MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS (HFD-570)

APPLICATION #:	20-831	APPLICATION TYPE:	NDA
SPONSOR:	Novartis	TRADE NAME:	Foradil®
CATEGORY:	Single-dose, dry powder	GENERIC NAME:	formoterol
	Beta-2 agonist	ROUTE:	oral inhaled
MEDICAL OFFICER:	Raymond F. Anthracite	REVIEW DATE:	

SUBMISSIONS REVIEWED IN THIS DOCUMENT

DOCUMENT DATE	CDER DATE	SUBMISSION TYPE	COMMENTS
8/17/2000	8/18/2000	complete response	financial disclosure

RELATED APPLICATIONS

DOCUMENT DATE	APPLICATION TYPE	COMMENTS

REVIEW SUMMARY:

Financial disclosure reviewed and is in compliance with 21 CFR 54.

OUTSTANDING ISSUES:

None

RECOMMENDED REGULATORY ACTION

NEW CLINICAL STUDIES:		PROCEED		HOLD		(HOLD TYPE)
NDA/SUPPLEMENTS:	XX	APPROVAL		APPROVABLE		NOT APPROVABLE
OTHER ACTION:						

SIGNATURES

Reviewer: _____ Date: 01/09/2001

Team Leader: _____ Date: _____

APPEARS THIS WAY
ON ORIGINAL

I. FINANCIAL DISCLOSURE

The sponsor is in compliance with 21 CFR Part 54 and has submitted an FDA form 3454 with a list of clinical investigators. These were checked against the disbarred list of investigators by the Project Manager and found to be acceptable. In accordance with 21 CFR 54.4(a)(1), the sponsor had certified that none of the clinical investigators have financial interests or arrangements described in this regulation that require more detailed disclosure [1:99-103].

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
ND#20-831
HFD-570/Division Files
HFD-570/Deputy Division Director/Mann
HFD-570/Medical Reviewer/Anthracite
HFD-570/Project Manager/Jani

APPEARS THIS WAY
ON ORIGINAL

/s/

Raymond Anthracite
1/9/01 08:54:32 AM
MEDICAL OFFICER

Marianne Mann
1/16/01 01:04:33 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS (HFD-570)

APPLICATION #:	20-831	APPLICATION TYPE:	NDA CR to "approvable' letter
SPONSOR:	Novartis	TRADE NAME:	Foradil
CATEGORY:	long-acting β-2 agonist	GENERIC NAME:	formoterol fumarate
		ROUTE:	oral inhaled
MEDICAL OFFICER:	Raymond F. Anthracite	REVIEW DATE:	

PRIMARY SUBMISSION REVIEWED IN THIS DOCUMENT

DOCUMENT DATE	CDER DATE	SUBMISSION TYPE	COMMENTS
11/23/99	11/24/99	NDA CR to "approvable"	71 volumes

RELATED APPLICATIONS

DOCUMENT DATE	APPLICATION TYPE	COMMENTS
3/17/00	Doc ID NC	Re-sent illegible figures
10/19/98	incomplete response to approvable	contains 10/98 safety update

REVIEW SUMMARY:

This review contains a disparate set of materials related to NDA #20-831. The first section contains a review of the responses to seven clinical deficiencies sent in the 26 June 1998 Division Director's approvable letter. Next is the resolution of three outstanding issues that couldn't be completed in the original Medical Officer's review. The following section deals with reviews of safety updates submitted in the Fall of 1998 and 1999. The former was a fairly large submission and the latter was subsumed in the review of pediatric protocol #049, the last section of this document.

OUTSTANDING ISSUES:

None.

RECOMMENDED REGULATORY ACTION

NEW CLINICAL STUDIES:	____	HOLD	____	MAY PROCEED
NDA/SUPPLEMENTS:	XX	APPROVABLE	____	NOT APPROVABLE
OTHER SUBMISSIONS:	____	(ACTION)		

SIGNATURES

Reviewer: /S/ Date: 4/11/2000

Team Leader: /S/ Date: 4/15/2000

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I. INTRODUCTION

This review contains a disparate set of materials related to NDA #20-831. The first section contains a review of the responses to seven clinical deficiencies sent in the 26 June 1998 Division Director's approvable letter. Next is the resolution of three outstanding issues that couldn't be completed in the original Medical Officer's review. The following section deals with safety updates submitted in the Fall of 1998 and 1999. The former was a fairly large submission and the latter was subsumed in the review of pediatric protocol #049, the last section of this document. A Table of Contents in the preceding section should identify where these items and elements are located.

II. NOTE TO READERS

This review has been written in a manner that permits the reader ever finer degrees of detail in tracking items of interest. The Introduction provides an overview. Greater detail is available in any of the sections shown in the Table Of Contents and still greater detail in any of its several subsections. The final level of detail is provided by the dated-submission referencing information within square brackets. The convention for these references is found in the following hierarchical ordering: [DATE VOLUME:PAGE, PAGE-Page, VOLUME:PAGE, PAGE-Page, DATE, COMMUNICATION TYPE & EXPLANATION]. Where no date is provided in a new reference, the date of the "Primary Submission Reviewed In This Document" is assumed. Where no date is provided in a reference and a prior date is available within the same square brackets, the earlier date is assumed. Where no volume is supplied and a prior volume is available within the same square brackets, the previously referenced volume is assumed.

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA #20-831
HFD-570/Division Files
HFD-570/Team Leader/Chowdhury
HFD-570/Medical Officer/Anthracite
HFD-570/PM/Jani

III. CLINICAL RESPONSES TO APPROVABLE LETTER

This submission represents a "complete response" to points raised in the Division Director's "approvable" letter dated 26 June 1998 which summarized all reviews of the original NDA, submitted 24 June 1997. Seven issues were raised during the clinical portion of the review. These (in sans serif font) and the responses to them (in this font) will be addressed in order that they were stated in section B of the original "approvable" letter [1:18-21].

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

   Pediatric protocol #049 is reviewed later in this document and adequately addresses safety and efficacy of 12 μg ———— of the formoterol dry powder inhaler administered twice daily to children 5-12 years of age.

