LCAK

FEB - 2 2000

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-831 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 26 JAN 2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	24-JUN-97	26-JUN-97	02-JUL-97
Amendment	16-OCT-97	17-OCT-97	02-NOV-97
Amendment	24-OCT-97	28-OCT-97	03-NOV-97
Amendment	05-FEB-98	06-FEB-98	18-FEB-98
Amendment	24-FEB-98	25-FEB-98	05-MAR-98
Amendment	20-MAR-1998	23-MAR-1998	31-MAR-1998
Amendment	01-JUN-1998	03-JUN-1998	03-JUN-1998
Amendment	19-OCT-1998	20-OCT-1998	20-OCT-1998
Amendment	10-NOV-1998	10-NOV-1998	12-NOV-1998
		SUBJECT OF THIS REVIEW	
Amendment	23-NOV-1999	24-NOV-1999	03-DEC-1999

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

DRUG PRODUCT NAME
Proprietary: Foradil Aerolizer ™
Nonproprietary/USAN: formoterol fumarate inhalation powder
Code Names/#s:
- Atock (Japan)
- BD40A
- CGP 25827A
- Eformoterol (England)
- Foradil (USA/Europe)
- FORADIL/A. S. fumarate
- FORADIL/A.S. fumarate, micronized
- FORADIL/W.S. fumarate
- (±)-2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dehydrate
- 2-Hydroxy-5-[(1RS)-1-hydroxy-2-{[(1RS)-2-p-methoxyphenyl)-l-methylethyl]-amino}ethyl]formanilide fumarate dehydrate
- (±)-2'-Hydroxy-5'-[(IRS)-l-hydroxy-2-{[(IRS)-2-p-methoxy-a-phenethyl-amino-ethylformanilide fumarate dehydrate
- (R*, R*)-(±)-N-[2-Hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butenedioate (2:1) (salt)
- YM-08316
- YM-8316

Chemical Abstracts registry number is 43229-80-7.

Chem.Type/Ther.Class: 1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: β_2-adrenergic bronchodilator for prevention and maintenance treatment of bronchoconstriction

DOSAGE FORM: Capsule containing powder for inhalation

STRENGTHS:

- 12 μg per capsule
- The recommended dose is one ———————— every 12 hours
- The emitted dose is 10μg when tested at 60L/min with 2 activations for 2 seconds each

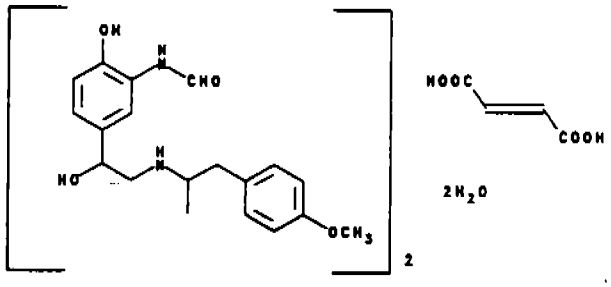
ROUTE OF ADMINISTRATION: oral inhalation for use with the Aeroliser™ Inhalation Device only

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

±2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate

Molecular Weight: 840.9
Molecular Formula:
$(C_{19}H_{24}N_2O_4)_2 \bullet C_4H_4O_4 \bullet 2H_2O$



APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

Support Doc#	Holder/ Applicant	Content/ Item	Status	Review Date	Letter Date
IND [redacted]	Novartis Pharmaceuticals Corporation	formoterol fumarate (dry powder capsules for inhalation)	active	4/15/96	4/16/97 meeting
DMF [redacted]		drug substance	adequate	10/21/98	
DMF [redacted]		drug substance	adequate	10/9/98	
DMF [redacted]	Novartis Pharmaceuticals Corporation	Novartis Manufacturing Switzerland	Type I		
DMF [redacted]		capsule shell manufacturer	Type I		
DMF [redacted]		blister components (formed side)	withdrawn 10/19/98	8/18/97	10/1/97
DMF [redacted]		blister components (formed side)	withdrawn 10/19/98	5/14/98	5/22/98
DMF [redacted]		blister components (backing)	adequate - not for commercial product	1/6/97	
DMF [redacted]		blister components (formed side)	adequate - not for commercial product	10/18/95	
DMF [redacted]		blister components (formed side and backing)	adequate	1/16/00	
DMF [redacted]		blister components (backing)	adequate	8/22/96	
DMF [redacted]		contract/sample packaging	Type I deficiencies not for commercial product	9/10/98	9/18/98
DMF [redacted]		contract/sample packaging	Type I	9/17/98	none
None	[redacted]	contract/sample packaging			
DMF [redacted]		Aeroliser™ device manufacturer	Type I		
DMF [redacted]		Aeroliser™ device manufacturer	adequate	9/22/98	10/27/98
DMF [redacted]		[redacted]	adequate	10/6/98	10/27/98
None	[redacted]				

