

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-831

MEDICAL REVIEW(S)

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, long-acting, beta-2 agonist GENERIC NAME: formoterol fumarate
ROUTE: inhaled
MEDICAL OFFICER: Raymond F. Anthracite REVIEW DATE: 1/31/2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

DOCUMENT DATE	CDER DATE	SUBMISSION TYPE	COMMENTS
06/24/1997	06/26/1997	NDA	
01/26/2001		Email	3-study safety analysis
01/30/2001		Email	expansion 1/26/01 Email

RELATED APPLICATIONS

DOCUMENT DATE	APPLICATION TYPE	COMMENTS
08/17/2000	08/18/2000	safety update & labeling
11/23/1999	11/24/1999	CR and pivotal Peds study (#49)
10/19/1998	incomplete response to "approvable"	10/98 safety update

REVIEW SUMMARY:

More SAE's, especially asthma, and more withdrawals for AE's, especially asthma, were noted with the higher dose (24 mcg b.i.d.) than the lower (12 mcg b.i.d.) of formoterol in the two adult pivotal trials originally reviewed for this NDA. The pediatric trial showed more SAE's in either formoterol group than in the placebo group and there was dose ordering for asthma between formoterol doses. Somewhat in contradiction to the last finding, dropouts due to AE's were greatest for the placebo group overall and for asthma. Two of the three studies informally submitted by the sponsor were applicable to this topic. In DP/RD3, analysis of AE's in patients over the age of 65 years showed that 12 or 24 mcg of formoterol given twice daily was safer than 400 mcg of dry powder salbutamol four times daily. In 103, comparison of three formoterol doses (6, 12 and 24 mcg) from the single-dose capsule device showed no dose related concerns in terms of AE's, SAE's and early dropouts, overall or specifically for asthma.

We have a weak safety signal that is supported by characteristics of chronic dosing (tachyphylaxis and broncho-provocation protection loss) that suggest mechanistic credibility. A further complication is that the safety concern, severe asthma, is an extreme condition of the very indication for which the drug is used. The data is not clear enough to accept or reject this as a real phenomenon and it is too important to defer.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

NEW CLINICAL STUDIES: _____ PROCEED _____ HOLD _____ (HOLD TYPE)
NDA/SUPPLEMENTS: _____ APPROVAL _____ APPROVABLE _____ NOT APPROVABLE
OTHER ACTION: RECOMMEND LARGE SAFETY STUDY OF 12 & 24 MCG FORMOTEROL BID

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

SIGNATURES

Reviewer: _____ **Date:** 01/31/2001
Team Leader: _____ **Date:** _____

APPEARS THIS WAY
ON ORIGINAL

I. EXECUTIVE SUMMARY

This reviewer noted more serious respiratory adverse events and more withdrawals for adverse events with the higher dose (24 mcg BID) than the lower (12 mcg BID) of formoterol in the two pivotal trials originally reviewed in this new drug application. The importance of this finding was judged within the context of:

- 1) the frequency of all and specific adverse events in multiple-dose placebo-controlled trials; and,
- 2) the frequency of early discontinuations due to adverse events in multiple-dose controlled trials.

Certain respiratory adverse events were more frequent during formoterol than placebo treatment, but there was no dose-ordering. Some of these same adverse events did not seem to be associated with more frequent withdrawals from the trials than placebo or short-acting beta-2 agonist comparator. These observations were noted, and judged not to have generated a clear enough signal to draw any conclusions.

The secondary reviewer on this application, looked at some of these same data, focussed on serious adverse events due to asthma and became concerned. The pediatric trial (#49) submitted two years after the original submission was examined and corroborative data was found. The higher formoterol dose (24 mcg BID) was associated with more serious adverse events than the lower dose (12 mcg BID) and most of these were asthma-related. Both formoterol doses were more frequently associated with serious adverse events than was placebo. However, adverse events leading to premature termination did not show a dose-ordered effect of formoterol in causing more patients to terminate the study early and, in fact, more placebo patients discontinued prematurely than did patients who received formoterol.

Our concerns about the higher of the two formoterol doses possibly contributing to more serious respiratory adverse events was consistent with other characteristics of the drug. The higher dose showed more tachyphylaxis than the lower and provocative challenge protection was reduced with chronic dosing. These two observations led to the speculation that chronic dosing, especially with the higher formoterol dose, might lead to improvement of stable asthma but permit exacerbations in response to natural triggers, challenges or provocative stimuli. These concerns were shared with the sponsor who sent us information from three studies that were submitted in the original new drug application, were not considered to be pivotal and were never reviewed. This document is a limited safety review of those trials within the context of summarized safety data from the original NDA.

DP/RD3 was a large 12-week study in the elderly (age ≥ 65 years) with asthma. Analysis of various measures of AE's in this study indicated that the elderly are safer taking either 12 or 24 mcg of formoterol b.i.d. than they are taking salbutamol q.i.d. Within the two formoterol doses the higher dose was associated with slightly more frequent AE's of all kinds and slightly more frequent drug-related AE's than the lower dose. Fewer patients taking the higher dose reported SAE's and fewer discontinued early than did patients given the lower dose.

DP/RD2 was not comparable to any of the other studies reviewed in this document. AE's had to be at least possibly attributable to a drug to be counted at all. Medical events were introduced as some kind of a *post hoc* categorization, and some of these were deemed "serious." SAE's weren't counted at all unless these were the serious medical events. If they were the serious medical events, these totals were not broken down by dose or type of event. The most early terminators due to AE's (no doubt drug attributable) were in the formoterol 24 mcg group, but this was a weak signal because of small numbers.

03 compared 6, 12 and 24 mcg doses b.i.d. administered by the single-dose capsular ISF device and by the _____ device in a 12-week trial. The latter device was dropped from development. The usual safety measures failed to indict higher formoterol doses presented with either of two devices as increasing patients reporting AE's, SAE's or discontinuing prematurely because of AE's. Only drug-related AE's showed dose-ordering within the ISF device and the highest dose for both devices was associated with more frequent drug-related AE's than lower doses for that device. Data dredging into treatment groups of patients reporting "asthma" or "respiratory AE's compatible with asthma" also did not show larger effects with higher doses.