2. The indication protection against exercise-induced bronchoconstriction (EIB) for children ———— of age is not supported by available data. The youngest patient studied in trial DP/PD3 was 10 years of age. Furthermore, the optimal dose for protection against EIB for the pediatric population has not been determined. An additional placebo-controlled trial that enrolls an appropriate number of pediatric patients over the entire age range proposed for approval and that adequately characterizes the optimal dose for the management of EIB in this age group is required for approval (see item 1 above). We encourage you to consult with the Division of Pulmonary Drug Products regarding the design of the study before it is initiated.

An additional study that addresses EIB was submitted to IND [redacted] 7/16/99 (serial #153) as a proposed pediatric exclusivity study request.

3. The Integrated Summary of Safety is incomplete in that it does not include analyses of, and case report forms (CRF's) for, all patients who prematurely discontinued participation in clinical trials due to adverse events and for patients who suffered serious adverse events in trials involving formoterol. Provide a complete accounting and index for previously submitted data as well as the CRF's that were not provided in this original NDA submission for all patients meeting the aforementioned criteria.

The indices of CRF's were adequate, but the complete analyses of withdrawals due to AE's and of SAE's were not and these latter were requested when these omissions in the current submission were recognized [3/27/2000 Telecon with Cathy Creedon]. In response, we received a FAX with tables all patients who had experienced SAE's or discontinued because of an AE and their treatment assignments for multiple-dose controlled and uncontrolled trials as of the 1998 data base. Tables with the same information were derived from the 1999 data base and sent for 5-12 year old children [4/5/2000 FAX from Pat McGovern]. As the sponsor contended, review of all of these data did not contribute any additional safety concerns.

4. Provide an analysis of the demography of patient exposure by duration of treatment and by formoterol dose for the following age categories: 6 to 12 years, 12 to 18 years, and equal to or greater than 18 years. Clarify in which of the categories 12-year-old and 18-year-old patients are included.

The sponsor offered a reference to Item 9, Volume 31, Pp 26-31 of the October 19, 1998 submission (Tables 2.2-11 to 2.2-13). As in the past, these references to table designations and pages were incorrect. The correct tables were found in the November 23 1999 submission [31:28-9, 36-7].

This report is on the dry powder formulation for the age range of 5 to 12 years, inclusive. These data do not include protocol #049 which has been reviewed separately in this document. These exposure data are unchanged since 1996 and are a recapitulation of the 1998 submission. Only one child was actually 5 years of age. One patient may have received more than one dose of formoterol in crossover and safety extensions of double-blind trials, so column totals sum to a number greater than the total number of enrolled patients [31:28, 30-1].

NDA #20-831 - DURATION OF DRUG EXPOSURE TO FORMOTEROL SINGLE-DOSE DRY POWDER FOR MULTIPLE DOSE CONTROLLED TRIALS BY DAILY DOSE FOR PATIENTS 5-12 YEARS OF AGE, DATA THROUGH 15 JULY 1998, COUNT (% TOTAL THESE AGES) [31:28]					
Duration of Exposure	**≤ 6 mcg n = 168**	**12 mcg n = 647**	**24 mcg n = 3392**	**48 mcg n = 873**	**> 48 mcg n = 62**
= 1 day	29 (100)	38 (32.8)	29 (17.0)	0	0
2 - 7 days	0	5 (4.3)	1 (0.6)	0	0
>1 wk - 4 wks	0	1 (0.9)	7 (4.1)	1 (3.2)	0
>4 wks - 12 wks	0	13 (11.2)	20 (11.7)	4 (12.9)	0
>12 wks - 24 wks	0	59 (50.9)	49 (28.7)	7 (22.6)	0
>24 wks - 36 wks	0	0	7 (4.1)	9 (29.0)	0
>36 wks - 48 wks	0	0	6 (3.5)	6 (19.4)	0
> 48 wks	0	0	52 (30.4)	4 (12.9)	0
Total Ages 5-12 (% n)	29 (17.3)	116 (17.9)	171 (5.0)	31 (3.6)	0
n = total all ages					

Comments on the age range 13 to 18 years of age, inclusive, are identical to those for the younger age range shown above except that patient counts were so low as to contribute little to the overall data base.

NDA #20-831 - DURATION OF DRUG EXPOSURE TO FORMOTEROL SINGLE-DOSE DRY POWDER FOR MULTIPLE DOSE CONTROLLED TRIALS BY DAILY DOSE FOR PATIENTS 13-18 YEARS OF AGE, DATA THROUGH 15 JULY 1998, COUNT (% TOTAL THESE AGES) [31:29]					
Duration of Exposure	**≤ 6 mcg n = 168**	**12 mcg n = 647**	**24 mcg n = 3392**	**48 mcg n = 873**	**> 48 mcg n = 62**
= 1 day	1 (100)	19 (57.6)	12 (12.9)	3 (7.0)	1 (50.0)
2 - 7 days	0	11 (33.3)	3 (3.2)	0	1 (50.0)
>1 wk - 4 wks	0	0	9 (9.7)	0	0
>4 wks - 12 wks	0	1 (3.0)	33 (35.5)	11 (25.6)	0
>12 wks - 24 wks	0	2 (6.1)	30 (32.3)	28 (65.1)	0
>24 wks - 36 wks	0	0	5 (5.4)	0	0
>36 wks - 48 wks	0	0	1 (1.1)	0	0
> 48 wks	0	0	0	1 (2.3)	0
Total Ages 13-18 (% n)	1 (0.6)	33 (5.1)	93 (2.7)	43 (4.9)	2 (3.2)
n = total all ages					

Patient counts are substantial in the table below, which represents adults exposed to the single-dose dry powder only [31:30].

