CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-911

Chemistry Review(s)

K1.2

K1.2

N20911

N20911

DIVISION OF PULMONARY DRUG PRODU
...view of Chemistry, Manufacturing, and Controls

REC - 11/29/00 - 8:35AM

NDA #: 20-911 **CHEM. REVIEW #:** 6 **REVIEW DATE:** 9/15/2000

RECOMMEND ACTION: APPROVAL

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	5/11/98	5/12/98	5/29/98
Amendment (BC)	9/23/98	10/1/98	10/5/98
Amendment (BC)	1/8/99	1/13/99	1/20/99
Amendment (BC)	3/22/99	3/23/99	3/24/99
Amendment (BL)	4/9/99	4/12/99	4/13/99
Amendment (BC)	8/11/99	8/12/99	
Resubmission (AZ)	8/17/99	8/18/99	9/10/99
Amendment (BZ)	11/10/99	11/12/99	
Amendment (BC)	12/2/99	12/6/99	12/8/99
Amendment (BL)	1/10/2000	1/14/2000	
Amendment (BZ)**	2/28/2000	2/29/2000	3/8/2000
Amendment (BC)	4/10/2000	4/11/2000	4/14/2000
Amendment (BZ)	4/14/2000	4/17/2000	5/2/2000
Amendment (BC)	4/20/2000	4/25/2000	5/2/2000
Amendment (BZ)	5/24/2000	5/25/2000	5/26/2000
Amendment (BC)	6/23/2000	6/26/2000	7/7/2000
Amendment (BC)	7/31/2000	8/1/2000	8/9/2000
Amendment (BC)	8/4/2000	8/7/2000	8/8/2000
Amendment (BC)	8/15/2000	8/16/2000	8/16/2000
Amendment (BC)	8/18/2000	8/22/2000	8/23/2000
Amendment (BL)*	**8/29/2000**		
Amendment (BC)*	**9/9/2000**		
Amendment 033 (BC/BL)*	**9/13/2000**		
Amendment 034 (BL)*	**9/13/2000**		
Amendment 035 (BC/BL)*	**9/14/2000**		
Amendment 036 (BC)*	**9/14/2000**		

***Subject of this review**

**(Note that clock was restarted based on DMF [redacted] amendment received 3/15/2000, which together with the 2/28/2000 amendment constituted a complete response.)

NAME & ADDRESS OF APPLICANT: 3M Pharmaceuticals
Building 270-3A-08, 3M Center
St. Paul, MN 55144-1000

DRUG PRODUCT NAME:

Proprietary: Qvar 40 mcg (80 mcg) Inhalation Aerosol

Nonproprietary/USAN: beclomethasone dipropionate HFA inhalation aerosol

Code Name/#: Project Bronze

Chem. Type/Ther. Class: 3S

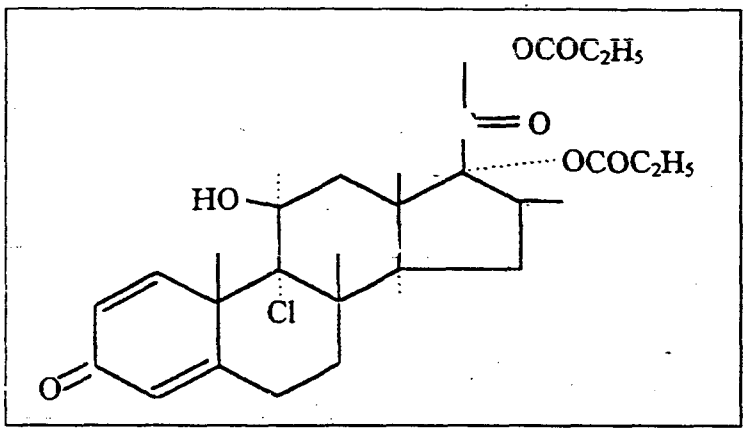
PHARMACOL. CATEGORY/INDICATION:	Anti-asthmatic (maintenance treatment of asthma as prophylactic therapy)
DOSAGE FORM:	inhalation aerosol
STRENGTHS:	40 mcg and 80 mcg per puff (ex-actuator)
ROUTE OF ADMINISTRATION:	oral inhalation
DISPENSED:	X Rx _ OTC
SPECIAL PRODUCTS: (If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)	_ YES _ _x NO

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Molecular Formula: $C_{28}H_{37}ClO_7$

M.W.



APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Review (section)
		beclomethasone dipropionate	Adequate.	8/12/98, 10/12/99, 7/7/00 and 9/8/00	A.1. of CR#1; and responses 6a, 17d(4), 17i(2) and 21 of CR#2. Multiple comments in CR#4 (#1,7,16); comment 1 in CR#5.
		propellant HFA-134a	Adequate.	5/3/99 and 10/15/99	B.3.B.2. of CR#1, and response 21 (CR#2).
	3M Pharmaceuticals	container/closure	Adequate.	4/26/2000	B.7. of CR#1; Response 21 (CR#2).
	3M Health Care Ltd.	type I (site manufacturer)	N.A.	N.A.	type I DMFs are not reviewed
	3M Pharmaceuticals	container/closure (canister)	adequate	2/16/2000 (K.Swiss)	B.7. of CR#1
			Adequate, IR letter	1/21/2000	Response 14c (CR#2)
			Adequate, IR letter	1/27/2000	Response 14c (CR#2)
			Reviewed in connection with N20-503 and found adequate. No more recent technical amendments.	8/13/96	Response 14c (CR#2)
			Adequate, IR letter.	1/28/2000, 7/25/2000	Response 14d(6) (CR#2), response 15 (CR#4).