We have a weak safety signal that is supported by characteristics of chronic dosing (tachyphylaxis and broncho-provocation protection loss) that suggest mechanistic credibility. A further complication is that the safety concern, severe asthma, is an extreme condition of the very indication for which the drug is used. The data is not clear enough to accept or reject this as a real phenomenon and it is too important to defer. Therefore, I recommend a large randomized safety study of 12 or 24 mcg of formoterol administered twice daily or placebo, all with albuterol rescue. The safety variables followed might include: SAE's, early termination because of AE's, asthma exacerbations, healthcare provider contacts and days lost from school/work. The minimum duration of this trial would be 12 weeks. The attack rate for asthma in the adult and pediatric studies was about 1-2% over the 12 weeks and we would need about 1000 patients per arm to have any comfort in the comparative results. The study would not have to be powered for any inferential endpoint.

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/PM/Jani

II. 040 — A TWELVE-WEEK, DOUBLE-BLIND, PARALLEL GROUP TRIAL COMPARING THE SAFETY, TOLERABILITY AND EFFICACY OF FORMOTEROL DRY POWDER CAPSULES FOR INHALATION DELIVERED BY A SINGLE-DOSE INHALER VERSUS ALBUTEROL METERED-DOSE INHALER (MDI) VERSUS PLACEBO IN PATIENTS WITH MILD TO MODERATE ASTHMA

More patients administered 24 mcg of formoterol BID reported an SAE than were reported by the lower dose formoterol, albuterol or placebo groups. The SAE reported by this high dose formoterol group was asthma marginally more often this was reported by other groups.

PROTOCOL #40 -- NUMBER OF PATIENTS REPORTING SAE's DURING TREATMENT [6/24/97 91:125, 127-32]				
Serious Adverse Event	Formoterol		Albuterol	Placebo
	12 mcg	24 mcg		
Asthma	0	4	2	0
Respiratory, not asthma	0	0	0	0
Other	1	1	0	1
TOTALS	1	5	2	1

Early terminators because of AE's were about equally common in the albuterol and the high dose formoterol arms and asthma was the cause marginally more often in the 24 mcg BID formoterol group.

PROTOCOL #40 -- NUMBER OF PATIENTS TERMINATING EARLY BECAUSE OF AN AE DURING TREATMENT [6/24/97 91:126, 133-47]				
Adverse Event	Formoterol		Albuterol	Placebo
	12 mcg	24 mcg		
Asthma	3	6	5	3
Respiratory, not asthma	0	0	0	3
Other	4	3	5	3
TOTALS	7	9	10	9

The following table shows the number and percent of patients reporting at least one adverse event during the 12-week double-blind treatment period for all randomized patients. If an AE was reported by $\geq 2\%$ of the patients in any one of the treatment groups then the AE was captured for all treatment groups. The table includes only the subset of these AE's in which the percent was greater for the highest formoterol dose than for placebo [6/24/97 91:118-22].

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PROTOCOL #41 -- NUMBER OF PATIENTS REPORTING SAE's DURING TREATMENT [6/24/97 178:134, 136-43, 157-8]				
Serious Adverse Event	Formoterol		Albuterol	Placebo
	12 mcg	24 mcg		
Asthma	1	5	0	2
Respiratory, not asthma	0	0	0	0
Other	0	2	2	1
TOTALS	1	7	2	3

Early terminators due to an AE reflect the same findings as reports of SAE's. This isn't a large surprise because the SAE patients tend to drop out.

PROTOCOL #41 -- NUMBER OF PATIENTS TERMINATING EARLY BECAUSE OF AN AE DURING TREATMENT [6/24/97 178:145-57, Telecon 4/3/98 with Dr. Kathleen Creedon]				
Adverse Event	Formoterol		Albuterol	Placebo
	12 mcg	24 mcg		
Asthma	4	5	0	6
Respiratory, not asthma	0	1	0	0
Other	3	4	4	3
TOTALS	7	10	4	9

The following table shows the number and percent of patients reporting at least one adverse event during the 12-week double-blind treatment period for all randomized patients. If an AE was reported by $\geq 2\%$ of the patients in any one of the treatment groups then the AE was captured for all treatment groups. The table includes only the subset of these AE's in which the percent was greater for the highest formoterol dose than for placebo [6/24/97 178:128-31].

PROTOCOL #41 -- NUMBER (%) OF ALL RANDOMIZED PATIENTS REPORTING AE's DURING TREATMENT WHERE AE FREQUENCY $\geq 2\%$ FOR ANY GROUP AND FORMOTEROL 24 > PLACEBO PERCENT [6/24/97 178:129-30]				
	Formoterol 12	Formoterol 24	Albuterol	Placebo
Total Treated	139 (100)	136 (100)	138 (100)	141 (100)
Total Reporting AE	95 (68.3)	88 (64.7)	96 (69.6)	95 (67.4)
Fatigue	3 (2.2)	4 (2.9)	3 (2.2)	1 (0.7)
Chest Pain	1 (0.7)	2 (1.5)	3 (2.2)	2 (1.4)
Abdominal Pain	2 (1.4)	3 (2.2)	8 (5.8)	2 (1.4)
Tooth Ache	0 (0.0)	3 (2.2)	0 (0.0)	2 (1.4)
Viral Infection	22 (15.8)	14 (10.3)	21 (15.2)	11 (7.8)
Headache	3 (2.2)	5 (3.7)	1 (0.7)	3 (2.1)
Anxiety	3 (2.2)	2 (1.5)	1 (0.7)	0 (0.0)
Nausea	3 (2.2)	3 (2.2)	2 (1.4)	2 (1.4)
Diarrhea	1 (0.7)	3 (2.2)	2 (1.4)	0 (0.0)
Tremor	0 (0.0)	3 (2.2)	1 (0.7)	2 (1.4)
Bronchitis	0 (0.0)	3 (2.2)	2 (1.4)	2 (1.4)
Epistaxis	0 (0.0)	3 (2.2)	0 (0.0)	2 (1.4)