NDA #20-831 - DURATION OF DRUG EXPOSURE TO FORMOTEROL SINGLE-DOSE DRY POWDER FOR MULTIPLE DOSE CONTROLLED TRIALS BY DAILY DOSE FOR PATIENTS >18 YEARS OF AGE, DATA THROUGH 15 JULY 1998, COUNT (% TOTAL THESE AGES) [31:30]					
Duration of Exposure	**≤ 6 mcg n = 168**	**12 mcg n = 647**	**24 mcg n = 3392**	**48 mcg n = 873**	**> 48 mcg n = 62**
= 1 day	138 (100)	334 (67.1)	310 (9.9)	61 (7.6)	45 (75.0)
2 - 7 days	0	17 (3.4)	60 (1.9)	4 (0.5)	15 (25.0)
>1 wk - 4 wks	0	5 (1.0)	196 (6.3)	49 (6.1)	0
>4 wks - 12 wks	0	41 (8.2)	1310 (41.9)	142 (17.8)	0
>12 wks - 24 wks	0	100 (20.1)	576 (18.4)	414 (51.8)	0
>24 wks - 36 wks	0	0	260 (8.3)	18 (2.3)	0
>36 wks - 48 wks	0	0	30 (1.0)	51 (6.4)	0
> 48 wks	0	1 (0.2)	386 (12.3)	60 (7.5)	0

NDA #20-831 - DURATION OF DRUG EXPOSURE TO FORMOTEROL SINGLE-DOSE DRY POWDER FOR MULTIPLE DOSE CONTROLLED TRIALS BY DAILY DOSE FOR PATIENTS >18 YEARS OF AGE, DATA THROUGH 15 JULY 1998, COUNT (% TOTAL THESE AGES) [31:30]					
Duration of Exposure	≤ 6 mcg n = 168	12 mcg n = 647	24 mcg n = 3392	48 mcg n = 873	> 48 mcg n = 62
Total Age > 18 (% n)	138 (82.1)	498 (77.0)	3128 (92.2)	799 (91.5)	60 (96.8)
n = total all ages					

5. The qualitative analysis of electrocardiographic (ECG) data from Studies #40 and #41 are inadequate without a complete description of the criteria and methodology used to categorize the data. Describe the ECG criteria for categorization, the methodology for assuring consistency and bias control in interpretation by readers, and the relative frequency of these interpretations within treatment groups. If these criteria and methodology were not applied to the original categorical analyses of the qualitative database, a reanalysis of the database is required.

There was one central location for all ECG data from studies #40 and #41. with a sole designated reader. The ECG's were electronically transmitted from the study sites to the central location. A printed hard copy served as the source documentation and all interpretations were performed "totally blinded." One presumes that this means blinding as to treatment, but the blinding was not further explicated. The four categorizations assigned to each tracing were "normal," "abnormal but clinically insignificant," "abnormal" and "abnormal and clinically significant." The criteria for these categories were presented and appear reasonable. The frequency distributions of categories for baseline, 2, 4 and 6 hours post-treatment at visits 2, 4, 5 and 6 for study #40 were presented and reviewed and were not revealing of any new safety concerns [1:20-1, 66-7, 69-87, 31:82-4].

6. The categorical analysis of electrocardiographic intervals (e.g., PR, QRS, QT/QTc) from the available ECG database is inadequate. Provide summary variables of central tendency (i.e., mean and standard deviations) as well as sensitivity analyses (e.g., change from baseline of 0-10%, 10-15%, 15-20%, 20-30%, etc.) to describe distributions and comparisons between treatment groups and formoterol doses. If not previously performed, ECGs should be read in a blinded fashion, QT should be corrected for rate using conventional methodologies (e.g., Bazett's formula), and QT/QTc analyses should include a presentation of mean change as well as mean maximum change from baseline, when available.

PR, QRS, QT and QTc intervals were presented as pre-dose means (± SD) for visits 2, 4, 5 and 6 for the combined pivotal trials, protocols #40 and #41. Sensitivity analyses were also done as frequency counts for various maximum

increases and decreases during treatment from the pre-dose baseline at visit 2. Pre-dose PR interval means showed small increases from baseline to visits 4, 5 and 6 for the 48 mcg/day group but no other consistent findings. Frequency categories of 24 and 48 mcg of dry powder formoterol, salbutamol and placebo were very similar. Pre-dose means of QRS intervals rose slightly at post-baseline visits for both formoterol but showed inconsistent changes in salbutamol and placebo groups. Frequency categories of all four drugs were similar. Means and frequency categories of QT and QTc intervals and changes were virtually identical among all treatment groups. Acute effects on these intervals were also shown as baseline, 2, 4 and 6 hours after treatment on the first treatment visit and the 3-month visit. PR intervals declined from baseline over the ensuing six hours in all groups at both visits. No such acute effect was seen for QRS, QT or QTc intervals [31:84-105]. The net result of this is that there was not much effect on any of these variables after acute or chronic dosing.

7. Provide original and English translations of approved product labels from countries in which formoterol is approved and/or marketed.

Formoterol dry powder formulation (12 mcg capsules) is presently approved for marketing in 61 countries, is available in 53 and has never been withdrawn from the market in any country. Seventeen product labels, or English translations of them, were provided from the countries with the largest markets. Largest was defined as ———— In addition, the international product label (IPL), which has been adopted by several other countries was included [2:63-5]. Non-exhaustive perusal of this partial list of product labels revealed some differences.

The IPL suggests that formoterol is for adults and children down to 5 years of age. One-to-Two 12 mcg capsules given twice daily are indicated for asthma and chronic bronchitis and some acute use is suggested; e.g., "1-2 capsules in addition to those required for maintenance therapy may be used each day..." but if additional use is more than 2 days each week, the patient is encouraged to call a physician. Caution is given against QTc prolonging drugs as being proarrhythmic. Hyperglycemia and hypokalemia are specifically addressed. Storage below 25 degrees Celsius is recommended. Austria, New Zealand and Portugal seem to favor occasional acute use. Austria, Germany, Ireland, Italy, Denmark, Portugal, Sweden and the Netherlands recommend a 3-year storage life. France suggests storage below 30 degrees but doesn't mention shelf life. Greece wants it refrigerated for no more than 9 months then used within 3 months of dispensing [2:67-270].