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND		3M Pharmaceuticals	beclomethasone dipropionate HFA inhalation aerosol

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	original submitted to OC 23-SEP-98; update request of 10/27/99 update request of 3/22/2000 (FUR)	acceptable on 9/14/2000	Facility previously not ready for inspection [redacted] Applicant has since withdrawn that facility. Applicant has withdrawn the actuator test lab 3M Sante (Pithiviers, France) since it has not yet been inspected.
Biometrics, HFD-710	submitted 4/27/00; amendment to consult was submitted 7/12/2000	[redacted] months expiry not supported by stability data per 8/25/00 Biometrics review.	Consult for statistical evaluation of expiration dating period based on stability data and proposed specifications. (See review of 6/23/2000 amendment in Chemist's Review #4). **See comments in current review (CR#6) for explanation of decision to approve 18 month expiry.**
Clinical	3/19/99 re: assessment of occluded MDIs in clinical studies (vol. 1.3, pp. 53-62).	Acceptable on 9/14/2000.	This issue was deemed to be of no clinical concern: see Division Director's memo to file dated 9-14-00.
Environmental Assessment	N.A.	OK	None needed (satisfactory categorical exclusion claimed)
Pharmacology, HFD-570	9/9/98 request for safety assessment of applicant's "Bioassessment of Extractable Compounds in the Drug Product" and the USP Biological Reactivity Tests conducted on Actuator extractables. (This includes a safety assessment for [redacted] see B.7., section under valve, evaluation of [redacted] extractables). (Chemistry consult #1)	Satisfactory.*	Additional qualification requested for [redacted] extractables. (Previously unsatisfactory per 5/12/99 consult review). *
	12/23/98 request for safety assessment of proposed (drug related) impurity specifications for drug product, and for proposed drug product impurity specification for [redacted] content. (Chemistry consult #2)	Satisfactory.*	Limits for [redacted] degradation product and [redacted] impurity needed to be tightened or qualified. (Previously unsatisfactory per 5/11/99 consult review).*
	10/15/99 safety evaluation request for responses to comments 6b(2), 13o and 22 in our 5/12/99 action letter. This pertains to qualification data for specific impurities, degradation products and extractables. (Chemistry consult #3)	Satisfactory*	Deficiencies were the same as listed above for consults #1 & #2. (Previously unsatisfactory per 1/27/2000 consult rev.)*:
	10/30/99 safety evaluation request from Dr. K. Swiss re: specifications for residual canister extractables and foreign particulates. (Chemistry consult #4)	Adequate in 2/17/2000 consult review.	Extractables and foreign particulates are OK at indicated levels.
	01/04/2000 safety evaluation request for updated data on placebo leachables in 8/17/1999 amendment. (Chemistry consult #4 – combined with above consult.)	Satisfactory*	Specifications for certain impurities needed to be limited or qualified (same as for chemistry consult #2, above). (Previously unsatisfactory per 2/17/2000 consult rev.)*:
	3/31/00 safety evaluation request from Dr. K. Swiss re: proposed impurity specifications for the drug substance by the supplier (DMF [redacted] (Chemistry consult #5)	DMF Adequate: see 9/8/00 chem. review.	Specification limit for [redacted] impurity needed to be tightened or qualified in *drug substance*.

Labeling & Nomenclature Committee	8/98 sent by project manager.	Acceptable.	Proposed name (QVAR) is acceptable per 4/9/99 memo.

***NOTE - All drug product pharm./tox. deficiencies above are satisfactorily addressed (see 8/22/00 consult review).**

Other Consult Related Issues: NA

REMARKS/COMMENTS:

BACKGROUND:

Drug Substance (original NDA, vol. 1.3, pg. 4) – It is noted that "in CFC formulations, beclomethasone dipropionate (BDP) exists as a ' suspension of the drug. In the HFA formulations discussed here, the drug is totally dissolved in the ethanol/propellant solvent system."

Drug Product:
This drug product is a solution MDI and it comes in two strengths, 40 µg ex-actuator per puff, and 80 µg ex-actuator per puff. (These correspond to 50 µg and 100 µg ex-valve, which are sometimes used in the NDA as terms in referring to the two strengths). The valve volume is nominally 50 mcL, and valve delivery is 59.0 mg. Each strength MDI comes in two sizes, 100 and 200 actuations, with target fill weights of 8.70 g and 14.60 g, respectively. (Labeled fill weights are 7.3g and 13.2 g, respectively, however, minimum release specifications are —— g, respectively.) **The recommended dose is as low as *one actuation* twice a day, and as high as 320 mcg twice a day.** Repriming is to be performed after 10 days of non-use, using two actuations to reprime. The only excipients are the propellant, HFA-134a, and ethanol.

The canister is a 10 mL —— canister , —— , fitted with a 50 µL metered dose valve (—— —— made of —— rubber, and a gasket made of —— from —— Also, a —— O-ring is used as an additional seal when the valve is crimped onto the canister. ——are said to be identical to those used in Proventil HFA MDI. Actuator and dust cap are made from —— Actuators are either dark mauve or beige, and the dust cap is grey.). Orifice diameter in the actuator has limits of ——

The previously submitted labeling from HMR (now Aventis) has been withdrawn.

Since the product is a solution formulation, shaking is not required before use, and the proposed labeling reflects this.

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS AND RECOMMENDATIONS:

From a CMC standpoint, this application may be approved.

The applicant should be reminded of their commitments (agreements) in the action letter (see end of this review). A standard statement should also be included in the action letter pertaining to the applicant's cooperation in methods validation (see end of this review).

Note that all approved specifications for this NDA are attached to Chemist's Review #5.

S

Alan C. Schroeder, Ph.D., Review Chemist

cc:
Orig. NDA 20-911
HFD-570/Division File
HFD-570/ASchroeder/9-15-2000
HFD-570/CSO SBarnes
HFD-570/GPoochikian
HFD-570/RNicklas
R/D Init. by: S 9-15-2000
filename: n20911_R6_rev.doc

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commercial

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AUG 2 4 2000

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

NDA #: 20-911 **CHEM. REVIEW #:** 5 **REVIEW DATE:** August 24, 2000

RECOMMEND ACTION: **APPROVABLE**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	5/11/98	5/12/98	5/29/98
Amendment (BC)	9/23/98	10/1/98	10/5/98
Amendment (BC)	1/8/99	1/13/99	1/20/99
Amendment (BC)	3/22/99	3/23/99	3/24/99
Amendment (BL)	4/9/99	4/12/99	4/13/99
Amendment (BC)	8/11/99	8/12/99	
Resubmission (AZ)	8/17/99	8/18/99	9/10/99
Amendment (BZ)	11/10/99	11/12/99	
Amendment (BC)	12/2/99	12/6/99	12/8/99
Amendment (BL)	1/10/2000	1/14/2000	
Amendment (BZ)**	2/28/2000	2/29/2000	3/8/2000
Amendment (BC)	4/10/2000	4/11/2000	4/14/2000
Amendment (BZ)	4/14/2000	4/17/2000	5/2/2000
Amendment (BC)	4/20/2000	4/25/2000	5/2/2000
Amendment (BZ)	5/24/2000	5/25/2000	5/26/2000
Amendment (BC)	6/23/2000	6/26/2000	7/7/2000
Amendment (BC)	**7/31/2000**	**8/1/2000**	**8/9/2000**
Amendment (BC)*	**8/4/2000**	**8/7/2000**	**8/8/2000**
Amendment (BC)*	**8/15/2000**	**8/16/2000**	**8/16/2000**
Amendment (BC)*	**8/18/2000**	**8/22/2000**	**8/23/2000**

***Subject of this review**

**(Note that clock was restarted based on DMF [redacted] amendment received 3/15/2000, which together with the 2/28/2000 amendment constituted a complete response.)