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PROTOCOL #40 -- NUMBER (%) OF ALL RANDOMIZED PATIENTS REPORTING AE'S DURING TREATMENT WHERE AE FREQUENCY \geq 2% FOR ANY GROUP AND FORMOTEROL 24 > PLACEBO PERCENT [6/24/97 91:120-21]				
	Formoterol 12	Formoterol 24	Albuterol	Placebo
Total Treated	136 (100)	135 (100)	134 (100)	136 (100)
Total Reporting AE	92 (67.6)	103 (76.3)	94 (70.1)	96 (70.6)
Tachycardia	1 (0.7)	3 (2.2)	1 (0.7)	1 (0.7)
Viral Infection	22 (16.2)	24 (17.8)	10 (7.5)	22 (16.2)
Muscle Cramps	1 (0.7)	3 (2.2)	0 (0.0)	1 (0.7)
Musculoskeletal Pain	1 (0.7)	1 (0.7)	3 (2.2)	0 (0.0)
Insomnia	1 (0.7)	4 (3.0)	4 (3.0)	2 (1.5)
Nervousness	0 (0.0)	9 (6.7)	4 (3.0)	2 (1.5)
Wheezing	3 (2.9)	14 (10.4)	4 (3.0)	0 (0.0)
Coughing	9 (6.6)	9 (6.7)	11 (8.2)	6 (4.4)
Dyspnea	5 (2.2)	4 (3.0)	2 (1.5)	1 (0.7)
Rhinitis	9 (6.6)	13 (9.6)	10 (7.5)	9 (6.6)
URI	14 (10.3)	19 (14.1)	13 (9.7)	15 (11.0)
Urticaria	2 (1.5)	4 (3.0)	0 (0.0)	1 (0.7)
Ear Ache	6 (4.4)	2 (1.5)	1 (0.7)	1 (0.7)

The shaded rows emphasize a subset of AE's that were more frequent for both formoterol doses than for placebo and that showed dose proportionality between the two formoterol doses. Both formoterol doses resulted in more frequent dyspnea than either placebo or albuterol. Albuterol was associated with more coughing than either formoterol doses. Viral infection and URI appear to be distributed more or less randomly among the treatments, with a few more in the high dose formoterol group. Asthma and other respiratory AE's do not appear.

III. 041 A TWELVE-WEEK, DOUBLE-BLIND, PARALLEL GROUP TRIAL COMPARING THE SAFETY, TOLERABILITY AND EFFICACY OF FORMOTEROL DRY POWDER CAPSULES FOR INHALATION DELIVERED BY A SINGLE-DOSE INHALER VERSUS ALBUTEROL METERED-DOSE INHALER (MDI) VERSUS PLACEBO IN PATIENTS WITH MILD TO MODERATE ASTHMA

More of the high dose formoterol patients reported SAE's than any other group and the SAE reported was mostly asthma. This is the strongest signal from an individual study that high dose formoterol is associated with severe asthma.

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PROTOCOL #41 – NUMBER (%) OF ALL RANDOMIZED PATIENTS REPORTING AE'S DURING TREATMENT WHERE AE FREQUENCY \geq 2% FOR ANY GROUP AND FORMOTEROL 24 > PLACEBO PERCENT [6/24/97 178:129-30]				
	Formoterol 12	Formoterol 24	Albuterol	Placebo
Sinus Headache	0 (0.0)	2 (1.5)	4 (2.9)	2 (1.4)
Pharyngitis	13 (9.4)	11 (8.1)	20 (14.5)	7 (5.0)
Rhinitis	5 (3.6)	9 (6.6)	13 (9.4)	8 (5.7)
Rash	1 (0.7)	2 (1.5)	3 (2.2)	1 (0.7)

The shaded rows emphasize a subset of AE's that were more frequent for both formoterol doses than for placebo and that showed dose proportionality between the two formoterol doses. Asthma is absent in the table above although the selection criteria for inclusion in the table would favor it, if the 24 mcg formoterol dose were really associated with more asthma. The only two other respiratory complaints, bronchitis and viral infection were more or less randomly distributed among treatment groups.

IV. 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.

There were more SAE's in either formoterol groups than in the placebo group and there was dose ordering for asthma between formoterol doses.

PROTOCOL #49 – NUMBER OF PATIENTS REPORTING SAE'S DURING TREATMENT [11/23/99 13:70, 72]			
Serious Adverse Event	Formoterol		Placebo (n = 176)
	12 mcg (n = 171)	24 mcg (n = 171)	
Asthma	8	11	0
Respiratory, not asthma	1	1	2
Other	2	1	1
TOTALS	11	13	3

Somewhat at variance with the above, dropouts due to AE's were greatest for the placebo group overall and for asthma.

PROTOCOL #49 – NUMBER OF PATIENTS TERMINATING EARLY BECAUSE OF AN AE DURING TREATMENT [11/23/99 13:72-3]			
Adverse Event	Formoterol		Placebo (n = 176)
	12 mcg (n = 171)	24 mcg (n = 171)	
Asthma	1	3	7
Respiratory, not asthma	0	0	1
Other	9	2	4
TOTALS	10	5	12

The numbers of patients who reported adverse events was comparable in the three treatment groups: 146 patients (85%) on formoterol 24 mcg; 147 patients (86%) on formoterol 12 mcg; and, 151 patients (86%) on placebo. Slightly more AE's were reported in the placebo group (664) than in the formoterol 12 mcg (639) or the formoterol 24 mcg (617) groups. The following table presents the numbers of patients (%) with the most frequent AE's (frequency > 2.5% in ≥ 1 of the treatment groups and ≥ 5 patients in ≥ 1 treatment group) by WHO term [11/23/99 13:67-8].