IV. OUTSTANDING ISSUES

Three issues were identified in the original NDA and 120-Day Safety Update review by this Medical Officer as outstanding at the time of review completion.

1. All DSI audits and returned data sheets had not been completed.
2. SAE's and AE's linked to premature termination from trials were incompletely summarized and analyzed. Tables were constructed identifying those groups truncated by the AE occurring in ≥ 2% of formoterol patients. This summary and display strategy left about 40% of AE's and early discontinuations due to AE's available only as line listings.
3. CRF's of deaths and early discontinuations due to AE's were planned to spot check concordance with summary data ascribed to them. These couldn't be completed because of incomplete indexing of the submission.

IV.A. DSI AUDITS

Below are the four investigator and site audits that we requested. Each was subject to the routine Division of Special Investigation (DSI) audit and we prepared a sheet with nine patient numbers and dates and the line listings for three lab values (glucose, potassium, QTc) for each. The investigator was to check the primary data listings at the sites for the three data points for each of the nine patients and either mark that they were correct or fill in the correct values.

NDA #20-831 - DSI AUDITS			
Protocol Number	Investigator	Center Number	Location
40	Bensch	M0177Z	Stockton, California
40	Lumry	M0137N	Dallas, Texas
41	Pollard	M0160U	Louisville, Kentucky
41	Pleskow	M0159B	Encinitas, California

Three of the evaluations were classified as NAI (no deviation from regulations - data acceptable. The evaluation of investigator Bensch was classified as VAI (minor deviations from regulations - data acceptable). Both NAI and VAI classifications are, as the definitions of the classifications state, acceptable. All DSI evaluators noted that no discrepancies were noted in the data tables that they reviewed, but only three of the four data tables were returned to this reviewer. The table from investigator Pleskow was not returned. DSI auditors Cynthia L. Evitt and Kelly J. Pegg did an especially detailed job in filling out the three-decimal-place values from which rounding to two decimal places was done [4/7/2000 FAX from Hsien W. Ju].

IV.B. SAE'S & EARLY DISCONTINUATIONS DUE TO AE'S

The response to the third clinical question was complete and satisfactorily presented complete accounting of patients and treatment groups to which they were

assigned for those reporting SAE's and early termination because of AE's [4/5/2000 FAX from Pat McGovern].

IV.C. CRF SPOT-CHECKS

Ten deaths were recorded during the 39 trials including 6 patients who had received formoterol inhalation capsules, 2 who had received salbutamol and 2 who had gotten placebo. With the new index, the CRF's were located and reviewed [Excel Spreadsheet INDX_CRF.XLS in current submission]. Short narratives of these deaths follow [6/24/97 377:125-32].

Case T92HQ20641, Great Britain 21/242 (Protocol DP/RD3F) Formoterol
A 77 year old male with an 11-year history of Type II Diabetes who had received formoterol inhalation capsules 24 µg/day collapsed an died of a myocardial infarction 199 days after beginning treatment [6/24/97 418:284-320].

Case T92HQ22601, Great Britain 41/116 (Protocol DP/RD3F) Formoterol
A 73 year old male with "bundle branch block and ventricular ectopics" (not further specified) at entry who had been treated with formoterol inhalation capsules 24 µg/day experienced abdominal pain, later diagnosed as a myocardial infarction, after 125 days on this drug and died 21 days later of ischemic heart disease [6/24/97 413:248-332].

Case T93HQ44661, Netherlands 4/3062/358 (Protocol [redacted].02) Placebo
A 60 year old male with complete LBBB, 1°AV block and sinus bradycardia on entrance ECG was found dead 3 days after taking the third trial medication (placebo) of a presumed myocardial infarction [6/24/97 393:1-52].

Case T96USA00061, USA M0161Y/4625/6410 (Protocol 41) Formoterol
A 66 year old female treated with formoterol inhalation capsules 48 µg/day for 19 days was found unresponsive after calling for help because of a severe exacerbation of asthma. Her eosinophil differential was initially 4% but rose to 13% shortly before her death [6/24/97 437:83-139].

T93HQ34801, Great Britain 37/354 (Protocol DP/RD3F) Formoterol
A 69 year old female with a 3-year history of colon cancer resection was treated with 48 µg/day of formoterol in the double-blind phase and 24 µg/day in the follow up period for a total of 313 days. She contracted bronchopneumonia from which she died three days later [6/24/97 418:166-282].

T92HQ23011, Great Britain 14/161 (Protocol DP/RD3) Salbutamol

A 69 year old male ex-smoker was hospitalized with a chest infection after 79 days of treatment with salbutamol 1600 µg/day. The trial treatment was stopped and the patient died after the trial of a bronchogenic carcinoma [6/24/97 395:173-229].

T92HQ00921, Denmark Unk/425 (Protocol DP/RD1) Placebo

A 47 year old female had taken placebo as the last trial medication 4 weeks prior to her death from a respiratory arrest at her home. The sponsor addressed this as a post-trail death for which reporting was unnecessary [Excel Spreadsheet INDX_CRF.XLS in current submission].

T94HQ00077, Great Britain 5/58 (Protocol DP/RD3F) Formoterol

A 78 year old male received a total of 14 months of treatment, first with formoterol 48 µg/day in the double-blind period, then 24 µg/day in the follow up period. He died of metastatic cancer, primary unknown. His death was not captured in the CRF's submitted and referenced [6/24/97 412:189-313].

T95USA00332, USA M0171B/4313/6208 (Protocol 41) Salbutamol

A 26 year old 275-pound female was treated with salbutamol 720 µg/day for 12 days experienced chest pain 3 days prior to her death. Symptoms of nausea and vomiting developed and she died of autopsy-proven hemorrhagic pancreatitis, peritonitis and hypovolemic shock from a gastrointestinal hemorrhage [6/24/97 438:184-230].

T94HQ00311, Norway 2/2016 (Protocol [redacted]03) Formoterol

A 56 year old male had received formoterol inhalation capsules 24 µg/day for 84 days when he completed the trial. Ten days after completion of the study he was hospitalized for hemiparesis the etiology of which was squamous cell carcinoma of the lung metastatic to the brain and adrenal glands. The sponsor contends that this condition led to a post-trial death the reporting of which is not required [Excel Spreadsheet INDX_CRF.XLS in current submission].