NAME & ADDRESS OF APPLICANT: 3M Pharmaceuticals
Building 270-3A-08, 3M Center
St. Paul, MN 55144-1000

DRUG PRODUCT NAME:

Proprietary: Qvar 40 mcg (80 mcg) Inhalation Aerosol

Nonproprietary/USAN: beclomethasone dipropionate HFA inhalation aerosol

Code Name/#: Project Bronze

Chem. Type/Ther. Class: 3S

PHARMACOL. CATEGORY/INDICATION: Anti-asthmatic (maintenance treatment of asthma as prophylactic therapy)

DOSAGE FORM: inhalation aerosol

STRENGTHS: 40 mcg and 80 mcg per puff (ex-actuator)

ROUTE OF ADMINISTRATION: oral inhalation

DISPENSED: X Rx _ OTC

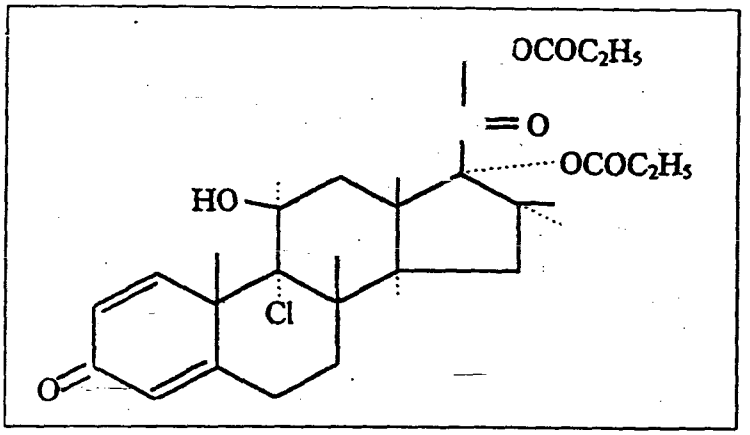
SPECIAL PRODUCTS: _ YES _x NO
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Molecular Formula: $C_{28}H_{37}ClO_7$

M.W.



SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Review (section)
		beclomethasone dipropionate	Inadequate (deficiency letter is dated 7/27/00)	8/12/98, 10/12/99, and 7/7/00	A.1. of CR#1; and responses 6a, 17d(4), 17i(2) and 21 of CR#2. Multiple comments in CR#4 (#1,7,16); comment 1 in CR#5.
		propellant HFA-134a	Adequate.	5/3/99 and 10/15/99	B.3.B.2. of CR#1, and response 21 (CR#2).
	3M Pharmaceuticals	container/closure	Adequate.	4/26/2000	B.7. of CR#1; Response 21 (CR#2).
	3M Health Care Ltd.	type I (site manufacturer)	N.A.	N.A.	type I DMFs are not reviewed
	3M Pharmaceuticals	container/closure (canister)	adequate	2/16/2000 (K.Swiss)	B.7. of CR#1
			Adequate, IR letter	1/21/2000	Response 14c (CR#2)
			Adequate, IR letter	1/27/2000	Response 14c (CR#2)
			Reviewed in connection with N20-503 and found adequate. No more recent technical amendments.	8/13/96	Response 14c (CR#2)
			Adequate, IR letter.	1/28/2000, 7/25/2000	Response 14d(6) (CR#2), response 15 (CR#4).

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND	[redacted]	3M Pharmaceuticals	beclomethasone dipropionate HFA inhalation aerosol

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CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	original submitted to OC 23-SEP-98; update request of 10/27/99 update request of 3/22/2000 (FUR)	acceptable on 12/21/1999 PENDING FUR	Facility previously not ready for inspection \ —— —— Applicant has since withdrawn that facility.
Biometrics, HFD-710		submitted 4/27/00 (pending); amendment to consult was submitted 7/12/2000 (PENDING)	Consult for statistical evaluation of expiration dating period based on stability data and proposed specifications. (See review of 6/23/2000 amendment in Chemist's Review #4)
Clinical	3/19/99 re: assessment of occluded MDIs in clinical studies (vol. 1.3, pp. 53-62).	PENDING	
Environmental Assessment		OK	None needed (satisfactory categorical exclusion claimed in v. 1.14, pg. 282)
Pharmacology, HFD-570	9/9/98 request for safety assessment of applicant's "Bioassessment of Extractable Compounds in the Drug Product" and the USP Biological Reactivity Tests conducted on Actuator extractables. (This includes a safety assessment for see B.7., section under valve, evaluation of —— extractables). (Chemistry consult #1)	Satisfactory.*	Additional qualification requested for and —— extractables. (Previously unsatisfactory per 5/12/99 consult review). *
	12/23/98 request for safety assessment of proposed (drug related) impurity specifications for drug product, and for proposed drug product impurity specification for —— content. (Chemistry consult #2)	Satisfactory.*	Limits for —— degradation product and —— impurity needed to be tightened or qualified. (Previously unsatisfactory per 5/11/99 consult review).*
	10/15/99 safety evaluation request for responses to comments 6b(2), 13o and 22 in our 5/12/99 action letter. This pertains to qualification data for specific impurities, degradation products and extractables. (Chemistry consult #3)	Satisfactory*	Deficiencies were the same as listed above for consults #1 & #2. (Previously unsatisfactory per 1/27/2000 consult rev.)*:
	10/30/99 safety evaluation request from Dr. K. Swiss re: specifications for —— extractables and foreign particulates. (Chemistry consult #4)	Adequate in 2/17/2000 consult review.	Extractables and foreign particulates are OK at indicated levels.
	01/04/2000 safety evaluation request for updated data on placebo leachables in 8/17/1999 amendment. (Chemistry consult #4 - combined with above consult.)	Satisfactory*	Specifications for certain impurities needed to be limited or qualified (same as for chemistry consult #2, above). (Previously unsatisfactory per 2/17/2000 consult rev.)*:
	3/31/00 safety evaluation request from Dr. K. Swiss re: proposed impurity specifications for the drug substance by the supplier (DMF) (Chemistry consult #5)	DMF Deficient per 6/27/2000 consult review.	Specification limit for —— impurity should be tightened or qualified in *drug substance*.
Labeling & Nomenclature Committee	8/98 sent by project manager.	Acceptable.	Proposed name (QVAR) is acceptable per 4/9/99 memo.