RELATED DOCUMENTS (if applicable):
None.

CONSULTS:
EER - Submitted to compliance 12/8/99; as of this review, the compliance recommendation is "acceptable" for all facilities except [redacted] which is awaiting inspection.
EA - Submitted for consult 7/15/97; withdrawn 9/19/97 with claim for categorical exclusion and accepted by Agency.
MV - Deferred pending adequacy of all methods (See remark 5 below).
Microbiology - Submitted for consult 11/3/98; satisfactory 12/16/98

REMARKS/COMMENTS:

Previous chemist's review #3 (JLeak, 12/28/98) found the application not approvable. Deficiencies were sent to the applicant in a 3/25/98 IR letter and an approvable letter was sent to the applicant 6/26/98. A submission from the applicant dated 6/1/98 addressing our 3/25/98 IR letter was an incomplete response and was indicated in our 6/26/98 approvable letter as correspondence. Deficiencies in the 10/19/98 and 11/10/98 submissions were noted in chemist's review #3. After a meeting with the applicant 3/4/99, a submission from the applicant dated 11/23/99 labeled "Complete Response to Approvable Letter" was received 11/24/89 and is the subject of this review.

The following commitments are made by the applicant:

1. a. ——————————— will be the sole supplier of lactose and any alternate suppliers will be qualified on an individual basis, through a prior approval supplement.

   b. The certificate of analysis from the supplier will not be relied upon for release of this material, but be released based on the Novartis testing monograph.

   c. The particle size distribution will be used to diferentiate between mesh grades of the lactose.

2. There will be no planned reprocessing of the drug product and none will be introduced without prior FDA approval.

3. Packaging components from ——————— (DMF # ——— and ——————————— (DMF # ——— will not be used to package commercial drug product.

4. "Novartis commits to submit stability data from the first three Drug Product production lots as part of standard post-approval commitments. These production lot stability studies will be conducted according to the protocol (Attachment 17) which is consistent with the FDA draft guidances on "Stability Testing of Drug Substances and Drug Products" and "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products." The stability protocol includes the storage conditions and temperatures requested in the 26-Jun-98 approvable letter in the proposed final market package. As requested by FDA, no expiration date extension protocol is proposed at this time."

5. [ ] . Methods validation by our labs should confirm this.

CONCLUSIONS & RECOMMENDATIONS:

The November 23, 1999 amendment to the NDA adequately responds to all of the items in our approvable letter dated June 26, 1998, so the amendment may be filed. This was agreed to at the reviewing team meeting on January 10, 2000. However, there still remain deficiencies which need correction and are listed in the draft letter at the end of this review. The CSO should draft a letter to the applicant requesting correction of the listed deficiencies.

N.B.: EER of ——— is pending.

cc:
Orig. NDA 20-831
HFD-570/Division File
HFD-570/JLeak
HFD-570/CSO 2/8/00
HFD-570/GPoochikian
HFD-820/JGibbs
R/D Init by:

/S/

John C. Leak, Review Chemist
filename:

APPEARS THIS WAY
ON ORIGINAL

D IV

JAN 14 1999

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-831 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 28-DEC-1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	24-JUN-97	26-JUN-97	02-JUL-97
Amendment	16-OCT-97	17-OCT-97	02-NOV-97
Amendment	24-OCT-97	28-OCT-97	03-NOV-97
Amendment	05-FEB-98	06-FEB-98	18-FEB-98
Amendment	24-FEB-98	25-FEB-98	05-MAR-98
Amendment	20-MAR-1998	23-MAR-1998	31-MAR-1998
Amendment	01-JUN-1998	03-JUN-1998	03-JUN-1998
		SUBJECT OF THIS REVIEW	
Amendment	19-OCT-1998	20-OCT-1998	20-OCT-1998
Amendment	10-NOV-1998	10-NOV-1998	12-NOV-1998

NAME & ADDRESS OF APPLICANT:

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

DRUG PRODUCT NAME

Proprietary: Foradil™ Capsules - Inhalation Powder

Nonproprietary/USAN: formoterol fumarate

Code Names/#s:

- Atock (Japan)
- BD40A
- CGP 25827A
- Eformoterol (England)
- Foradil (USA/Europe)
- FORADIL/A. S. fumarate
- FORADIIL/A.S. fumarate, micronized
- FORADIIL/W.S. fumarate
- (±)-2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dehydrate
- 2-Hydroxy-5-[(1RS)-1-hydroxy-2-{[(1RS)-2-p-methoxyphenyl)-l-methylethyl]-amino}ethyl]formanilide fumarate dehydrate
- (±)-2'-Hydroxy-5'-[(IRS)-l-hydroxy-2-{[(IRS)-2-p-methoxy-a-phenethyll-aminol-ethyllformanilide fumarate dehydrate
- (R*, R*)-(±)-N-[2-Hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butenedioate (2:1) (salt)
- YM-08316
- YM-8316

Chemical Abstracts registry number is 43229-80-7.

Chem.Type/Ther.Class: 1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: $ß_2$-adrenergic bronchodilator for prevention and maintenance treatment of bronchoconstriction

DOSAGE FORM: Capsule containing powder for inhalation

STRENGTHS:

- 12 µg per capsule
- The recommended dose is one ———————— every 12 hours
- The emitted dose is 10µg when tested at 60L/min with 2 activations for 2 seconds each

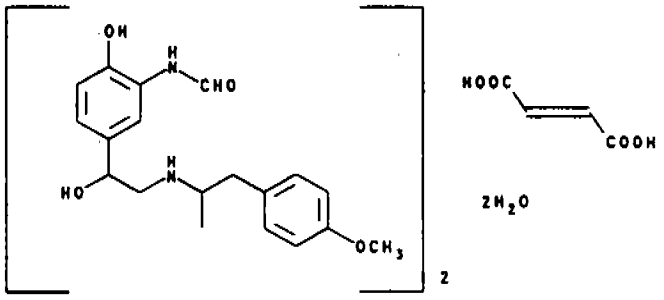
ROUTE OF ADMINISTRATION: oral inhalation for use with the Aeroliser™ Inhalation Device only

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

±2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate

Molecular Weight: 840.9
Molecular Formula: $(C_{19}H_{24}N_2O_4)_2 \bullet C_4H_4O_4 \bullet 2H_2O$



APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

Support Doc#	Holder/ Applicant	Content/ Item	Status	Review Date	Letter Date
IND	Novartis Pharmaceuticals Corporation	formoterol fumarate (dry powder capsules for inhalation)	active	4/15/96	4/16/97 meeting
DMF		drug substance	adequate	10/21/98	
DMF		drug substance	adequate	10/9/98	
DMF	Novartis Pharmaceuticals Corporation	Novartis Manufacturing-Switzerland	Type I		
DMF		capsule shell manufacturer	Type I		
DMF		blister components (formed side)	withdrawn 10/19/98	8/18/97	10/1/97
DMF		blister components (formed side)	withdrawn 10/19/98	5/14/98	5/22/98
DMF		blister components (backing)	adequate	1/6/97	
DMF		blister components (formed side)	adequate	10/18/95	
DMF		blister components (backing)	adequate	8/22/96	
DMF		contract/sample packaging	Type I deficiencies	9/10/98	9/18/98
DMF		contract/sample packaging	Type I - deficiencies listed in NDA ltr.	9/17/98	none
DMF		Aeroliser™ device manufacturer	Type I		
DMF		Aeroliser™ device manufacturer	deficiencies	9/22/98	10/27/98
DMF			deficiencies	10/6/98	10/27/98