NDA #20-831 TRIAL #049 - NUMBER OF PATIENTS WITH THE MOST FREQUENT* AE'S SUMMARIZED BY WHO CATEGORIES WHERE PATIENTS IN BOTH FORMOTEROL GROUPS WERE MORE FREQUENT THAN THE PLACEBO GROUP, COUNT (%) [11/23/99 13:68]			
WHO Term	Placebo n = 176	Formoterol 12 mcg n = 171	Formoterol 24 mcg n = 171
number of patients with any AE	151 (86)	147 (86)	146 (85)
infection viral	58 (33)	64 (37)	64 (37)
rhinitis	30 (17)	32 (19)	35 (20)
abdominal pain	11 (6)	15 (9)	20 (12)
tonsillitis	5 (3)	13 (8)	8 (5)
gastroenteritis	6 (3)	11 (6)	9 (5)
nausea	6 (3)	8 (5)	9 (5)
dyspepsia	4 (2)	6 (4)	5 (3)
dizziness	2 (1)	5 (3)	6 (4)
allergy aggravated	2 (1)	5 (3)	3 (2)
rash	2 (1)	5 (3)	3 (2)

* Most Frequent = >2.5% of patients in ≥ 1 treatment group AND ≥ 5 patients in ≥ 1 treatment group

Asthma is not found and the only respiratory AE that is represented, viral infection, shows a similar frequency in all treatment arms.

Of the 77 AE's which were assessed by the investigators as at least possibly drug-related; 17 were reported by 12 patients (7%) in the formoterol 24 mcg group; 28 were reported by 18 patients (11%) in the formoterol 12 mcg group; and, 32 were reported by 24 patients (14%) in the placebo group [11/23/99 13:69].

V. DP/RD3 - MULTI-CENTER, DOUBLE-BLIND, PARALLEL-GROUP TRIAL TO COMPARE THE 3-MONTH EFFICACY AND TOLERABILITY OF INHALED FORMOTEROL DRY POWDER AND SALBUTAMOL DRY POWDER IN ELDERLY PATIENTS SUFFERING FROM REVERSIBLE OBSTRUCTIVE AIRWAYS DISEASE (ROAD) [6/24/97 333:3-4].

V.A. SUMMARY

Analysis of AE's in this study indicate that the elderly are safer taking either 12 or 24 mcg of formoterol b.i.d. than they are taking salbutamol q.i.d. Within the two

formoterol dose the higher dose was associated with slightly more frequent AE's of all kinds and slightly more frequent drug-related AE's than the lower dose.

V.B. PROTOCOL [6/24/97 333:23]

This was done in the UK and consisted of a two-week run-in period followed by 12 weeks of double-blind treatment in three parallel arms with visits at enrollment (day 1, week 1), randomization (day 14, week 2), visit 3 (day 42, week 6), visit 4 (day 70, week 10) and visit 5 (day 98, week 14).

V.C. SUBJECTS

262 patients (157 males) aged 64-82 years
83 on formoterol 12 mcg b.i.d.
91 on formoterol 24 mcg b.i.d.
88 on salbutamol dry powder 400 mcg q.i.d.

V.D. TREATMENT

formoterol dry powder capsules, 12 or 24 mcg per capsule
Ventolin Rotahaler, 400 mcg per dose (200 mcg per capsule)

V.E. PATIENTS WITH ADVERSE EVENTS [6/24/97 333:48]

The number of patient reporting any AE in each of the three treatment groups and overall groups is summarized below. More patients in the 24 mcg formoterol group reported AE's than in the 12 mcg group, but the salbutamol group has the most patients who reported AE's.

167 (64%) of the 262 randomized patients
49 (59%) in the formoterol 12 mcg b.i.d. group
58 (64%) in the formoterol 24 mcg b.i.d. group
60 (68%) in the salbutamol 400 mcg q.i.d. group

Drug-related AE's shows about the same trends as summarized below. Both of these measures implicate the higher formoterol dose as being associated with slightly worse outcome than the lower dose, but both formoterol doses were superior to salbutamol by these measures.

57 (22%) of the 262 randomized patients
14 (17%) in the formoterol 12 mcg b.i.d. group
20 (22%) in the formoterol 24 mcg b.i.d. group
23 (26%) in the salbutamol 400 mcg q.i.d. group

V.F. SERIOUS ADVERSE EVENTS [6/24/97 333:48, 51]

This measure failed to implicate the higher formoterol dose with a less safe outcome than the lower dose and, further, both formoterol doses looked superior to salbutamol. Asthma was less associated with either dose of formoterol than it was with salbutamol.

- 15 (6%) of the 262 randomized patients
- 6 (7%) in the formoterol 12 mcg b.i.d. group (asthma-1, bronchitis-1)
- 1 (1%) in the formoterol 24 mcg b.i.d. group (no respiratory)
- 8 (9%) in the salbutamol 400 mcg q.i.d. group (chest infection-3, asthma-2)

V.G. PREMATURE DISCONTINUATIONS DUE TO AE'S

This measure showed the same outcome as the last. It failed to implicate the higher formoterol dose with a less safe outcome than the lower dose and, further, both formoterol doses looked superior to salbutamol.

- 14 (5%) of the 262 randomized patients
- 5 (6%) in the formoterol 12 mcg b.i.d. group
- 1 (1%) in the formoterol 24 mcg b.i.d. group
- 8 (9%) in the salbutamol 400 mcg q.i.d. group

VI. DP/RD2 - MULTI-CENTER, DOUBLE-BLIND, BETWEEN-PATIENT COMPARISON OF 12 MCG AND 24 MCG FORMOTEROL DRY POWDER TWICE DAILY WITH 400 MCG SALBUTAMOL DRY POWDER FOUR TIMES DAILY PATIENTS WITH REVERSIBLE OBSTRUCTIVE AIRWAYS DISEASE [6/24/97 331:1-3].

VI.A. SUMMARY

This was not comparable to any of the other studies reviewed in this document. AE's had to be at least possibly attributable to a drug to be counted at all. Medical events were introduced as some kind of a *post hoc* categorization, and some of these were deemed "serious." SAE's weren't counted at all unless these were the serious medical events. If they were the serious medical events, these totals were not broken down by dose or type of event. Early terminators due to AE's (no doubt drug attributable) did show more in the formoterol 24 mcg group, but this was a weak signal because of small numbers.

VI.B. PROTOCOL

This was done in the Netherlands and consisted of a one-week run-in period followed by 12 weeks of double-blind treatment in three parallel arms.