***NOTE - All drug product pharm./tox. deficiencies above are satisfactorily addressed (see 8/22/00 consult review).**

Other Consult Related Issues: NA

REMARKS/COMMENTS:

NOTE that the applicant refers to the volumes of its response (2/28/00 amendment) as volume 4.1, 4.2, etc. These are catalogued by our document room (and referred to in this review) as volumes 12.1, 12.2, etc. (respectively).

BACKGROUND:

Drug Substance (original NDA, vol. 1.3, pg. 4) – It is noted that "in CFC formulations, beclomethasone dipropionate (BDP) exists as a suspension of the drug. In the HFA formulations discussed here, the drug is totally dissolved in the ethanol/propellant solvent system."

Drug Product:
This drug product is a solution MDI and it comes in two strengths, 40 µg ex-actuator per puff, and 80 µg ex-actuator per puff. (These correspond to 50 µg and 100 µg ex-valve, which are sometimes used in the NDA as terms in referring to the two strengths). The valve volume is nominally 50 mcL, and valve delivery is 59.0 mg. Each strength MDI comes in two sizes, 100 and 200 actuations, with target fill weights of 8.70 g and 14.60 g, respectively. (Labeled fill weights are 7.3g and 13.2 g, respectively, however, minimum release specifications are g, respectively.) **The recommended dose is as low as *one actuation* twice a day, and as high as 320 mcg twice a day.** Repriming is to be performed after 10 days of non-use, using two actuations to reprime. The only excipients are the propellant, HFA-134a, and ethanol.

The canister is a 10 mL canister fitted with a 50 µL metered dose valve made of rubber, and a gasket made of from Also, a O-ring is used as an additional seal when the valve is crimped onto the canister. are said to be identical to those used in Proventil HFA MDI. Actuator and dust cap are made from Actuators are either dark mauve or beige, and the dust cap is grey.). Orifice diameter in the actuator has limits of

The previously submitted labeling from HMR (now Aventis) has been withdrawn.

Since the product is a solution formulation, shaking is not required before use, and the proposed labeling reflects this.

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS AND RECOMMENDATIONS:

From a CMC standpoint, this application is APPROVABLE, pending a satisfactory resolution of the following issues:

- Response to DMF [redacted] deficiency letter dated July 27, 2000.
- Biometrics consult review of stability data and proposed expiration dating period.
- Clinical consult review re: assessment of occluded MDIs in clinical studies.
- CGMP status of manufacturing, packaging and testing facilities (3/22/2000 EES request).
- CMC approval of final draft labeling. Package insert and patient package insert are to contain a statement pertaining to upright storage of the drug product. All carton labels must contain this statement as well, as per agreement by applicant in the 8/18/2000 amendment.

The applicant should be reminded of their commitments in the action letter (see end of this review, but in front of attachments). The action letter should also indicate the approved expiration dating period (pending Biometrics consult review). A standard statement should also be included in the action letter pertaining to the applicant's cooperation in methods validation (see end of this review).

/S/ 8/24/00

Alan C. Schroeder, Ph.D., Review Chemist

cc:
Orig. NDA 20-911
HFD-570/Division File
HFD-570/ASchroeder/8-24-00
HFD-570/CSO SBarnes
HFD-570/GPoochikian
HFD-570/RNicklas
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DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-911 **CHEM. REVIEW #:** 3 **REVIEW DATE:** May 2, 2000

RECOMMEND ACTION:

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
[Original NDA	5/11/98	5/12/98	5/29/98]
Resubmission*	2/28/2000	2/29/2000	3/8/2000
BC amendment*	4/10/2000	4/11/2000	4/14/2000
BZ amendment*	4/14/2000	4/17/2000	5/2/2000
BC amendment*	4/20/2000	4/25/2000	5/2/2000

*Subject of this review

NAME & ADDRESS OF APPLICANT: 3M Pharmaceuticals
Building 270-3A-08, 3M Center
St. Paul, MN 55144-1000

DRUG PRODUCT NAME:

Proprietary: Qvar 40 mcg (80 mcg) Inhalation Aerosol

Nonproprietary/USAN: beclomethasone dipropionate HFA inhalation aerosol

Code Name/#: Project Bronze

Chem. Type/Ther. Class: 3S

PHARMACOL. CATEGORY/INDICATION: Anti-asthmatic (maintenance treatment of asthma as prophylactic therapy)

DOSAGE FORM: inhalation aerosol

STRENGTHS: 40 mcg and 80 mcg per puff (ex-actuator)

ROUTE OF ADMINISTRATION: oral inhalation

DISPENSED: X Rx _ OTC

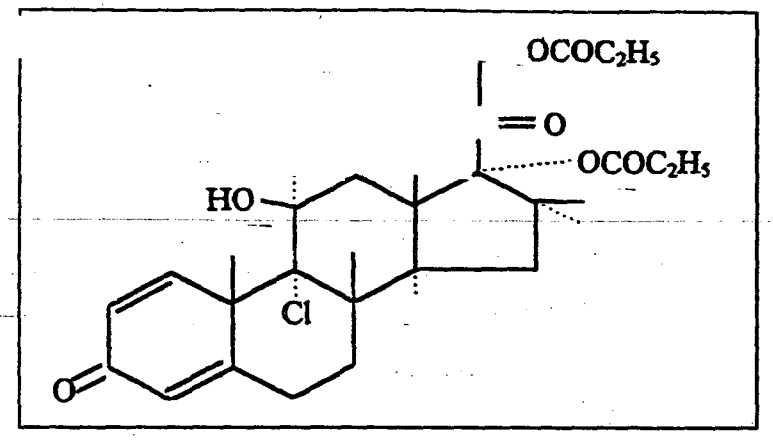
SPECIAL PRODUCTS: _ YES _x NO
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Molecular Formula: $C_{28}H_{37}ClO_7$

