. Of these, one was discontinued because of an adverse event, one because it was destroyed by a dog, and 7 because of malfunction of the device.

7.1.5. Common Adverse Events

There were 26 patients (16.6%) in study 2304 who reported an adverse event. There were 2 patients who had severe adverse events suspected of being related to Foradil administration – insomnia and feeling jittery. There were 2 patients who were discontinued from the study; one developed moderate tremor which went away when Foradil was discontinued; the other patient developed exacerbation of asthma not suspected of being related to the study medication. There were no serious adverse events reported. There were 19 adverse events (12%) reported from study 2306. One patient developed a severe headache requiring discontinuation from the study that was suspected of being related to Foradil administration. There were no serious adverse events reported. *Comment: In general, the adverse events that were reported were those frequently seen after administration of an inhaled beta agonist and were not serious or unexpected. No safety issues are raised from the data in this study*

7.15.4. Common Adverse Event Tables

Adverse events in study 2304 that occurred in 1% or more of patients after receiving formoterol 10 mcg bid

Adverse event	incidence
Influenza	1.9%
URI	3.8%
Sinsusitis	1.3%
Asthma	1.9%
Pharyngolaryngo pain	1.9%
Vomiting	1.3%
Tremor	1.3%

Adverse events in study 2306 that occurred in 1% or more of patients after receiving formoterol 10 mcg bid

Adverse event	incidence
Nasopharyngitis	1.3%
URI	1.3%
Cough	1.9%
Headache	1.9%

7.2.9. Additional Submissions, Including Safety Update

In the approvable letter of 17 October 2003, the applicant was told to include a safety update. However, this issue was further discussed on the conference calls of 19 November 2003 and 23 December 2003, and it was agreed that a safety update was not necessary since the only additional clinical studies conducted since the 120 day safety update are the studies that are included in this submission. In addition, Foradil Certihaler has not been marketed in any other country so there is no post-marketing data available.

9 OVERALL ASSESSMENT

9.1 Conclusions

The applicant has responded to the deficiencies stated in the approvable letter of 17 October 2003. This response is based on simulated in-use studies and patient use clinical studies performed to demonstrate that the device did not display the same counter and actuation flow rate problems which had been seen in phase 3 studies. The applicant demonstrated that no significant incidence of device malfunction could be demonstrated by in-vitro assessment with use of the devise.

However, this drug product can not be approved until the applicant has taken appropriate action to improve patient understanding on how to correctly use the Certihaler device. In patient use studies, despite what should have been adequate instruction on the use of the device, an unacceptably high percentage of patients found the device difficult to use. Specifically, 14-18% did not feel that the dose counter decreased by one with use of the device at some point during use of the device, 10-13% felt that they did not get the dose at some point during use of the device, 52% indicated that they noticed a difference in triggering the device and 41% had to breathe harder to make the device work. This clearly indicates confusion on the part of patients, even after careful instruction, on how to correctly use the device. Patient understanding about the use of the device is linked to the efficacious and safe use of the drug product. Therefore, this drug product can not be approved unless the applicant can formulate a plan to improve patient understanding about the correct use of the device.

9.2. Recommendation on Regulatory Action.

Foradil Certihaler is approvable. This drug product can not be approved until it has been clearly shown that patients can reliably and consistently use the Certihaler device. In order to do that, patients must be more effectively instructed in the use of the device. In patient use studies, despite instruction in the use of the device, an unacceptably high percentage of patients found the device difficult to use. Specifically, 14-18% did not feel that the dose counter decreased by one with use of the device at some point during use of the device, 10-13% felt that they did not get the dose at some point during use of the device, 52% indicated that they noticed a difference in triggering the device and 41% had to breathe harder to make the device work. It will be necessary to perform a patient use study with new and more comprehensive instructions for use

of the device. Such as study will need to demonstrate that the patient difficulties seen in the patient use studies submitted with the Complete Response can be overcome with more effective instruction. This study should be performed in a representative sample of patients with the intensity of instruction that could be expected in a clinical setting.

Although not a deficiency, in regard to educational activities to avoid confusion between the use of Foradil Aerolizer and Foradil Certihaler, the plan submitted for differentiation in use of these two products is unacceptable. In the promotional material for this drug product, in order to address the comment made in the approvable letter, educational activities should compare the Certihaler and the Aerolizer and indicate that the Certihaler should only be used for the treatment of asthma.

In regard to the labeling for this drug product:

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