VI.C. SUBJECTS

318 patients (178 males) aged 18-74 years
105 on formoterol 12 mcg b.i.d.
107 on formoterol 24 mcg b.i.d.
106 on salbutamol dry powder 400 mcg q.i.d.

VI.D. TREATMENT

formoterol dry powder capsules, 12 or 24 mcg per capsule
salbutamol, 400 mcg per dose

VI.E. PREMATURE DISCONTINUATIONS FROM AE'S [6/24/97 331:74]

8 (3%) of the 318 randomized patients
2 (2%) in the formoterol 12 mcg b.i.d. group
4 (4%) in the formoterol 24 mcg b.i.d. group
2 (2%) in the salbutamol 400 mcg q.i.d. group

VI.F. PATIENTS WITH ADVERSE EVENTS DRUG ATTRIBUTED

[6/24/97 331:43-4]

46 (14%) of the 318 randomized patients
15 (14%) in the formoterol 12 mcg b.i.d. group
18 (17%) in the formoterol 24 mcg b.i.d. group
13 (12%) in the salbutamol 400 mcg q.i.d. group

VI.G. MEDICAL EVENTS [6/24/97 331:44-5]

134 medical events in 87 (27%) of the 318 randomized patients
9 were considered serious; 7 were considered drug attributable
40 events in 25 (25%) patients in the formoterol 12 mcg b.i.d. group
39 events in 26 (24%) patients in the formoterol 24 mcg b.i.d. group
55 events in 36 (34%) patients in the salbutamol 400 mcg q.i.d. group

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VII. — 03 - MULTI-CENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, BETWEEN-PATIENT TRIAL COMPARING EFFICACY AND SAFETY OF DIFFERENT MULTIPLE DOSES OF INHALED FORMOTEROL DRY POWDER FROM — DEVICE AND THE ISF DEVICE IN PATIENTS WITH REVERSIBLE OBSTRUCTIVE AIRWAYS DISEASE (ROAD) [6/24/97 283:1-3]

VII.A. SUMMARY

The usual safety measures failed to indict higher formoterol doses presented with either of two devices as increasing patients reporting AE's, SAE's or discontinuing prematurely because of AE's. Only drug-related AE's showed dose-ordering within the ISF device and the highest dose for both devices was associated with more frequent drug-related AE's. Data dredging into treatment groups of patients reporting "asthma" or "respiratory AE's compatible with asthma" also did not show larger effects with higher doses.

VII.B. PROTOCOL

This was a European study which consisted of a 10-29 day run-in and a 12-week blinded period where 7 parallel groups of patients who received the following medication dose b.i.d. from the two different devices.

NUMBER OF RANDOMIZED PATIENTS IN EACH TREATMENT GROUP [6/24/97 238:1]							
ISF Device			— Device			PBO	Total
6 mcg	12 mcg	24 mcg	6 mcg	12 mcg	24 mcg		
147	146	149	149	149	146	147	1033

A total of 442 of these randomized patients were exposed to the single dose ISF capsule formulation, which is the equivalent to the Foradil administered by Aerolizer.

VII.C. SUBJECTS

These were over age 18, clinically stable for 4 weeks, had an FEV_{1.0} ≥ 40% predicted and greater than 1 liter and demonstrated 15% FEV_{1.0} reversibility.

VII.D. TREATMENT

See table above. Rescue was salbutamol 100 mcg MDI

VII.E. ADVERSE EVENTS

There really is no signal here to suggest that higher doses of either formulation are associated with more AE's.

NUMBER (%) OF RANDOMIZED PATIENTS IN EACH TREATMENT GROUP REPORTING ADVERSE EVENTS [6/24/97 238:59]							
ISF Device			Device				
6 mcg	12 mcg	24 mcg	6 mcg	12 mcg	24 mcg	PBO	Total
65 (45)	63 (44)	65 (44)	64 (43)	62 (42)	71 (49)	75 (51)	465 (45)

When these data were broken down into numbers of patients reporting drug-related AE's, there is dose-ordering within the ISF device and the highest doses from both devices were associated with more AE's than the two lower doses. When AE's were broken down by three levels of severity and by those that were "asthma" and "respiratory," no signal incriminating the higher doses emerged [6/24/97 238:60-1].

VII.F. SERIOUS ADVERSE EVENTS

This endpoint also fails to incriminate higher doses as being associated with more SAE's.

NUMBER (%) OF RANDOMIZED PATIENTS IN EACH TREATMENT GROUP REPORTING SERIOUS ADVERSE EVENTS [6/24/97 238:59]							
ISF Device			Device				
6 mcg	12 mcg	24 mcg	6 mcg	12 mcg	24 mcg	PBO	Total
8 (5)	4 (3)	0 (0)	3 (2)	5 (3)	5 (3)	4 (3)	29 (3)

VII.G. PREMATURE DISCONTINUATIONS DUE TO AE'S

This measure fails to implicate higher doses of either formulation with more early terminations due to AE's.

NUMBER (%) OF RANDOMIZED PATIENTS IN EACH TREATMENT GROUP WITHDRAWING BECAUSE OF ADVERSE EVENTS [6/24/97 238:59]							
ISF Device			Device				
6 mcg	12 mcg	24 mcg	6 mcg	12 mcg	24 mcg	PBO	Total
13 (9)	12 (8)	6 (4)	10 (7)	13 (9)	12 (8)	15 (10)	81 (8)

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I. SUMMARY

This report covered the temporal interval from 16 July 1999 through 15 February 2000. First presented were separate safety evaluations from three completed marketing studies. Most of this information was previously reported in earlier safety updates. Next were safety reports from ongoing trials that fell into this reporting period. Third, was an update of spontaneous reports. Fourth, were post-marketing observational studies and, last, reports in the published literature were presented. With minor exception, this update did not include information on patients exposed to Foradil Aerolizer who were primarily diagnosed with Chronic Obstructive Pulmonary Disease (COPD), but rather dealt primarily with asthma [2:11-2].