M.W. [illegible]



SUPPORTING DOCUMENTS:

DMFs

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Review (section)
1	—	beclomethasone dipropionate	**Currently under review by Kevin Swiss (waiting pharm/tox consult).**	8/12/98 and 10/12/99	A.1. of CR#1; and responses 6a, 17d(4), 17i(2) and 21 of CR#2.
1	—	propellant HFA-134a	Adequate.	5/3/99 and 10/15/99	B.3.B.2. of CR#1, and response 21 (CR#2).
	3M Pharmaceuticals	container/closure	Adequate.	4/26/2000	B.7. of CR#1; Response 21 (CR#2).
1	3M Health Care Ltd.	type I (site manufacturer)	N.A.	N.A.	type I DMFs are not reviewed
1	3M Pharmaceuticals	container/closure (canister)	adequate	2/16/2000 (K.Swiss)	B.7. of CR#1
1			Adequate, IR letter	1/21/2000	Response 14c (CR#2)
1			Adequate, IR letter	1/27/2000	Response 14c (CR#2)
1			Reviewed in connection with N20-503 and found adequate. No more recent technical amendments.	8/13/96	Response 14c (CR#2)
1		—	**Deficient.** (2/4/2000 deficiency letter)	1/28/2000	Response 14d(6) (CR#2)

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND	[redacted]	3M Pharmaceuticals	beclomethasone dipropionate HFA inhalation aerosol

CONSULTS: (clarified and updated)

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	original submitted to OC 23-SEP-98; update request of 10/27/99 update request of 3/22/2000	acceptable on 12/21/1999 pending FUR	Facility previously not ready for inspection. Applicant has since withdrawn that facility.
Biometrics, HFD-710		submitted 4/27/00 (pending)	Consult for statistical evaluation of expiration dating period based on stability data and proposed specifications.
Clinical	3/19/99 re: assessment of occluded MDIs in clinical studies (vol. 1.3, pp. 53-62).	pending as of 2/04/2000	
Environmental Assessment		OK	None needed (satisfactory categorical exclusion claimed in v. 1.14, pg. 282)
Pharmacology, HFD-570	9/9/98 request for safety assessment of applicant's "Bioassessment of Extractable Compounds in the Drug Product" and the USP Biological Reactivity Tests conducted on Actuator extractables. (This includes a safety assessment for — see B.7., section under valve, evaluation of —— extractables).	unsatisfactory (5/12/99 consult review)	Additional qualification requested for — extractables.
	12/23/98 request for safety assessment of proposed (drug related) impurity specifications for drug product*, and for proposed drug product impurity specification for —— content.	unsatisfactory (5/11/99 consult review)	limits for certain impurities and degradation products should be tightened, or qualified.
	10/15/99 safety evaluation request for responses to comments 6b(2), 13o and 22 in our 5/12/99 action letter. This pertains to qualification data for specific impurities, degradation products and extractables.	deficiencies identified (1/27/2000 consult rev.):	Tighter limits or qualification is necessary. Pharmacology to separately review applicant's responses (in 2/28/2000 amend).
	10/30/99 safety evaluation request from Dr. K. Swiss re: specifications for —— extractables and foreign particulates.	satisfactory as of 2/17/2000	
	01/04/2000 safety evaluation request for updated data on placebo leachables in 8/17/1999 amendment.	deficiencies identified as of 2/17/2000	Specifications for certain impurities should be limited or qualified. Pharmacology to separately review applicant's responses (2/28/2000 amend).
	3/31/00 safety evaluation request from Dr. K. Swiss re: proposed impurity specifications for the drug substance by the supplier (DMF [redacted]	PENDING	
Labeling & Nomenclature Committee	8/98 sent by project manager.	Acceptable.	Proposed name (QVAR) is acceptable per 4/9/99 memo.

*Note: A pharmacology consult request for proposed specifications for *drug substance* impurities was not made because these specifications are contained within the drug product impurity specifications. Drug substance and drug product impurities and their proposed specifications were identified to the pharmacology reviewer.

Other Consult Related Issues: (if any)

Outstanding informal e-mail requests to pharmacology reviewer:

3/31/2000 - reminder that applicant responded to comments related to previous deficiencies raised by pharm/tox, pertaining to impurity and degradation product specifications. See applicant's responses to comments #4, 5, 18b and 18c in their 2/28/00 amendment. (Note that evaluation of responses 4, 5 and 18 may be affected by the pharm/tox reviews.)

4/13/2000 - asked whether the use of ——— *aerosol spray* on the ——— raised any safety concerns. (——— is used by the ——— fabricators, ——— ——— ——— aid.)

REMARKS/COMMENTS:

NOTE that the applicant refers to the volumes of its response (2/28/00 amendment) as volume 3.1, 3.2, etc. These are catalogued by our document room (and referred to in this review) as volumes 9.1, 9.2, etc. (respectively).

BACKGROUND:

Drug Substance (original NDA, vol. 1.3, pg. 4) – It is noted that "in CFC formulations, beclomethasone dipropionate (BDP) exists as a ' suspension of the drug. In the HFA formulations discussed here, the drug is totally dissolved in the ethanol/propellant solvent system."

Drug Product:
This drug product is a solution MDI and it comes in two strengths, 40 µg ex-actuator per puff, and 80 µg ex-actuator per puff. (These correspond to 50 µg and 100 µg ex-valve, which are sometimes used in the NDA as terms in referring to the two strengths). The valve volume is nominally 50 mcL, and valve delivery is 59.0 mg. Each strength MDI comes in two sizes, 100 and 200 actuations, with target fill weights of 8.70 g and 14.60 g, respectively. (Labeled fill weights are 7.3g and 13.2 g, respectively, however, minimum release specifications are ——— g, respectively.) **The recommended dose is as low as *one actuation* twice a day, and as high as 320 mcg twice a day.** Repriming is to be performed after 10 days of non-use, using two actuations to reprime. The only excipients are the propellant, HFA-134a, and ethanol.

The canister is a 10 mL — canister, ——— fitted with a 50 µL metered dose valve ——— made of ' rubber, and a gasket made of from ——— Also, a ——— O-ring is used as an additional seal when the valve is crimped onto the canister. — are said to be identical to those used in Proventil HFA MDI. Actuator and dust cap are made from — Actuators are either dark mauve or beige, and the dust cap is grey.). Orifice diameter in the actuator has limits of ———

The previously submitted labeling from HMR (now Aventis) has been withdrawn.