These fatalities afflicted mostly elderly patients and were too small in number to suggest any meaningful trend, however the CRF's did accurately reflect the information in the patient narratives.

V. SAFETY UPDATES

V.A. 19 OCTOBER 1998 SU

V.A.1. SUMMARY

This safety update was submitted as a complete response (CR), was not accepted as such by our division and went on to dispute resolution at the center level. Most of the additional dry-powder (ISF) formoterol-treated patients came from multiple-dose uncontrolled trials (1383) with lesser contributions from one multiple-dose salmeterol controlled trial (241) and a single-dose crossover trial (24). A total of 1887 new patients, of which 1648 were treated with formoterol, were available for this safety review. Ninetynine percent (1632) of these new formoterol-treated patients received a dose of 12 mcg twice daily, or a daily dose of 24 mcg. The modal treatment duration was 12-24 weeks in controlled trials and 4-12 weeks in uncontrolled trials. The safety database continued to be dominated by Caucasian adults of European extraction, the geographic area where most of the studies were done. The majority of participants had mild-to-moderate asthma ($FEV_{1.0}$ > 50% predicted). Among the adverse events in multiple-dose controlled trials with a greater report frequency in formoterol-treated than placebo-treated patients, "tremor," "cramps muscle" and "insomnia" remained dose-ordered. "Tachycardia," "tremor" and "cramps muscle" were also frequently considered to be drug-related. Early discontinuations due to adverse events were about equally frequent in all treatment and control groups. The active treatment and active control groups were comprised of various beta-2 agonists; formoterol dry powder, other formoterol formulations, salmeterol and salbutamol. Serious adverse events were slightly more common in active treatment and active control groups than in the placebo group. No new insights emanated from this safety update.

V.A.2. DATA SETS & SUBJECT ACCOUNTING

Since the cut-off date of the Integrated Safety Summary (ISS) and 120-Day Safety Update (SU), five clinical study reports of the dry powder (12 mcg ISF capsule) formulation have been incorporated into the safety dataset. These were protocol #54 (single-dose, 12 patients), protocol DP/DF0 (single-dose, 12 patients), protocol #27 (multiple-dose controlled vs. salmeterol, 480 total patients), protocol #50 (multiple-dose controlled vs. salmeterol, 127 total patients) and protocol FFOR14/F (multiple-dose uncontrolled, 1383 total patients). Protocols #54, DP/DF0 and #27 were fully integrated, but this was not the case with protocols #50 and FFOR14/F. Protocol #50 and FFOR14/F provided data for SAE's and the latter trial contributed some data for all adverse events (AE's). The five new trials included three data sets: single-dose, multiple-dose controlled and multiple-dose uncontrolled studies [31:12-4].

V.A.3. EXPOSURE

The following table shows the number of patients evaluated for safety by dataset and treatment. If a patient count for any treatment changed since the 1996 ISS, the number in parentheses indicates the change. The row totals did not always add up to the marginal totals because of single-dose crossover and multiple-dose uncontrolled trials. The crossover design usually meant that one patient received several treatments. The multiple-dose uncontrolled trial patients were extensions of controlled studies and different treatments may have been given to the same patient in each. The single-dose placebo cell (SD x PBO) correction of -1 was due to misclassification in 1996 that was corrected. Most of the added patients came from multiple-dose uncontrolled trials (1383 additional) with a lesser contribution from a multiple-dose salmeterol controlled trial (241). A total of 1887 new patients, of which 1648 were treated with formoterol, were available for this safety review [31:15]. "Compar" in the table below represents Formoterol Comparator, which was considered to be any other formoterol formulation [6/24/97 377:17].

NDA #20-831 1998 SU - FORMOTEROL SINGLE-DOSE DRY POWDER: NUMBER OF PATIENTS (CHANGE SINCE 1996) EVALUATED FOR SAFETY BY DATASET, OR TRIAL TYPE, AND TREATMENT [31:15]

Trial	Formot	Salbut	PBO	Compar	Budes	Salmet	All
SD	523 (24)	172	417 (-1)	238 (12)	0	0	528 (24)
MDC	2123 (241)	821	692	444	21	239 (239)	4220 (480)
MD PC	1252	463	692	444	21	0	2882
40 & 41	546	272	277	0	0	0	1095
MDU	2049 (1383)	0	0	0	0	0	2049 (1383)
All	4277 (1648)	993	1109 (-1)	682 (12)	21	239 (239)	6131 (1887)

Formot = formoterol fumarate dry powder for inhalation
Salbut = salbutamol
PBO = placebo
Compar = formoterol comparator (other formoterol formulations)
Budes = budesonide
Salmet = salmeterol

SD = single-dose
MDC = multiple-dose controlled
MD PC = multiple-dose placebo-controlled
40 & 41 = pivotal trial designators in adults
MDU = multiple-dose uncontrolled
(###) = change since 1996

Exposure to different doses of formoterol dry powder by study group is shown in the table below. As before, if a cell value changed since the 1996 ISS, that change was reflected by the number within the parentheses. The sponsor did not provide marginal row totals. The crossover and uncontrolled trials make simple addition of marginal column totals misleading, but one assumes that these are the 4277 total and 1648 new formoterol-treated patients from the last table. The largest increase in patient counts since 1996 was in patients who received 12 mcg BID (24 mcg/day) [31:16]. The shaded rows are the trial types that will be further scrutinized in tables to follow.