RELATED DOCUMENTS (if applicable):

CONSULTS:
EER - Submitted to compliance 8/25/97; as of this review, the compliance recommendation is "Acceptable".
EA - Submitted for consult 7/15/97; withdrawn 9/19/97 with claim for categorical exclusion and accepted by Agency.
MV - pending corrections in methods before being submitted to our labs (see attached deficiency draft letter)
Microbiology - Comments # 2, 9h, 11d, 16f, 20, 23 - submitted on November 3, 1998, report pending

REMARKS/COMMENTS:
Previous chemist's review #2 (JLeak, 10/26/98) found the application not approvable. Deficiencies were sent to the applicant in a 3/25/98 IR letter and an approvable letter was sent to the applicant 6/26/98. A submission from the applicant dated 6/1/98 addressing our 3/25/98 IR letter was an incomplete response and was indicated in our 6/26/98 approvable letter as correspondence

and was reviewed in chemist's review #2. Deficiencies listed in chemist's review #2 are compared with information included in the 10/19/98 and 11/10/98 submissions and are reported here.

Several supporting DMFs were cited as deficient in our 6/26/98 approvable letter.

> The referenced DMFs —— and —— for the synthesis of the drug substance were reviewed and found adequate, but final specifications rest with the NDA applicant.
>
> The referenced DMFs —— and —— for the blister packaging components and the referenced DMF —— for the device were reviewed and deficiencies were addressed to the DMF holders. (Reference to DMFs —— and —— were withdrawn by the applicant 10/19/98)

In addition, DMF —— for packaging the drug product was reviewed 9/10/98 and found deficient; a letter was sent listing the deficiencies.

The only supplier for the lactose will be ——————————

CONCLUSIONS & RECOMMENDATIONS:
A meeting was held with the applicant on December 14. Resulting deficiencies from this review will be sent to the applicant.

cc:
Orig. NDA 20-831
HFD-570/Division File
HFD-570/JLeak
HFD-570/CSO
HFD-570/GPoochikian
HFD-820/JGibbs
R/D Init by /S/ 1/14/99

/S/

John C. Leak, Review Chemist
filename: ——

Jan 1

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-831 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 10/26/98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	24-JUN-97	26-JUN-97	02-JUL-97
Amendment	16-OCT-97	17-OCT-97	02-NOV-97
Amendment	24-OCT-97	28-OCT-97	03-NOV-97
Amendment	05-FEB-98	06-FEB-98	18-FEB-98
Amendment	24-FEB-98	25-FEB-98	05-MAR-98
		SUBJECT OF THIS REVIEW	
Amendment	20-MAR-1998	23-MAR-1998	31-MAR-1998
Amendment	01-JUN-1998	03-JUN-1998	03-JUN-1998

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

DRUG PRODUCT NAME

Proprietary: Foradil™ Capsules - Inhalation Powder
Nonproprietary/USAN: formoterol fumarate
Code Names/#s:

- Atock (Japan)
- BD40A
- CGP 25827A
- Eformoterol (England)
- Foradil (USA/Europe)
- FORADIL/A. S. fumarate
- FORADIIL/A.S. fumarate, micronized
- FORADIIL/W.S. fumarate
- (±)-2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dehydrate
- 2-Hydroxy-5-[(1RS)-1-hydroxy-2-{[(1RS)-2-p-methoxyphenyl)-l-methylethyl]-amino}ethyl]formanilide fumarate dehydrate
- (±)-2'-Hydroxy-5'-[(IRS)-l-hydroxy-2-{[(IRS)-2-p-methoxy-a-phenethyll-aminol-ethyllformanilide fumarate dehydrate
- (R*, R*)-(±)-N-[2-Hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butenedioate (2:1) (salt)
- YM-08316
- YM-8316

Chemical Abstracts registry number is 43229-80-7.

