

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-831

CHEMISTRY REVIEW(S)

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

NDA #: 20-831 **CHEM.REVIEW #:** 7 addendum #2 **REVIEW DATE:** 08-DEC-00

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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
Amendment	23-NOV-1999	24-NOV-1999	03-DEC-1999
Amendment	16-FEB-2000		22-FEB-2000
Amendment	30-MAR-2000	31-MAR-2000	06-APR-2000
Amendment	17-JUL-2000		20-JUL-2000
Amendment	17-AUG-2000	18-AUG-2000	21-AUG-2000
Amendment	29-SEP-2000	02-OCT-2000	05-OCT-2000

SUBJECTS OF THIS REVIEW

Amendment	01-DEC-2000	04-DEC-2000	07-DEC-2000
Amendment	07-DEC-2000	08-DEC-2000	08-DEC-2000

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'-[(1RS)-l-hydroxy-2-[[[(1RS)-2-p-methoxy-a-phenethyl-amino-ethyl]formanilide 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 mcg per capsule
- The recommended dose is one _____ every 12 hours
- The emitted dose is 10 mcg when tested at 60L/min with 2 activations for 2 seconds each

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

SPECIAL PRODUCTS: Yes No

DISPENSED: Rx OTC

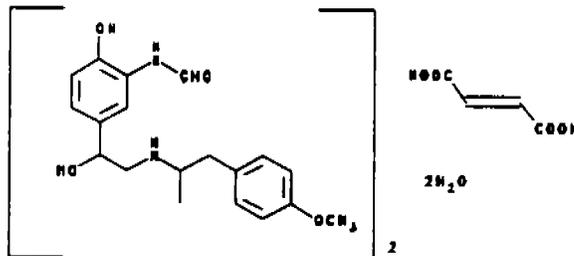
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:

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

Molecular Weight: 840.9

Molecular Formula:

$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$



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 -- not for commercial product	1/6/97	
DMF _____	_____	blister components (formed side)	adequate -- not for commercial product	10/18/95	
DMF _____	_____	blister components (formed side and backing)	adequate	1/16/00	
DMF _____	_____	blister components (backing)	adequate	8/22/96	
DMF _____	_____	contract/sample packaging	Type I deficiencies not for commercial product	9/10/98	9/18/98
DMF _____	_____	contract/sample packaging	Type I - deficiencies listed in NDA ltr.	9/17/98	none
None	_____	contract/sample packaging			
DMF _____	_____	Aerolizer™ device manufacturer	Type I		
DMF _____	_____	Aerolizer™ device manufacturer	adequate	9/22/98	10/27/98
DMF _____	_____	_____	adequate	10/6/98	10/27/98
None	_____	_____			

RELATED DOCUMENTS (if applicable): None.

CONSULTS:

See first addendum to chemistry review dated 25-OCT-00 for summary. Note that the method validation packages were submitted with the 01-DEC-00 amendment and have been forwarded to the appropriate Agency laboratories for evaluation.

REMARKS/COMMENTS:

See review notes.

CONCLUSIONS & RECOMMENDATIONS:

The application, as amended on 07-DEC-00 is considered sufficient from a CMC perspective for approval (AP).

cc:

Orig. NDA 20-831

HFD-570/Division File

HFD-570/CBertha/12/8/00

HFD-570/PJani

HFD-570/GPoochikian

HFD-820/JGibbs

R/D Init by:

Craig M. Bertha, Ph.D., Review Chemist
filename: _____

APPEARS THIS WAY
ON ORIGINAL

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

NDA #: 20-831 **CHEM. REVIEW #:** 7 addendum #1 **REVIEW DATE:** 25-OCT-00

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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
Amendment	23-NOV-1999	24-NOV-1999	03-DEC-1999
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Amendment	30-MAR-2000	31-MAR-2000	06-APR-2000
Amendment	17-JUL-2000		20-JUL-2000
Amendment	17-AUG-2000	18-AUG-2000	21-AUG-2000

<u>SUBJECT OF THIS REVIEW</u>			
Amendment	29-SEP-2000	02-OCT-2000	05-OCT-2000

NAME & ADDRESS OF APPLICANT:

Novartis Pharmaceuticals Corporation
 59 Route 10
 East Hanover, NJ 07936

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Names/#s:

Foradil Aerolizer™
 formoterol fumarate inhalation powder

- 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]-1-methylethyl]-amino]ethyl]formanilide fumarate dehydrate
- (±)-2'-Hydroxy-5'-[(1RS)-1-hydroxy-2-[(1RS)-2-p-methoxy-a-phenethyl-amino-ethyl]formanilide 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 SANDA Suitability Petition/DESI/Patent Status: N/APHARMACOL. CATEGORY/INDICATION: β_2 -adrenergic bronchodilator for prevention and maintenance treatment of bronchoconstrictionDOSAGE FORM: Capsule containing powder for inhalation

STRENGTHS:

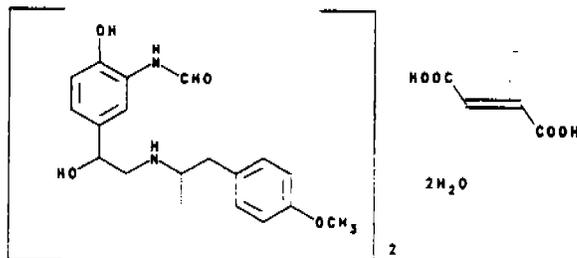
- 12 μg per capsule
- The recommended dose is one _____ every 12 hours
- The emitted dose is 10 μg when tested at 60L/min with 2 activations for 2 seconds each

ROUTE OF ADMINISTRATION: oral inhalation for use with the Aeroliser™ Inhalation Device onlyDISPENSED: Rx OTCCHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

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

Molecular Weight: 840.9

Molecular Formula:

 $(\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_4)_2 \bullet \text{C}_4\text{H}_4\text{O}_4 \bullet 2\text{H}_2\text{O}$ 

APPEARS THIS WAY
ON CD/CD/CD/CD

SUPPORTING DOCUMENTS:

Support Doc#	Holder/Applicant	Content/Item	Status	Review Date	Letter Date
IND	Novartis Pharmaceuticals Corporation	fomoterol 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 - not for commercial product	1/6/97	
DMF		blister components (formed side)	adequate - not for commercial product	10/18/95	
DMF		blister components (formed side and backing)	adequate	1/16/00	
DMF		blister components (backing)	adequate	8/22/96	
DMF		contract/sample packaging	Type I deficiencies not for commercial product	9/10/98	9/18/98
DMF		contract/sample packaging	Type I - deficiencies listed in NDA ltr.	9/17/98	none
None		contract/sample packaging			
DMF		Aeroliser™ device manufacturer	Type I		
DMF		Aeroliser™ device manufacturer	adequate	9/22/98	10/27/98
DMF			adequate	10/6/98	10/27/98
None					

RELATED DOCUMENTS (if applicable):

None.

CONSULTS:

EER - Submitted to compliance 9/18/00; as of this review, the compliance recommendation is "acceptable" for all facilities except Novartis, Locarno, SZ which is awaiting recommendation.

EA - Submitted for consult 7/15/97; withdrawn 9/19/97 with claim for categorical exclusion and accepted by Agency.

MV - Deferred pending acceptance of recommended storage/expiry recommendation.

Microbiology - Submitted for consult 11/3/98; satisfactory 12/16/98.

REMARKS/COMMENTS:

Previous chemist's review #7 (JLeak, 8/29/00) found the applicant had responded to the deficiencies in the Approvable letter dated 5/24/00. However, an expiration period and storage conditions could not be established at that time. The two-month data was not extensive enough to reach any conclusion on the protective effect of the over-wrap. The current amendment contains three-month stability data for the protective effect of the over-wrap.

CONCLUSIONS & RECOMMENDATIONS:

The applicant should continue the study of the overwrap stability of the drug product and commercial drug product should be packaged with overwrap until such time as the data shows there is no benefit to the drug stability. The stability protocol presented in attachment X in volume 39 of the 8/17/2000 amendment specifies that stability testing of the drug product in the overwrap will be performed on only the first three production batches.