NDA #20-831 1998 SU - FORMOTEROL SINGLE-DOSE DRY POWDER: NUMBER OF PATIENTS EVALUATED (CHANGE SINCE 1996) FOR SAFETY BY DATASET, OR TRIAL TYPE, AND TOTAL DAILY FORMOTEROL DOSE, IN MCG/DAY [31:16]					
Trial	≤ 6	12	24	48	> 48
SD	168	407 (12)	352 (8)	56 (4)	45 (12)
[redacted]					
MD PC	0	163	629	476	17
40 & 41	0	0	275	271	0
[redacted]					
All	168	647 (12)	3392 (1632)	873 (4)	62 (12)
SD = single-dose MDC = multiple-dose controlled MD PC = multiple-dose placebo-controlled			40 & 41 = pivotal trial designators in adults MDU = multiple-dose uncontrolled (###) = change since 1996		

The next table shows the distribution of doses of formoterol by duration of exposure in multiple dose controlled trials. From the table above one can see that the dose-group that had the virtually all of the change since 1996 was the 24 mcg/day group, which contributed 241 additional multiple-dose-control patients. The shaded column in the table below draws attention to this dose-group. Unlike previous tables, no attempt was made to address changes since the 1996 submission. However, most of the patient increase was in the exposure categories of 12-24 and 24-36 weeks for the 24 mcg/day group [31:20].

NDA #20-831 1998 SU - FORMOTEROL SINGLE-DOSE DRY POWDER: NUMBER OF PATIENTS (% OF COLUMN TOTAL) IN MULTIPLE-DOSE CONTROLLED TRIALS EVALUATED FOR SAFETY BY EXPOSURE DURATION AND TOTAL DAILY FORMOTEROL DOSE, IN MCG/DAY [31:20]				
Duration	12	[redacted]	48	> 48
= 1 day	0		8 (1.2)	1 (5.9)
2 - 7 days	17 (7.2)		3 (0.4)	16 (94.1)
> 1 - 4 weeks	6 (2.5)		45 (6.7)	0
> 4 - 12 weeks	53 (22.4)		156 (23.2)	0
> 12 - 24 weeks	161 (67.9)		461 (68.5)	0
> 24 - 36 weeks	0		0	0
> 36 - 48 weeks	0		0	0
> 48 weeks	0		0	0
Total	237 (100)		673 (100)	17 (100)

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The next table provides similar information to the last, but on multiple-dose uncontrolled trials. As before the only dose group to change since the 1996 report was 24 mcg/day and the exposure duration with the largest number of new patients was 4-12 weeks with lesser increases in exposures bracketing it, 1-4 weeks and 12-24 weeks [31:22].

NDA #20-831 1998 SU - FORMOTEROL SINGLE-DOSE DRY POWDER: NUMBER OF PATIENTS (% OF COLUMN TOTAL) IN MULTIPLE-DOSE UNCONTROLLED TRIALS EVALUATED FOR SAFETY BY EXPOSURE DURATION AND TOTAL DAILY FORMOTEROL DOSE, IN MCG/DAY [31:22]			
Duration	12	[redacted]	48
= 1 day	0	[redacted]	0
2 - 7 days	0	[redacted]	3 (1.6)
> 1 - 4 weeks	0	[redacted]	6 (3.2)
> 4 - 12 weeks	2 (66.7)	[redacted]	13 (6.8)
> 12 - 24 weeks	0	[redacted]	23 (12.1)
> 24 - 36 weeks	0	[redacted]	30 (15.8)
> 36 - 48 weeks	0	[redacted]	68 (35.8)
> 48 weeks	1 (33.3)	[redacted]	47 (24.7)
Total	3 (100)	[redacted]	190 (100)

V.A.4. DEMOGRAPHICS

The table below shows various demographic characteristics at baseline of the two trial types that changed most dramatically since 1996, multiple-dose controlled and uncontrolled trials. In its entirety, this remains a series of trials of Caucasians, adults and patients with mild-to-moderate asthma [32:89]. Many of the trials were carried out in Europe. It should be noted again that many of the patients in the uncontrolled trials had also been participants in the controlled trials, so summing row totals tends to overestimate the number of unique patient participants. The patients reported newly in this safety update were all adults, so the numbers of pediatric-aged patients hasn't changed since 1996. The numbers of patients in dichotomous baseline $FEV_{1.0}$ classes also hasn't changed since 1996.

SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF PATIENTS WHO RECEIVED FORMOTEROL INHALATION CAPSULES [32:84, 88, 91, 95]		
Baseline Characteristics	Multi-Dose Controlled n(%)	Uncontrolled n(%)
Total Patients	2123	2049
Sex:		
Male	1125 (53.0)	1091 (53.2)
Female	998 (47.0)	958 (46.8)
Age Range:		
< 7	13 (0.6)	8 (0.4)
7 - 11	126 (5.9)	59 (2.9)
12 - 18	130 (6.1)	38 (1.9)
19 - 64	1536 (72.4)	1434 (70.0)
> 64	318 (15.0)	510 (24.9)
% Predicted FEV1.0 At Baseline:		
≤ 50 (% Available)	358 (19.2)	145 (24.9)
> 50 (% Available)	1507 (80.8)	437 (75.1)
Available (% Total)	1865 (87.8)	582 (28.4)
Not Stated	258	1467

V.A.5. ADVERSE EVENTS

The following table shows all reported AE's that were more common in the formoterol group than the placebo group as judged by frequency (%) in multiple-dose controlled trials. These were derived from a larger table of formoterol and all control treatments censored to exclude AE's occurring in ≤ 1% of formoterol-treated patients. The shaded cells represent those AE's that additionally showed dose-ordering among the three daily formoterol doses, 12, 24 and 48 mcg/day [31:41-2, 46-7]. The only change since the review of the original 1996 safety information was the loss of "tachycardia" from among the shaded cells. "Tachycardia" remained dose-ordered in the 1998 update, but was not represented in the table of AE's occurring in > 1% of the formoterol group [31:42-3]. "Tachycardia," "tremor" and "cramps muscle" were also among the most frequent AE's considered to be drug-related in multiple-dose controlled trials [31:49-50].