Chem.Type/Ther.Class: 1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: β_2-adrenergic bronchodilator for prevention and maintenance treatment of bronchoconstriction

DOSAGE FORM: Capsule containing powder for inhalation

STRENGTHS:

- 12 µg per capsule
- The recommended dose is one ———— every 12 hours
- The emitted dose is 10µg when tested at 60L/min with 2

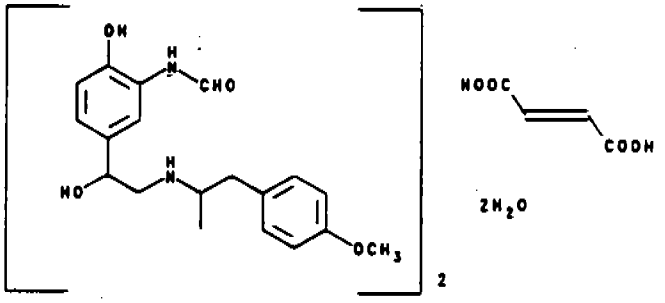
ROUTE OF ADMINISTRATION: oral inhalation for use with the Aeroliser™ Inhalation Device only

DISPENSED: ___X___ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

±2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate

Molecular Weight: 840.9
Molecular Formula: $(C_{19}H_{24}N_2O_4)_2 \bullet C_4H_4O_4 \bullet 2H_2O$



SUPPORTING DOCUMENTS:

Support Doc#	Holder/ Applicant	Content/ Item	Status	Review Date	Letter Date
INC [redacted]	Novartis Pharmaceuticals Corporation	formoterol fumarate (dry powder capsules for inhalation)	active	4/15/96	4/16/97 meeting
DMF [redacted]		drug substance	adequate	10/21/98	
DMF [redacted]		drug substance	adequate	10/9/98	
DMF [redacted]	Novartis Pharmaceuticals Corporation	Novartis Manufacturing Switzerland	Type I		
DMF [redacted]		capsule shell manufacturer	Type I		
DMF [redacted]		blister components (formed side)	deficiencies	8/18/97 WD	10/1/97
DMF [redacted]		blister components (formed side)	deficiencies	5/14/98 WD	5/22/98
DMF [redacted]		blister components (backing)	adequate	1/6/97	
DMF [redacted]		blister components (formed side)	adequate	10/18/95	
DMF [redacted]		blister components (backing)	adequate	8/22/96	
DMF [redacted]		contract/sample packaging	Type I deficiencies	9/10/98	9/18/98
DMF [redacted]		contract/sample packaging	Type I - deficiencies listed in NDA ltr.	9/17/98	none
DMF [redacted]		Aeroliser™ device manufacturer	Type I		
DMF [redacted]		Aeroliser™ device manufacturer	deficiencies	9/22/98	10/27/98
DMF [redacted]			deficiencies	10/6/98	10/27/98

RELATED DOCUMENTS (if applicable):

CONSULTS:
EER - Submitted to compliance 8/25/97; as of this review, the compliance report on Novartis Switzerland is pending and [redacted] is reported as not approvable (WH). The other faciities are reported as acceptable.
EA - Submitted for consult 7/15/97; withdrawn 9/19/97 with claim for categorical exclusion and accepted by Agency.
MV - pending corrections in methods before being submitted to our labs (see attached deficiency draft letter)
Microbiology - Comments # 2, 9h, 11d, 16f, 20, 23 - submitted on November 3, 1998, report pending

REMARKS/COMMENTS:
Previous chemist's review (JLeak, 3/8/98) found the application not approvable. Deficiencies listed in the draft letter portion of that review were sent to the applicant in the 3/25/98 IR letter. An approvable letter was sent to the applicant 6/26/98. A submission from the applicant dated 6/1/98 addressing our 3/25/98 IR letter was an incomplete response and was indicated in our 6/26/98 approvable letter as correspondence and was not reviewed. That submission is reviewed here.

Several supporting DMFs were cited as deficient in our 6/26/98 approvable letter.

> The referenced DMFs [redacted] for the synthesis of the drug substance were reviewed and found adequate, but final specifications rest with the NDA applicant.
>
> The referenced DMFs [redacted] for the blister packaging components and the referenced DMF [redacted] for the device were reviewed and deficiencies were addressed to the DMF holders. (Reference to DMFs [redacted] and [redacted] were withdrawn by the applicant 10/ /98)

In addition, DMF [redacted] for packaging the drug product was reviewed 9/10/98 and found deficient; a letter was sent listing the deficiencies.