The drug product should be stored at refrigeration temperatures for a maximum of 18 months and should be overwrapped in the foil pouch. Once the overwrap is removed and the drug product brought to room temperature, it should be used within 3 months, _____ . If subsequent to following the stability protocol and generating data on several commercial batches, analysis of the data indicate that overwrap may not be needed, then a prior approved supplement should be submitted to that effect as discussed earlier.

By storing the drug product for 3 months rather than _____ at room temperature, the total unaccounted mass loss should be not more than _____ rather than _____ this should be reflected in the specifications. It seems that a smaller package than the proposed 60 capsule trade package is needed for patients taking Foradil for EIB so that opened packages do not need to remain at room temperature for up to 6 months. Since the trade package is a one-month supply for patients taking Foradil 12 µg on a BID maintenance schedule, the unopened of multiple packages received by the patient could be stored in the refrigerator. The 16 capsule physician sample could serve for the low use patients.

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:

John C. Leak, Review Chemist
filename: _____

APPEARS THIS WAY
ON ORIGINAL

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

NDA #: 20-831 CHEM. REVIEW #: 7 REVIEW DATE: 12-OCT-00

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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
Amendment	23-NOV-1999	24-NOV-1999	03-DEC-1999
Amendment	16-FEB-2000		22-FEB-2000
Amendment	30-MAR-2000	31-MAR-2000	06-APR-2000
Amendment	17-JUL-2000		20-JUL-2000
Amendment	17-AUG-2000	18-AUG-2000	21-AUG-2000

<u>SUBJECT OF THIS REVIEW</u>			
Amendment	29-SEP-2000	02-OCT-2000	05-OCT-2000

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
Chem. Type/Ther. Class: 1 S

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

PHARMACOL. CATEGORY/INDICATION: β₂-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: Rx OTC

NDA 20-831

Page 2

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ON ORIGINAL

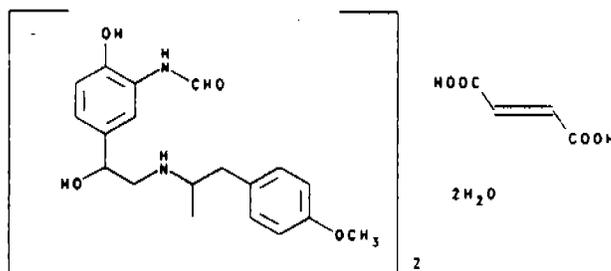
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

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

Molecular Weight: 840.9

Molecular Formula:

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REMARKS/COMMENTS:

Previous chemist's review #7 (JLeak, 8/29/00) found the applicant had responded to the deficiencies in the Approvable letter dated 5/24/00. However, an expiration period and storage conditions could not be established at that time. The two-month data was not extensive enough to reach any conclusion on the protective effect of the over-wrap. The current amendment contains three-month stability data for the protective effect of the over-wrap.

CONCLUSIONS & RECOMMENDATIONS:

The applicant should continue the study of the overwrap stability of the drug product and commercial drug product should be packaged with overwrap until such time as the data shows there is no benefit to the drug stability.

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:

John C. Leak, Review Chemist
filename: _____

APPEARS THIS WAY
ON ORIGINAL

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

NDA #: 20-831 **CHEM. REVIEW #:** 6 **REVIEW DATE:** 09-APR-2000

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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
Amendment	23-NOV-1999	24-NOV-1999	03-DEC-1999
Amendment	16-FEB-2000		22-FEB-2000
<u>SUBJECT OF THIS REVIEW</u>			
Amendment	30-MAR-2000	31-MAR-2000	06-APR-2000

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
Chem. Type/Ther. Class: 1 S

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

PHARMACOL. CATEGORY/INDICATION: β₂-adrenergic bronchodilator for
prevention and maintenance treatment of
bronchoconstriction

DOSAGE FORM: Capsule containing powder for inhalation

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

DISPENSED: X Rx OTC

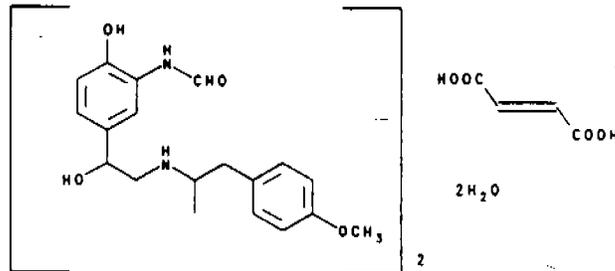
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