NDA #20-831 1998 SU - NUMBER AND FREQUENCY (%) OF AE's >1% IN THE FORMOTEROL GROUP IN ALL MULTIPLE-DOSE, CONTROLLED TRIALS, WITHOUT REGARD TO TREATMENT ATTRIBUTION, WHERE FREQUENCY IN FORMOTEROL GROUP WAS GREATER THAN IN PLACEBO GROUP [31:41-2, 46-7]

Adverse Event	Formoterol Capsule n(%)	Placebo n(%)
Total Patients	2123 (100)	692 (100)
Total Patients With AE's	1231 (58.0)	412(59.5)
Infection viral	318 (15.0)	99 (14.3)
Rhinitis	124 (5.8)	35 (5.1)
Pharyngitis	113 (5.3)	31 (4.5)
Coughing	92 (4.3)	29 (4.2)
Infection chest	84 (4.0)	4 (0.6)
Bronchitis	72 (3.4)	14 (2.0)
[redacted]	[redacted]	[redacted]
Dyspnea	57 (2.7)	9 (1.3)
Pain abdominal	34 (1.6)	8 (1.2)
Pain chest	33 (1.6)	10 (1.4)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

shaded rows showed dose-ordering among formoterol powder daily doses of 12, 24 and 48 mcg; i.e., sequentially higher doses had a greater frequencies (%) of the specific AE

Multiple-dose uncontrolled trials studied daily formoterol doses of both 24 and 48 mcg/day; 2034 patients exposed to the former and 190 to the latter. Comparing these dose groups, 51.2% of the 24 mcg/day group and 64.7% of the 48 mcg/day reported one or more AE's, a grossly dose-ordered measure [31:55-6]. Subgroup analyses were not reviewed for the 2123 patients in this 1998 update, which added only 241 patients since 1996 and were reported to be not much different by the sponsor [31:59-61].

V.A.6. EARLY DISCONTINUATIONS DUE TO ADVERSE EVENTS

The table below shows patients terminating early due to AE's or laboratory abnormalities in multiple-dose controlled trials. No difference between any of the treatment groups was evident. If anything, formoterol showed a slightly lower frequency of premature terminations due to AE's. The frequency of early terminations from multiple-dose uncontrolled trials of formoterol because of AE's or lab abnormalities was very similar, 95/2049 patients (4.6%) [31:66, 68].

NDA #20-831 1998 SU - NUMBER OF EARLY DISCONTINUATIONS DUE TO AE's OR LABORATORY ABNORMALITIES (% OF TOTAL PATIENTS) IN MULTIPLE-DOSE CONTROLLED TRIALS [31:66]				
Adverse Event	Formoterol Powder	Salbutamol	Salmeterol	Placebo
Total Patients	2123	821	239	692
Patients With Any AE's	1231 (58.0)	507 (61.8)	192 (80.3)	412 (59.5)
Patients Stopped Early	90 (4.2)	35 (4.3)	11 (4.6)	32 (4.6)

V.A.7. SERIOUS ADVERSE EVENTS

These data are little changed from the 1996 submission and include an additional 302 patients exposed to formoterol and 305 exposed to salmeterol. The frequency of serious adverse events (SAE's) is fairly similar across all active treatments and slightly greater than for placebo. The relatively high percent of SAE's in the salmeterol group is curious, but total numbers for that group are relatively small [31:74]. SAE's in multiple-dose uncontrolled trials, without regard to drug-relatedness, were 149/2049 (7.3%) [31:74, 78].

NDA #20-831 1998 SU - NUMBER OF PATIENTS WITH SERIOUS ADVERSE EVENTS IN MULTIPLE-DOSE CONTROLLED TRIALS WITHOUT REGARD TO ATTRIBUTION [31:74]					
Patients With Serious AE's	Treatment				
	Formoterol	Salbutamol	Salmeterol	Placebo	Comparator
Total Patients	2184	821	305	692	444
Patients with SAE's (%)	65 (3.0)	18 (2.2)	21 (6.9)	13 (1.9)	12 (2.7)
Formoterol = single-dose dry powder formulation Comparator = any other formoterol formulation					

V.A.8. DEATHS

No new deaths have been reported since the 1996 submission [31:81].

V.A.9. CLINICAL LABORATORY

No new clinical laboratory data were collected in any of the patients studied since the 1996 submission [31:81].

V.A.10. ELECTROCARDIOGRAMS

No new electrocardiograms were collected in any of the patients studied since the 1996 submission [31:81].

V.B. 23 NOVEMBER 1999 SU

This SU consisted of seven old studies which were added to the data base and protocol #049. The seven older studies did not contribute significant safety information to the present submission because all were carried out on different formoterol formulations. Study #049 has been separately reviewed in this document for both efficacy and safety. Therefore, no further analysis of the 11/23/99 safety update will be done in this section of the review [40:13].

VI. PROTOCOL #049 - A Twelve-Month, Double-Blind, Between-Patient, Placebo-Controlled Trial Comparing The Safety, Tolerability And Efficacy Of 12 mcg And 24 mcg Twice Daily Formoterol Dry Powder Capsules For Inhalation Delivered By A Single-Dose Inhaler (Aerolizer™) In Children With Asthma In Need Of Daily Treatment With Inhaled Bronchodilators And anti-inflammatory Treatment.

VI.A. SUMMARY

This was an international, multi-center, randomized, double-blind, placebo-controlled, year-long trial comparing the safety and efficacy of 12 and 24 mcg doses of twice-daily formoterol dry powder single-dose capsules. The patients were 5-12 year-old children with mild-to-moderate asthma ($FEV_{1.0}$ 50-85% of predicted) and $FEV_{1.0}$ reversibility (≥ 15%) after inhaled salbutamol who were already using daily inhaled bronchodilators and corticosteroids and/or cromones. Concomitant nasal steroids, theophylline and desensitization therapy were allowed if regimens were stable. Various salbutamol formulations were used as rescue treatment but the formulation was constant for each individual. There were prespecified criteria for treatment of exacerbations with oral or parenteral corticosteroids and for treatment failure withdrawal. Sixhundred-one patients were screened and 518 were randomized (1:1:1) to formoterol 12 mcg, 24 mcg or to placebo. There were disproportionately more Caucasians and males than other categories of race and gender and the younger ages were under-represented. The dropout rate was 21% over the 12-months, leaving 407 patients who finished.