Adverse events associated with formoterol were familiar and some could have been ascribed to general beta agonist effects; e.g., insomnia, leg cramps, tremor, palpitations and chest pain. Eight of thirty-six (22%) new publications were a result of Novartis sponsored studies. Two publication summaries were considered to be relevant and were included in this review. One abstract covered the acute use of formoterol compared with albuterol in the Emergency Room treatment of asthma. Both were judged to be efficacious but albuterol had a more rapid onset of action, inferred from a greater PEFR and greater change from baseline 30 minutes after treatment. A report of albuterol responsiveness 24 hours after cessation of chronic formoterol treatment or placebo showed a lower albuterol responsiveness in the formoterol pretreatment group suggestive of tachyphylaxis to beta-2 agonists. This was partially ameliorated by bolus intravenous or inhaled corticosteroid administration. The labeling review was complete at the conclusion of the last complete response but now requires minor re-editing because of unannotated changes authored by the sponsor. It will be submitted as a separate document either by myself or by the Project Manager.

II. COMPLETED STUDIES

II.A. FOR-INT-02

This was an open-label study comparing two dry powder formoterol formulations, one from Novartis (single dose Foradil Aerolizer) and one from AstraZeneca (multi-dose — Turbuhaler). Both of these are approved in Europe and neither are currently approved in the US. Twelve microgram doses of each formulation administered twice daily in adult asthma patients (age ≥ 18 years) were compared over 12 weeks of treatment in 28 international centers (Argentina, Austria, Canada, Israel, Italy, Mexico, Portugal, Spain). Two-hundred patients were randomized into one of the two active treatment groups and the disposition of these patients is shown in the table below [2:13-4]:

NDA #20-831 - PATIENT DISPOSITION IN STUDY FOR-INT-02 [2:14]			
	Foradil Aerolizer n (%)	— Turbuhaler n (%)	Total n(%)
Randomized	98 (100.0)	102 (100.0)	200 (100.0)

NDA #20-831 - PATIENT DISPOSITION IN STUDY FOR-INT-02 [2:14]			
	Foradil Aerolizer n (%)	— Turbuhaler n (%)	Total n(%)
Completed	95 (96.9)	96 (94.1)	191 (95.5)
Discontinued Prematurely	3 (3.1)	6 (5.9)	9 (4.5)
Adverse Events	0 (0.0)*	4 (3.9)	4 (2.0)
Protocol Violations	0 (0.0)	1 (1.0)	1 (0.5)
Lost To Follow-Up	3 (3.1)*	1 (1.0)	4 (2.0)

*One of the patients reported lost-to-follow-up also had AE's reported as leading to discontinuation.

II.A.1. DEATHS

None [2:16].

II.A.2. SERIOUS ADVERSE EVENTS (SAE'S)

None [2:16].

II.A.3. DISCONTINUATIONS DUE TO ADVERSE EVENTS (AE'S)

The asterisked Foradil patient who discontinued prematurely because of both loss to follow-up and because of AE's, reported nausea and asthenia as the AE's. The four patients who discontinued prematurely in the — group reported AE's as proximate to the discontinuation. Two of these four could be beta agonist effects [2:16].

1. dry skin, pruritis, somnolence and abnormal lacrimation
2. migraine, palpitations and tremor
3. dry mouth and palpitations
4. viral infection

II.A.4. FREQUENT ADVERSE EVENTS

AE's reported by $\geq 2\%$ of the patients in either group were deemed to be "frequent" and are listed for the current study in the table below [2:16]. The two formulations provide similar AE frequencies with the possible exception of palpitations and gastritis, that were more frequent with the — formulation, and nausea, that was more frequent with Foradil.

NDA #20-831 - ADVERSE EVENTS ($\geq 2\%$ IN EITHER ARM) IN STUDY FOR-INT-02 [2:16]		
	Foradil Aerolizer n (% column total)	— Turbuhaler n (% column total)
Total Patients	98 (100.0)	102 (100.0)
Total Patients With ≥ 1 AE	16 (16.3)	15 (14.7)
Infection, Viral	5 (5.1)	4 (3.9)
Headache	3 (3.1)	1 (1.0)
Nausea	2 (2.0)	0 (0.0)

NDA #20-831 - ADVERSE EVENTS (≥ 2% IN EITHER ARM) IN STUDY FOR-INT-02 [2:16]		
	Foradil Aerolizer n (% column total)	Turbuhaler n (% column total)
Gastritis	0 (0.0)	2 (2.0)
Shaded cells are possible beta agonist induced effects.		

II.B. STUDY 62 (FOR-AUS-01)

This was a double-blind, randomized trial to compare an increase in inhaled corticosteroids (ICSs) with the addition of inhaled formoterol in Australian asthma patients who were still symptomatic after being treated with chronic ICS's. The study had a 2-4 week run-in period followed by a 24-week treatment period. The run-in treatment was 2 puffs of 250 mcg/puff of beclomethasone (BDP) MDI administered twice daily. The BDP was a non-US approved formulation administered on a dosing schedule that was also non-US approved. The two treatment arms were: 1) formoterol 12 mcg BID by Aerolizer, placebo-beclomethasone MDI 2 puffs BID and beclomethasone MDI 2 puffs of 250 mcg/puff BID (1000 mcg/day); or, 2) placebo Aerolizer BID and beclomethasone MDI 4 puffs of 250 mcg/puff BID (2000 mcg/day) [2:17-8, 3:14-5]. The disposition of these patients is found in the table below:

NDA #20-831 - PATIENT DISPOSITION IN STUDY 62 [2:18]			
	Foradil 12 mcg BID & BDP 500 mcg BID n (%)	Placebo BID & BDP 1000 mcg BID n (%)	Total n(%)
Randomized	102 (100.0)	101 (100.0)	203 (100.0)
Completed	95 (93.1)	89 (88.1)	184 (90.6)
Discontinued Prematurely	7 (6.9)	11 (10.9)	18 (8.9)
Adverse Events	2 (2.0)	4 (4.0)	6 (3.0)
Unsatisfactory Efficacy	0 (0.0)	1 (1.0)	1 (0.5)
Protocol Violations	2 (2.0)	3 (3.0)	5 (2.5)
Patient Non-Compliance	0 (0.0)	1 (1.0)	1 (0.5)
Patient Withdrew Consent	0 (0.0)	2 (2.0)	2 (1.0)
Lost To Follow-Up	3 (2.9)	0 (0.0)	3 (1.5)
BDP = beclomethasone		BID = <i>bis in deum</i> (twice daily)	

Premature discontinuations because of AE's and unsatisfactory efficacy were more frequent in the placebo-high-dose-BDP arm, but numbers were small.