Since the product is a solution formulation, shaking is not required before use, and the proposed labeling reflects this.

New clarification has been provided concerning the site of [redacted] used as a testing facility for [redacted] extractables. The address previously submitted for the [redacted] facility was incorrect (see CR#1, which provided the address as: [redacted] It is amended as follows:

[redacted]

The EER has been modified to incorporate the above information.

Outstanding items:

- There is an outstanding deficiency letter dated 2/4/2000 for DMF [redacted] for the actuator.
- Pharm/tox, biometrics and clinical consults (see earlier in this review).
- Review of drug substance DMF [redacted] is on hold pending a pharm/tox consult. (The pharm/tox response may affect the evaluation of response 5, and the drug product specifications for some impurities/degradation products.)
- Responses to an IR letter which is requested in this review.
- A pharm/tox consult for an updated safety assessment may be needed (see Response 16), once information is clarified by the applicant in response to our IR letter.
- The review team should be aware of the proposed statement in the description section of the package insert: [redacted] The acceptability of such a statement in the labeling should be carefully considered, as this would set a precedent.
- A methods validation/verification request to FDA laboratories has yet to be made.
- An EES update request was submitted on March 22, 2000 and remains pending.
- See pharm/tox consult review dated 27 Jan 2000, by Dr. McGovern. The last page (recommendation #3) asked for qualification for certain [redacted] extractables. **This request does not appear to be in our 2/18/2000 AE letter, and should be sent to the applicant.** Note that the 2/28/2000 amendment (vol. 9.1, Attachment 5) provides a bioassessment of various extractables, including [redacted]

CONCLUSIONS AND RECOMMENDATIONS:
From a CMC standpoint, this application is approvable pending *satisfactory* responses to (or resolution of) the following issues:

- IR letter to be sent based on this review (see draft comments at end of this review).
- Deficiency letter sent on 2/4/2000 to holder of DMF [redacted]
- Outstanding consult reviews (pharm/tox, biometrics and clinical).
- DMF [redacted] review, currently pending a pharm/tox consult.
- EER
- Labeling

Before an action letter is finalized for this NDA, pharmacological/toxicological review of the responses to previous pharm/tox comments should be performed; this refers particularly to comments # 4, 5, 18b and 18c of our previous AE letter dated February 18, 2000. In addition, the applicant, in accordance with the pharm/tox review completed on 1/27/2000, should satisfactorily address the issue of the qualification of certain extractables (see "outstanding items," above).

/S/

Alan C. Schroeder, Ph.D., Review Chemist

cc:
Orig. NDA 20-911
HFD-570/Division File
HFD-570/ASchroeder/5-2-2000
HFD-570/CSO SBarnes
HFD-570/GPoochikian
HFD-570/RM
R/D Init. by: /S/ 5/10/00
filename: n20911_R3_rev.doc

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Barnes.

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

FEB 10 2000

NDA #: 20-911 **CHEM. REVIEW #:** 2 **REVIEW DATE:** February 9, 2000

RECOMMEND ACTION: APPROVABLE

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
[Original NDA	5/11/98	5/12/98	5/29/98]
Amendment*	8/11/99	8/12/99	
Resubmission*	8/17/99	8/18/99	9/10/99
Amendment*	11/10/99	11/12/99	
Amendment*	12/2/99	12/6/99	12/8/99
Amendment*	1/10/2000	1/14/2000	

*Subject of this review

NAME & ADDRESS OF APPLICANT: 3M Pharmaceuticals
Building 260-6A-22, 3M Center
St. Paul, MN 55144-1000

DRUG PRODUCT NAME:

Proprietary: Qvar 40 mcg (80 mcg) Inhalation Aerosol

Nonproprietary/USAN: beclomethasone dipropionate HFA inhalation aerosol

Code Name/#:

Chem. Type/Ther. Class: 3S

PHARMACOL. CATEGORY/INDICATION: Anti-asthmatic (maintenance treatment of asthma as prophylactic therapy)

DOSAGE FORM: inhalation aerosol

STRENGTHS: 40 mcg and 80 mcg per puff (ex-actuator)

ROUTE OF ADMINISTRATION: oral inhalation

DISPENSED: X Rx _ OTC

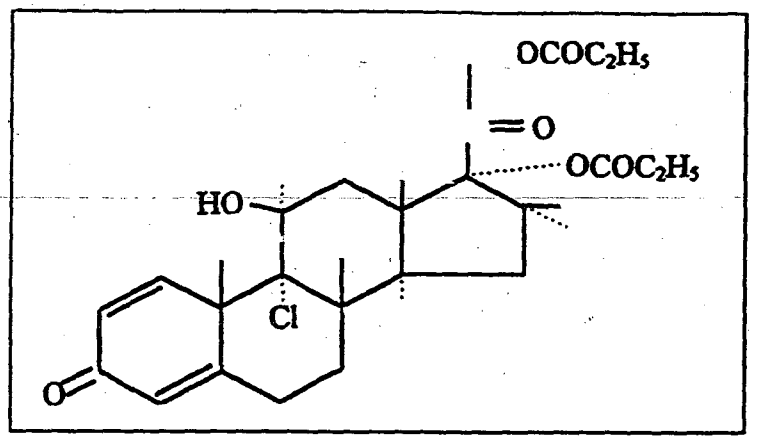
SPECIAL PRODUCTS: _ YES _X NO
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Molecular Formula: $C_{28}H_{37}ClO_7$

M.W.