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

Molecular Weight: 840.9

Molecular Formula:

$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$



REMARKS/COMMENTS:

Previous chemist's review #5 (JLeak, 3/14/2000) found the application still contained deficiencies which need correction. A meeting was held with the applicant on 4/6/00 to discuss the stability data, which was the subject of the last chemist's review, and a possible expiration period for the drug product. The current amendment is a response to the information request letter dated 2/2/00 containing concerns based on the applicant's 11/23/99 amendment. (Chemist's review of 11/23/99 amendment - 1/26/00, doc # 20831c2.doc)

CONCLUSIONS & RECOMMENDATIONS:

There are still deficiencies remaining which should be corrected by the applicant. The list of deficiencies found in the current amendment and listed in the draft letter portion of this review should 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

JSI 2/27/00

JSI

John C. Leak, Review Chemist
filename: _____

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

NDA #: 20-831 CHEM. REVIEW #: 5 REVIEW DATE: 14 MAR 2000

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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
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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
Amendment	23-NOV-1999	24-NOV-1999	03-DEC-1999
	<u>SUBJECT OF THIS REVIEW</u>		
Amendment	16-FEB-2000		22-FEB-2000

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

DRUG PRODUCT NAME
Proprietary:
Nonproprietary/USAN:
Chem. Type/Ther. Class: 1 s

Foradil Aerolizer™
formoterol fumarate inhalation powder

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

PHARMACOL. CATEGORY/INDICATION:
β₂-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
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ROUTE OF ADMINISTRATION:
oral inhalation for use with the Aeroliser™ Inhalation Device only

DISPENSED: X Rx _____ OTC

APPEARS THIS WAY
ON ORIGINAL

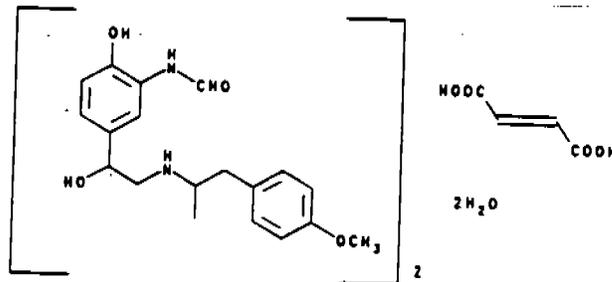
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT.:

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

Molecular Weight: 840.9

Molecular Formula:

(C₁₉H₂₄N₂O₄)₂•C₄H₄O₄•2H₂O



REMARKS/COMMENTS:

Previous chemist's review #4 (JLeak, 1/26/2000) found the application still contained deficiencies which need correction. Deficiencies were sent to the applicant in a February IR letter. A submission from the applicant dated 2/16/200 contained updated (6 month) stability data and is the subject of this review.

CONCLUSIONS & RECOMMENDATIONS:

This submission satisfies the agreement between the applicant and the Agency to supply six-month stability data on the drug product manufactured and packaged as a commercial product. Additional data will be submitted as committed by the applicant. Additional decisions will be made after receipt of a response to the February IR letter and the pending April conference with the applicant.

The six month stability data submitted in this amendment is very limited and results exhibit a high variability. Results from the _____ particle size distribution determination indicate a greater decrease in the fine particle mass for samples stored at 25°C/75%RH than samples stored at either 25°C/60%RH or 30°C/60%RH; it may be prudent to use a secondary protective moisture barrier packing and/or refrigeration. There is need to account for loss of drug substance on storage that is not reported as related substances and for the variability in the emitted dose.

cc:

Orig. NDA 20-831
 HFD-570/Division File
 HFD-570/JLeak
 HFD-570/CSO
 HFD-570/GPoochikian
 HFD-820/JGibbs
 R/D Init *[Signature]* 4/1/00

/S/

John C. Leak, Review Chemist
 filename: _____