II.B.1. DEATHS

None [2:21].

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II.B.2. SERIOUS ADVERSE EVENTS

One SAE occurred in each treatment arm. One formoterol-low-dose-BDP patient was hospitalized for a bronchial carcinoma and one placebo-high-dose-BDP patient was hospitalized for asthma [2:21].

II.B.3. DISCONTINUATIONS DUE TO ADVERSE EVENTS

Two patients (2%) in the formoterol-low-dose-BDP arm withdrew prematurely; one because of chest pain and one because of leg cramps. Four patients in the placebo-high-dose-BDP arm discontinued before the end of the study: three patients because of respiratory complaints (asthma, bronchitis and asthma + URI) and one because of headache [2:21].

II.B.4. FREQUENT ADVERSE EVENTS

AE's reported by $\geq 2\%$ of the patients in either group were deemed to be "frequent" and were listed for the current study. The table below shows these AE's further truncated by AE frequency of formoterol-low-dose-BDP arm > placebo-high-dose-BDP arm [2:20]. This restricted list of frequent AE's was chosen to better manage an otherwise long list to best highlight possible Foradil-associated AE's. Overall, both treatment arms showed about an equal frequency of patients reporting AE's. Foradil showed a greater association with insomnia, leg cramps, tremor and chest pain (shaded cells), but these differences, by themselves were of insufficient magnitude to provide a strong signal. These particular AE's might have been expected of a beta agonist, but most of the ten other AE's in the table would not be expected, or even be reasonable, as AE's related to the use of a beta agonist.

NDA #20-831 - ADVERSE EVENTS ($\geq 2\%$ IN EITHER ARM) WHERE FREQUENCY IN FORADIL-LO-BDP-DOSE GROUP > IN PLACEBO-HI-BDP-DOSE GROUP IN STUDY 62 [2:20]		
	Foradil 12 mcg BID & BDP 500 mcg BID n (%)	Placebo BID & BDP 1000 mcg BID n (%)
Total Patients	102 (100.0)	101 (100.0)
Total Patients With ≥ 1 AE	69 (67.6)	71 (70.3)
URI	25 (24.5)	20 (19.8)
Bronchitis	10 (9.8)	7 (6.9)
Head Cold	5 (4.9)	3 (3.0)
Nausea	4 (3.9)	3 (3.0)
Dizziness	3 (2.9)	1 (1.0)
Rash	2 (2.0)	0 (0.0)
Skin Disorder	2 (2.0)	0 (0.0)
Conjunctivitis	2 (2.0)	0 (0.0)
Dry Mouth	2 (2.0)	0 (0.0)

NDA #20-831 - ADVERSE EVENTS (≥ 2% IN EITHER ARM) WHERE FREQUENCY IN FORADIL-LO-BDP-DOSE GROUP > IN PLACEBO-HI-BDP-DOSE GROUP IN STUDY 62 [2:20]		
	Foradil 12 mcg BID & BDP 500 mcg BID n (%)	Placebo BID & BDP 1000 mcg BID n (%)
Infection	2 (2.0)	0 (0.0)

Shaded cells are possible beta agonist induced effects.

II.C. STUDY 73 (FOR-USA-01)

This was a multicenter, randomized, parallel-group, open-label, US-study comparing formoterol powder, 12 mcg BID (Foradil Aerolizer), to salmeterol, 50 mcg BID (Serevent Diskus®), administered to adults with moderately severe reversible obstructive airways disease requiring concomitant ICS over twenty-four weeks. The primary efficacy parameter was the PEFR five minutes after dosing. Soft secondary efficacy measures included health-related quality of life, patient satisfaction, health care resource utilization and socioeconomic variables [2:21-2]. The disposition of patients is found in the table below:

NDA #20-831 - PATIENT DISPOSITION IN STUDY 73 [2:23]			
	Foradil 12 mcg BID & ICS n (%)	Serevent 50 mcg BID & ICS n (%)	Total n(%)
Randomized	262 (100.0)	266 (100.0)	528 (100.0)
Completed	224 (85.5)	236 (88.7)	460 (87.1)
Discontinued Prematurely	38 (14.5)	30 (11.3)	68 (12.9)
Adverse Events	15 (5.7)	9 (3.4)	24 (4.5)
Unsatisfactory Efficacy	4 (1.5)	3 (1.1)	7 (1.3)
Protocol Violations	7 (2.7)	7 (2.6)	14 (2.7)
Patient Withdrew Consent	7 (2.7)	8 (3.0)	15 (2.8)
Lost To Follow-Up	2 (0.8)	2 (0.8)	4 (0.8)
Administrative Problems	3 (1.1)	1 (0.4)	4 (0.8)

BID = *bis in deum* (twice daily)

Foradil was associated with more premature discontinuations overall than Serevent. This was reflected primarily in discontinuations due to AE's.

II.C.1. DEATHS

None [2:26].

II.C.2. SERIOUS ADVERSE EVENTS

Nine SAE's occurred in seven formoterol patients and 15 SAE's occurred in twelve salmeterol patients. Of these, three formoterol and four salmeterol patients discontinued due to SAE's. The breakdown of SAE's in formoterol patients follows [2:26, 29]:

1. chest pain, dyspnea, syncope
2. asthma exacerbation
3. status asthmaticus
4. asthma exacerbation
5. colon carcinoma
6. fractured right tibia
7. cholelithiasis

II.C.3. DISCONTINUATIONS DUE TO ADVERSE EVENTS

Fifteen formoterol patients and nine salmeterol patients terminated the study prematurely because of an AE. The table below shows AE's reported by each discontinuing patient [2:27, 31-2]. Regrettably, it also sites seventeen formoterol patients who prematurely discontinued, instead of the promised fifteen.