SUPPORTING DOCUMENTS:

DMFs

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Review (section)
		beclomethasone dipropionate	Remains deficient. Def. letters dated 11/5/98 (response 12/29/98), 10/19/99, and 11/22/99	8/12/98 and 10/12/99	A.1. of CR#1; and responses 6a, 17d(4), 17i(2) and 21 of CR#2.
		propellant HFA-134a	Adequate.	5/3/99 and 10/15/99	B.3.B.2. of CR#1, and response 21 (CR#2).
	3M Pharmaceuticals	container/closure	Deficient -identical information reviewed in 3M'S DMF [redacted] D[redacted] defic. letters dated 11/24/98 and 11/2/99. Response to 11/2/99 letter is in, but not reviewed yet. D[redacted] pharm. consult for placebo leachables: acceptable on 10/28/99.	5/3/99; related D[redacted] reviews dated 11/18/98, 10/22/99.	B.7. of CR#1; Response 21 (CR#2).
	3M Health Care Ltd.	type I (site manufacturer)	N.A.	N.A.	type I DMFs are not reviewed
	3M Pharmaceuticals	container/closure (canister)	Incomplete/awaiting a pharm/tox consult)	4/22/99 (5/3/99 letter)	B.7. of CR#1
			Adequate, IR letter	1/21/2000	Response 14c (CR#2)
			Adequate, IR letter	1/27/2000	Response 14c (CR#2)
			Reviewed in connection with N20-503 and found adequate. No more recent technical amendments.	8/13/96	Response 14c (CR#2)
			Deficient.	1/28/2000	Response 14d(6) (CR#2)

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND	[redacted]	3M Pharmaceuticals	beclomethasone dipropionate HFA inhalation aerosol

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	original submitted to OC 23-SEP-98; update request of 10/27/99	acceptable on 12/21/1999	Facility previously not ready for inspection [redacted] Applicant has since withdrawn that facility.
Biometrics, HFD-710		not initiated	Consult not yet initiated for statistical evaluation of expiration dating period pending final agreement on specifications.
Clinical	3/21/99 re: assessment of occluded MDIs in clinical studies (vol. 1.3, pp. 53-62).	pending as of 2/04/2000	
Environmental Assessment		OK	None needed (satisfactory categorical exclusion claimed in v. 1.14, pg. 282)
Pharmacology, HFD-570	9/9/98 request for safety assessment of applicant's "Bioassessment of Extractable Compounds in the Drug Product" and the USP Biological Reactivity Tests conducted on Actuator extractables. (This includes a safety assessment for [redacted] see B.7., section under valve, evaluation of [redacted] extractables). 12/23/98 request for safety assessment of proposed (drug related) impurity specifications for drug product, and for proposed drug product impurity specification for [redacted] content. 10/15/99 safety evaluation request for responses to comments 6b(2), 13o and 22 in our 5/12/99 action letter. This pertains to qualification data for specific impurities, degradation products and extractables. 10/30/99 safety evaluation request from Dr. K. Swiss re: specifications for [redacted] extractables and foreign particulates. 01/04/2000 safety evaluation request for updated data on placebo leachables in 8/17/1999 amendment.	satisfactory (5/12/99 consult review) satisfactory (5/11/99 consult review) deficiencies identified (1/27/2000 consult review) pending as of 2/04/2000 pending as of 2/04/2000	A pharmacology consult request for proposed specifications for *drug substance* impurities was not made because these specifications are contained within the drug product impurity specifications. Drug substance and drug product impurities and their proposed specifications were identified to the pharmacology reviewer.
Labeling & Nomenclature Committee	8/98 sent by project manager.	Acceptable.	Proposed name (QVAR) is acceptable per 4/9/99 memo.

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It is not clear at this time if the applicant intends to withdraw the 200 actuation fill weight presentation (based on labeling submitted). If this fill weight is to be withdrawn, the stability protocol and stability commitment will need to be revisited, since they include a matrix based on fill weights.

CONCLUSIONS AND RECOMMENDATIONS:

From a CMC standpoint, this application is approvable, pending resolution of the issues in the attached draft letter and any issues identified in the completed and outstanding clinical and pharmacological/toxicological consult reviews (see summary table of Consult Reviews, earlier in this review), including review of the November 10, 1999 amendment.

/S/

Alan C. Schroeder, Ph.D., Review Chemist

cc:
Orig. NDA 20-911
HFD-570/Division File
HFD-570/ASchroeder/2-9-2000
HFD-570/CSO SBarnes
HFD-570/GPoochikian
HFD-570/RNicklas
R/D Init. by: /S/ 11/10/00
filename: n20911_C2_rev.doc

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S. Baines

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

5 May 11, 1999

NDA #: 20-911 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 5/10/99 MAY 10 1999

RECOMMEND ACTION:

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	5/11/98	5/12/98	5/29/98
Amendment	9/23/98	10/1/98	10/5/98
Amendment	1/8/99	1/13/99	1/20/99
Amendment	3/22/99	3/23/99	3/24/99
Amendment	4/9/99	4/12/99	4/13/99

NAME & ADDRESS OF APPLICANT: 3M Pharmaceuticals
Building 260-6A-22, 3M Center
St. Paul, MN 55144-1000

DRUG PRODUCT NAME:

Proprietary: Qvar 40 mcg (80 mcg) Inhalation Aerosol

Nonproprietary/USAN: beclomethasone dipropionate HFA inhalation aerosol

Code Name/#:

Chem. Type/Ther. Class: 3S

PHARMACOL. CATEGORY/INDICATION: Anti-asthmatic (maintenance treatment of asthma as prophylactic therapy)

DOSAGE FORM: inhalation aerosol

STRENGTHS: 40 mcg and 80 mcg per puff (ex-actuator)

ROUTE OF ADMINISTRATION: oral inhalation

DISPENSED: X Rx _ OTC

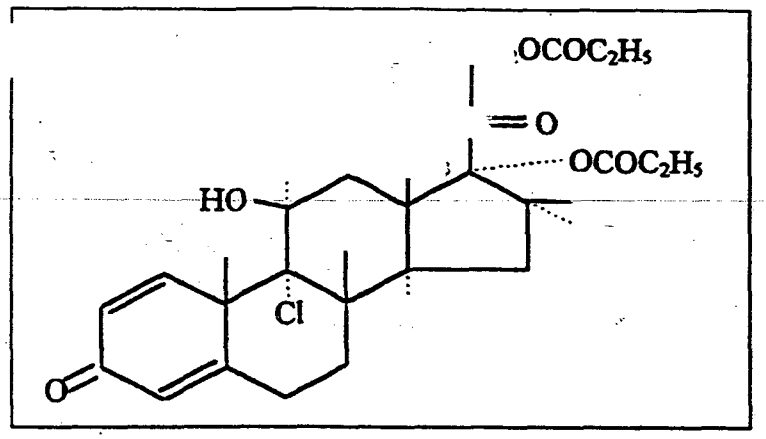
SPECIAL PRODUCTS: _ YES _X NO
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Molecular Formula: $C_{28}H_{37}ClO_7$

M.W.