Serial spirograms were performed over twelve hours at months 0, 3 and 12. The standardized 12-hour $FEV_{1.0}$ AUC at month 3 was the primary efficacy variable and showed statistical significance of both formoterol doses over placebo. The two active treatments were not statistically separable but did exhibit dose-ordering of the standardized least squares mean difference from placebo. Over time, the standardized $FEV_{1.0}$ AUC least squares mean difference of both active treatments from placebo declined, suggesting development of tachyphylaxis. Tachyphylaxis was difficult to confirm because $FEV_{1.0}$ values increased in all groups over the year of the study, probably due to dropout of the most symptomatic patients. Serial $FEV_{1.0}$ values showed an onset of action (near maximal at 15-30 minutes), peak effect (1-4 hours) and durably maintained bronchodilation, very similar to adults. Pre-dose (trough) morning and evening domiciliary PEFR's averaged over the last 7 days of each month reflected the greater effect of the 24 mcg formoterol dose over the 12 mcg dose and of both doses over placebo. Twice daily reflective mean Asthma Symptom Scores were also averaged over the last 7 days of each month and also showed a small effect of both treatments, without dose-ordering, that was between '0' and '1' (5 point scale) where '0' was "no symptoms." Daytime and nighttime rescue medicine use showed small reductions in all groups with slightly greater reductions in both formoterol treatment groups. The number

of asthma exacerbations recalled at each monthly visit were not helpful in differentiating the three treatment groups.

Slightly more total adverse events were reported in the placebo group, but about the same number of patients reported "any adverse event" in all three groups. The only dose-ordered adverse events were "rhinitis," "abdominal pain" and "dizziness." Conspicuously absent were the common beta adrenergic effects reported by adults (tremor, tachycardia, muscle cramps, insomnia). There were no deaths. Serious adverse events were more common in the formoterol groups than in the placebo group and were mostly asthma-related. The preponderance of asthma-related SAE's in the active treatment groups is a bit worrisome and may reflect the loss of challenge protection noted in the adult NDA. Adverse events leading to early withdrawal effected only 19 patients in all groups combined. They were most common in the placebo group, the majority of which were asthma-related. Salient laboratory events were hypokalemia (≤ 3.4 mmol/L) and hyperglycemia (>140 mg/dL) which were minimally more frequent in the formoterol groups than in the placebo group.

The pattern of efficacy of this drug in children is very similar to its pattern in adults, with similar onsets of action, peak effect, duration of action and durability of sustained bronchodilation. Its safety profile is oddly different. The usual beta adrenergic events that emerged from the adult trial (tremor, muscle cramps, tachycardia and insomnia) never appeared prominently in this pediatric study. The majority of asthma-related SAE's in active-treatment groups is of concern because it confirms similar findings in adult studies and may suggest loss of protection against episodic bronchoconstrictive stimuli.

VI.B. OBJECTIVE

This international, multi-center, randomized, year-long trial compared the safety and efficacy of two doses of twice-daily formoterol dry powder capsules delivered by a single-dose inhaler in 5-12 year old children with asthma ($FEV_{1.0}$ 50-85% of predicted) who were already using daily inhaled bronchodilators and corticosteroids and/or cromones [13:12, 16-7].

VI.C. PROTOCOL

This was a two-period trial with long-term (twelve-month) follow-up. Period 1 was a two-week placebo run-in baseline with salbutamol rescue medication. Period 2 was twelve months in duration, double-blinded and consisted of three groups, 12 mcg or 24 mcg of formoterol dry powder or placebo, all administered twice daily. The $FEV_{1.0}$ AUC over 12 hours was sampled at the 0th (randomization), 3rd and 12th double-blind months (2nd, 5th and 14th visits) and was considered to be the primary efficacy variable at the third month [13:17]. Medications that had to be discontinued prior to study visits and the requisite duration of cessation are found later in this review (see: TREATMENT,

CONCOMITANT MEDICATIONS & RESCUE MEDICATIONS). The scheduled visits for procedures and assessments are presented below [13:27].

NDA #20-831 TRIAL #049 - VISIT SCHEDULE OF PROCEDURES AND ASSESSMENTS [13:27, 34]														
	Period I	Period II												
	PBO Run-in	Double-Blind Treatment												
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Trial Month	-2 weeks	0	1	2	3	4	5	6	7	8	9	10	11	12
medical history	X													
concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE's	X	X	X	X	X	X	X	X	X	X	X	X	X	X
asthma exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X
vital signs	X	X			X									X
ECG	X1		X2	X2	X2	X2	X2	X2	X2	X2	X2	X2	X2	X1
fasting laboratories	X1		X2		X2			X2						X1
$FEV_{1.0}$ reversibility	X													
pre-dose & 12-h spirogram		X			X									X
1 = all center 2 = only US centers														

Patients who discontinued after randomization and before the scheduled twelfth month should have had all of the final assessments and procedures listed under the last column in the table above, identified as visit 14 and month 12 [13:27].

VI.D. PATIENTS

The sample consisted of 5-12 year-old children with asthma who used daily inhaled bronchodilators (regularly or on-demand) and daily "anti-inflammatory" treatments. About 500 patients were to be randomized to obtain about 300 who would complete twelve months of treatment. Enrollment began December 1996 and ceased two years later, in December 1998. The following inclusion and exclusion criteria applied [13:3, 12, 19-21]:

VI.D.1. INCLUSION CRITERIA

Patients 5-12 years of age of either gender whose parents gave informed consent. Patients had to meet the following criteria, in addition to the American Thoracic Society criteria (Am Rev Resp Dis 1987;136:225-244).

1. showed ≥ 15% reversibility of $FEV_{1.0}$ over baseline within 30 minutes of inhaling 200 mcg of salbutamol
2. baseline $FEV_{1.0}$ 50-85%, inclusive, of predicted normal after a 6-hour salbutamol washout period
3. needed daily treatment with bronchodilator, on-demand or regularly scheduled, and daily treatment with cromolyn sodium and/or inhaled corticosteroids