NDA #20-831 - DISCONTINUATIONS DUE TO ADVERSE EVENTS IN STUDY 73 [2:27, 31-2]	
Formoterol 12 mcg BID	Salmeterol 50 mcg BID
	spinal cord glioma
	breast cancer (2)
	trauma
asthma exacerbation (4)	worsening of asthma symptoms
status asthmaticus	asthma exacerbation
URI, asthma exacerbation	myopathy and dizziness
URI, asthma flare	depression
asthma flare	
nausea heartburn	
increased asthma symptoms	
acute bronchitis	

BID = *bis in deum* (twice daily)..... Shaded cells are possible beta agonist induced effects.

Lumping patients into a category of increasing respiratory symptoms leading to early termination yields 10 formoterol patients and 2 salmeterol patients. Though numbers were small, none of the patients exposed to salmeterol prematurely discontinued because of chest pain.

II.C.4. FREQUENT ADVERSE EVENTS

AE's reported by $\geq 2\%$ of the patients in either group were deemed to be "frequent" and were listed for the current study. The table below shows these AEs further truncated by AE frequency in the formoterol arm > frequency in the salmeterol arm [2:25]. As before, this restricted list of frequent AE's was chosen to better manage an otherwise long list and to highlight possible formoterol-associated AE's. Overall, the

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formoterol arm had slightly more patients who reported AE's than the salmeterol arm, but the difference was not great.

NDA #20-831 - ADVERSE EVENTS (≥ 2% IN EITHER ARM) WHERE FREQUENCY IN FORADIL GROUP > IN SALMETEROL GROUP IN STUDY 73 [2:25]		
	Formoterol 12 mcg BID & ICS n (%)	Salmeterol 50 mcg BID & ICS n (%)
Total Patients	262 (100.0)	266 (10.0)
Total Patients With ≥ 1 AE	202 (77.1)	201 (75.6)
URI	68 (26.0)	51 (19.2)
Asthma	53 (20.2)	49 (18.4)
Headache	18 (6.9)	13 (4.9)
Rhinitis	17 (6.5)	11 (4.1)
Arthralgia	11 (4.2)	1 (0.4)
Dyspepsia	10 (3.8)	5 (1.9)
Rash	6 (2.3)	2 (0.8)
BID = <i>bis in deum</i> (twice daily) Shaded cells are possible beta agonist induced effects.		

III. ONGOING TRIALS

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IV. POST-MARKETING SAFETY INFORMATION

IV.A. SPONTANEOUS CASE REPORTS

Properties of the Spontaneous Reporting System (SRS) did not permit patients receiving formoterol for COPD to be separated from those for which the indication was asthma, so the two indications were reported together. The data were summarized depending on whether previously reported to the FDA (cut-off date 15 July 1999) or not previously reported to the FDA (cut-off date 15 February 2000). As of the 15 July 1999 Safety Update to this NDA, 451 case reports were received 104 of which were classified as serious. An additional 101 spontaneous reports were received between that date and 15 February 2000. Seven of the 101 new reports were considered serious and 94, non-serious. The frequency of serious/total spontaneous reports before and after 15 July 1999 were quite different with more 23% of the reports classified as serious before July 1999 and 7% after that date [2:34-6]. These seven are summarized below [2:37]:

1. muscle ache, myopathy, asthenia
2. acute ischemic stroke, paralysis, numbness (70 year old female)
3. sinus tachycardia, anginal attack, nausea, BP drop, circulatory disturbance
4. chest infection
5. eosinophilia
6. asthma attack, lack of efficacy
7. deterioration of concomitant disease, dry throat, voice alteration, tumor

Review of the narratives of these patients also failed to reveal any suspicious safety concerns [2:111-4].

IV.B. POST-MARKETING OBSERVATIONAL STUDIES

Reports of adverse events from these are methodologically distinct from both spontaneous reports from the market and reports from clinical trials. As is the case with spontaneous reports, the treating physician has no reporting obligation. However, as with clinical trials, the physician participating in an observational study is specifically requested to report adverse events. Hence, the under-reporting typical of spontaneous reports is less of a problem. One serious case in this category came from a German study without a control group. This was a 10 year old female with asthma begun on formoterol who, two months later, discontinued it during a hospitalization for asthma [2:39; 114].

IV.C. JOURNAL REPORTS PUBLISHED

A total of 36 new publications on formoterol appeared in the literature between 16 July 1999 and 15 February 2000. Eight of these were Novartis sponsored trials and 28

were independent. Of note, one trial may have been the subject of more than one abstract and/or published paper. Selected items have been chosen for reporting in this review.

An abstract from Singapore, looked at the efficacy of repeated doses of formoterol up to 72 mcg total dose compared with salbutamol 10 mg by wet nebulizer in the ER treatment of 38 patients with acute asthma. Those who failed to improve their PEFR by 20% were crossed over to the other treatment. The failure rates of the original treatments were comparable, 57% (failed salbutamol) and 52% (failed formoterol). However, those who received formoterol had a lower PEFR and a smaller change from baseline after 30 minutes than those who receive salbutamol. The authors concluded that formoterol was effective for acute asthma, but that the onset of action of salbutamol was faster [2:210].

A summary of a Chest article evaluated whether regular treatment with formoterol for two weeks effects the bronchodilator response to repeated puffs of albuterol 24 hours after cessation of formoterol treatment. It also examined the effects of acute administration of a bolus intravenous or inhaled corticosteroid. A statistically significantly lower mean FEV_{1.0} response after formoterol alone compared with placebo was reported. This reduction in beta agonist response 24 hours following cessation of chronic formoterol treatment was partially reversed by a bolus of systemic or inhaled corticosteroids [2:48, 211-7].

V. LABELING

The labeling review was complete at the conclusion of the last complete response but now requires minor re-editing because of unannotated changes authored by the sponsor. It will be submitted as a separate review document either by myself or by the Project Manager.

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