SUPPORTING DOCUMENTS:

DMFs

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Review (section)
[redacted]	[redacted]	beclomethasone dipropionate	deficient	8/12/98; letter 11/5/98 (response of 12/29/98 un-reviewed)	A.1.
[redacted]	[redacted]	propellant HFA-134a	deficient	5/3/99	B.3.B.2.
[redacted]	3M Pharmaceuticals	container/closure [redacted]	deficient -identical information reviewed in DMF [redacted]	5/3/99	B.7.
[redacted]	3M Health Care Ltd.	type I (site manfacturer)	N.A.	N.A.	type I DMFs are not reviewed
[redacted]	3M Pharmaceuticals	container/closure (canister)	deficient	4/22/99 (5/3/99 letter)	B.7.

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND	[redacted]	3M Pharmaceuticals	beclomethasone dipropionate HFA inhalation aerosol

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	submitted to OC 23-SEP-98	withhold approval 5/7/99	facility not ready for inspection
Biometrics, HFD-710		not initiated	Consult not yet initiated since additional stability data will be requested.
Clinical	3/21/99 re: assessment of occluded MDIs in clinical studies (vol. 1.3, pp. 53-62).	pending	
Enviironmental Assessment		OK	None needed (satisfactory categorical exclusion claimed in v. 1.14, pg. 282)
Pharmacology, HFD-570	9/9/98 request for safety assessment of applicant's "Bioassessment of Extractable Compounds in the Drug Product" and the USP Biological Reactivity Tests conducted on Actuator extractables. (This includes a safety assessment for see B.7., section under valve, evaluation of extractables). 12/23/98 request for safety assessment of proposed (drug related) impurity specifications for drug product, and for proposed drug product impurity specification for content.	pending	A pharmacology consult request for proposed specifications for *drug substance* impurities was not made because these specifications are contained within the drug product impurity specifications. Drug substance and drug product impurities and their proposed specifications were identified to the pharmacology reviewer.
Labeling & Nomenclature Committee	8/98 sent by project manager.	OK	per 4/9/99 memo from Labeling & Nomenclature Committee

Other Consult Related Issues:

1. E-mail message of 11-MAR-99 from this reviewer to Dr. Tim McGovern. This referred to our pharmacological consult request dated 12/23/98 (see above): a clarification was provided, as follows. The degradant of beclomethasone dipropionate may be a concern (e.g., for mutagenicity) since are potential agents.

2. At the in-house QVAR wrap-up meeting on April 12, 1999, the medical officer was shown certain proposed labeling statements in the description section and how supplied section of the package insert which may have clinical implications (e.g., see below under "remarks/comments).

REMARKS/COMMENTS:

Developmental data and information for drug substance and drug product are found in volumes 1.3-1.5 of the NDA.

Drug Substance (vol. 1.3, pg. 4) – It is noted that "in CFC formulations, beclomethasone dipropionate (BDP) exists as a suspension of the drug. In the HFA formulations discussed here, the drug is totally dissolved in the ethanol/propellant solvent system."

Drug Product

This drug product is a solution MDI and it comes in two strengths, 40 µg ex-actuator per puff, and 80 µg ex-actuator per puff. (These correspond to 50 µg and 100 µg ex-valve). The valve volume is nominally 50 mcL, and valve delivery is 59.0 mg. Each strength MDI comes in two sizes, 100 and 200 actuations, with target fill weights of 8.70 g and 14.60 g, respectively. **The recommended dose is as low as *one actuation* twice a day, and as high as 320 mcg twice a day.** Proposed [redacted] (although the data supporting this are not conclusive). The only excipients are the propellant, HFA-134a, and ethanol.

The canister is a 10 mL [redacted] canister [redacted] fitted with a 50 µL metered dose valve [redacted] tank seal made of [redacted] rubber, [redacted] gasket [redacted] from [redacted] Also, a [redacted] O-ring is used as an additional seal when the valve is crimped onto the canister. [redacted] are said to be identical to those used in Proventil HFA MDI. Actuator and dust cap are made from [redacted] Actuators are either dark mauve or beige, and the dust cap is grey.). Orifice diameter in the actuator has limits of [redacted]

3M and Hoechst Marion Roussel "have agreed to co-promote this product in the U.S. under the same trade name of QVAR™."

A small, incompletely described study is provided (vol. 1.3, page 266), entitled "Measurement of MDI Spray Dynamics." The applicant has made the following conclusion: [redacted] This study is not sufficient to support a labeling or promotional claim at this time. (see section B.9. of this review).

In view of the observed differences in levels of foreign particulates and drug related impurities (degradation products), on stability storage of the drug product at different orientations, the applicant has been asked to consider storing the drug product in the upright position, to minimize such impurities, and to investigate the reason for such differences, and base the specifications on the preferred storage position. The pharmacological consult review of proposed impurity specifications may also have an impact on the appropriate storage orientation. The applicant's response to this issue may affect the labeling and the marketed stability protocol.

When stability data are updated, and other information is provided, parameter specifications proposed will need to be reevaluated [redacted]

The — concept in the proposed particle size distribution (PSD) specifications needs to be reconsidered. The proposed PSD specifications seem to be wide, especially for solution MDIs, and should be reevaluated pending an update of the data.

Since the product is a solution formulation, shaking is not required before use, and the proposed labeling reflects this. See "Developmental Studies of Drug Product" section in this review.

The proposed — for PSD specifications need to be reconsidered, when data are updated.

A study of the performance of the drug product after storage at cold temperatures doesn't support the use of cold drug product, since significant changes in dose delivered and particle size distribution resulted from operation after - °C storage (relative to storage at 25°C).

The medical officer should comment on the following statement in the description section of the package insert.

The medical officer should comment on the following statement in the how supplied section of the package insert.

A future consult review of foreign particulates in the drug product will be needed, once additional data are available.

CONCLUSIONS AND RECOMMENDATIONS:

Note that comments on drug product specifications in this review are based on stability data available at this time. These are tentative comments, pending an update of stability data and statistical analyses.

The application is not approvable from a CMC standpoint.

/S/ 5/10/99

Alan C. Schroeder, Ph.D., Review Chemist

cc:
Orig. NDA 20-911
HFD-570/Division File
HFD-570/ASchroeder/5-10-99
HFD-570/CSO SBarnes
HFD-570/GPoochikian
HFD-570/RNicklas
R/D Init. by: /S/ 1/11/99
filename: n20911_E+_rev.doc

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