The only supplier for the lactose will be [redacted]

CONCLUSIONS & RECOMMENDATIONS:
This application remains deficient. An approvable letter has already been sent to the applicant with a statement that the 6/1/98 submission (reviewed here) was considered correspondence. A response to the approvable letter dated 10/19/98 will be evaluated for filing at the 10/30/98 team meeting.
The CSO should send a letter to the applicant including the deficiencies found in this review of the 6/1/98 submission in the draft letter at the end of this review.

cc:
Orig. NDA 20-831
HFD-570/Division File
HFD-570/JLeak
HFD-570/CSO
HFD-570/GPoochikian
HFD-820/JGibbs
R/D Init by 11/21/98

/S/
John C. Leak, Review Chemist
filename:

MAR 17 1998

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-831 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 8-MAR-1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	24-JUN-97	26-JUN-97	02-JUL-97
Amendment	16-OCT-97	17-OCT-97	02-NOV-97
Amendment	24-OCT-97	28-OCT-97	03-NOV-97
Amendment	05-FEB-98	06-FEB-98	18-FEB-98
Amendment	24-FEB-98	25-FEB-98	05-MAR-98

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

DRUG PRODUCT NAME

Proprietary: Foradil™ Capsules for Inhalation

Nonproprietary/USAN: formoterol fumarate

Code Names/#s:

- Atock (Japan)
- BD40A
- CGP 25827A
- Eformoterol (England)
- Foradil (USA/Europe)
- FORADIL/A. S. fumarate
- FORADIIL/A.S. fumarate, micronized
- FORADIIL/W.S. fumarate
- (±)-2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dehydrate
- 2-Hydroxy-5-[(1RS)-1-hydroxy-2-{[(1RS)-2-p-methoxyphenyl)-l-methylethyl]-amino}ethyl]formanilide fumarate dehydrate
- (±)-2'-Hydroxy-5'-[(IRS)-l-hydroxy-2-{[(IRS)-2-p-methoxy-a-phenethyll-aminol-ethyllformanilide fumarate dehydrate
- (R*, R*)-(±)-N-[2-Hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butenedioate (2:1) (salt)
- YM-08316
- YM-8316

Chemical Abstracts registry number is 43229-80-7.

Chem.Type/Ther.Class: 1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: β_2-adrenergic bronchodilator for prevention and maintenance treatment of bronchoconstriction

DOSAGE FORM: Capsule containing powder for inhalation

STRENGTHS:

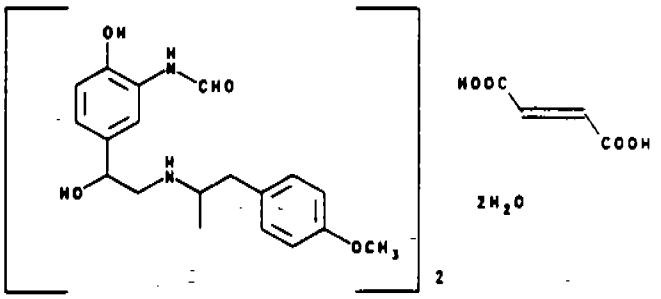
- 12 µg per capsule
- The recommended dose is one ———————— ; every 12 hours
- The emitted dose is 10µg when tested at 60L/min with 2 activations for 2 seconds each

ROUTE OF ADMINISTRATION: oral inhalation for use with the Aeroliser™ Inhalation Device only

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

±2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate



Molecular Weight: 840.9
Molecular Formula: $(C_{19}H_{24}N_2O_4)_2 \bullet C_4H_4O_4 \bullet 2H_2O$

SUPPORTING DOCUMENTS:

Support Doc#	Holder/ Applicant	Content/ Item	Status	Review Date	Letter Date
IND	Novartis Pharmaceuticals Corporation	formoterol fumarate (dry powder capsules for inhalation)	active	4/15/96	4/16/97 meeting
DMF		drug substance	deficiencies	8/5/97	2/10/98
DMF		drug substance	deficiencies	8/8/97	2/10/98
DMF	Novartis Pharmaceuticals Corporation	Novartis Manufacturing Switzerland	Type I		
DMF		capsule shell manufacturer	Type I		
DMF		blister components (formed side)	deficiencies	8/18/97	10/1/97
DMF		blister components (formed side)	deficiencies	1/23/98	2/10/98
DMF		blister components (backing)	adequate	1/6/97	
DMF		blister components (formed side)	adequate	10/18/95	
DMF		blister components (backing)	adequate	8/22/96	
DMF		contract/sample packaging	Type I		
DMF		contract/sample packaging	Type I		
DMF		Aeroliser™ device manufacturer	Type I		
DMF		Aeroliser™ device manufacturer	deficiencies	2/11/98	2/20/98

RELATED DOCUMENTS (if applicable):

CONSULTS:

EER - Submitted to compliance 8/25/97; as of this review, the compliance report on Novartis Switzerland is pending and [redacted] is reported as not approvable (WH). The other faciities are reported as acceptable.
EA - Submitted for consult 7/15/97; withdrawn 9/19/97 with claim for categorical exclusion and accepted by Agency.

MV - pending corrections in methods before being submitted to our labs (see attached deficiency draft letter)

REMARKS/COMMENTS:

Deficiencies listed in the attached draft letter should be sent to the applicant for correction. At this time, the application is not approvable. Deficiency letters have been sent to DMF holders which support this application (see table above). Labeling is not evaluated in this review. The last amendment requesting a change in specifications for Emitted Dose will be evaluated along with the applicants response to the deficiency letter.

The microbiological group has indicated that the applicant should not discontinue the microbial testing of the device at this time, as proposed in the 2/24/98 amendment.

CONCLUSIONS & RECOMMENDATIONS:

At this time, the application is not approvable. Deficiencies listed in the attached draft letter should be sent to the applicant for correction.

cc:
Orig. NDA 20-831
HFD-570/Division File
HFD-570/JLeak
HFD-570/CSO
HFD-570/GPoochikian
HFD-820/JGibbs
R/D Init by 3/17/98

/S/

John C. Leak, Review Chemist
filename:

APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

Support Doc#	Holder/ Applicant	Content/ Item	Status	Review Date	Letter Date
IND [redacted]	Novartis Pharmaceuticals Corporation	formoterol fumarate (dry powder capsules for inhalation)	active	4/15/96	4/16/97 meeting
DMF [redacted]	[redacted]	drug substance	adequate	10/21/98	
DMF [redacted]	[redacted]	drug substance	adequate	10/9/98	
DMF [redacted]	Novartis Pharmaceuticals Corporation	Novartis Manufacturing Switzerland	Type I		
DMF [redacted]	[redacted]	capsule shell manufacturer	Type I		
DMF [redacted]	[redacted]	blister components (formed side)	withdrawn 10/19/98	8/18/97	10/1/97
DMF [redacted]	[redacted]	blister components (formed side)	withdrawn 10/19/98	5/14/98 1/23/98	5/22/98 2/10/98
DMF [redacted]	[redacted]	blister components (backing)	adequate – not for commercial product	1/6/97	
DMF [redacted]	[redacted]	blister components (formed side)	adequate – not for commercial product	10/18/95	
DMF [redacted]	[redacted]	blister components (formed side and backing)	adequate	~~1/16/00~~ 1/7/00	
DMF [redacted]	[redacted]	blister components (backing)	adequate	8/22/96	
DMF [redacted]	[redacted]	contract/sample packaging	Type I deficiencies not for commercial product	9/10/98	9/18/98
DMF [redacted]	[redacted]	contract/sample packaging	Type I - deficiencies listed in NDA ltr.	9/17/98	none
None	[redacted]	contract/sample packaging			
DMF [redacted]	[redacted]	Aerolizer™ device manufacturer	Type I		
DMF [redacted]	[redacted]	Aerolizer™ device manufacturer	adequate	9/22/98 2/11/98	10/27/98 2/20/98
DMF [redacted]	[redacted]		adequate	10/6/98	10/27/98
None	[redacted]				

RELATED DOCUMENTS (if applicable): None.