

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-784

CHEMISTRY REVIEW(S)

NDA 20-784

**NASACORT[®] (triamcinolone acetonide)
HFA Nasal Aerosol**

Aventis Inc.

**Craig M. Bertha, Ph.D.
Division of Pulmonary and Allergy Drug Products (HFD-
570/820)**

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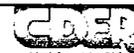
Chemistry Review Data Sheet

1. NDA 20784
2. REVIEW #8:
3. REVIEW DATE: 16-JAN-2004
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Amendments (BC)	18-DEC-2003
Amendments (BC)	17-DEC-2003
Amendments (BC)	16-DEC-2003
Amendments (AC)	09-DEC-2003
DR Letter (telephone facsimile)	14-NOV-2003
Correspondence	08-OCT-2003
Amendment	06-OCT-2003
Amendment	07-AUG-2003
DR Letter	20-MAY-2003
Amendment	21-MAR-2003
AE Letter	31-MAY-2002
Amendment	28-FEB-2002
Amendment	30-NOV-2001
AE Letter	04-FEB-2000
Amendment	30-JUL-1999
Amendment	09-DEC-1999
Amendment	20-DEC-1999
AE Letter	17-DEC-1997
Amendment	24-OCT-1997
Amendment	01-OCT-1997
Amendment	13-AUG-1997
IR Letter	19-MAY-1997



CHEMISTRY REVIEW #8



Chemistry Review Data Sheet

Amendment	07-APR-1997
Amendment	04-APR-1997
Amendment	21-MAR-1997
Amendment	14-MAR-1997
Amendment	04-MAR-1997
Amendment	28-FEB-1997
Original NDA	16-DEC-1996

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendments (BL)	09-JAN-2004
Amendment (BC)	14-JAN-2004
Amendment (BL) Revision of 09-JAN-2004 BL	14-JAN-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Aventis, Inc.
Address:	200 Crossing Boulevard P.O. Box 6890 Bridgewater, NJ 08807-0890
Representative:	Eric A. Floyd, Ph.D.
Telephone:	(908) 231-2474

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Nasacort® HFA Nasal Aerosol
- b) Non-Proprietary Name (USAN): triamcinolone acetonide HFA nasal aerosol
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Glucocorticosteroid for nasal treatment of seasonal and perennial allergic rhinitis (SAR and PAR)

11. DOSAGE FORM: nasal aerosol

Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 55 mcg of triamcinolone acetone (TAA)/actuation (ex-actuator) and 100 mcg TAA/act (ex-valve); target valve delivery is 65.0 mg (see discussion of valve delivery on p. 22 of CR#4) of formulation containing w/w TAA, w/w Dehydrated Alcohol, USP, and w/w HFA-134a (1,1,1,2-tetrafluoroethane). There is only one size of the product which is a 100 actuation unit containing a target amount of of formulation (overfill).

13. ROUTE OF ADMINISTRATION: intranasal

14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) :

 SPOTS product – Form Completed

 X Not a SPOTS product

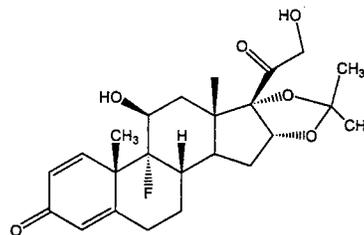
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: (11 β ,16 α)-9-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)is(oxy)]-pregna-1,4-diene-3,20-dione

Molecular Formula: C₂₄H₃₁FO₆

Molecular Wt: 434.51

CAS Reg. No.: 5611-51-8

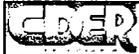


Triamcinolone Acetonide (TAA)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
<u> </u>	2			4	Adequate	17-DEC-2003	See review #14 of DMF and evaluation on p. 14 of CR#7
<u> </u>	3			1	Adequate	20-FEB-2002	Response to DMF



CHEMISTRY REVIEW #8



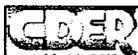
Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	3						Letter submitted to DMF
	3			1	Adequate	21-FEB-2002	
	3			1	Adequate	22-FEB-2002	
	3			1	Adequate	21-FEB-2002	
	5			7	Adequate	28-SEP-1994	See Pharm/Tox review
	3			3	Adequate	18-SEP-1998	28-MAY-1999 update revealed no change from 09-APR-1998 amendment reviewed on 18-SEP-1998
	3			7	NA	NA	
	3			1	Adequate	28FEB-2002	
	3			3	Adequate	31-OCT-2000	Reviewed for inhalation aerosol DPs
	3			3	Adequate	02-MAR-1997	

¹ Action codes for DMF Table:

- 1 – DMF Reviewed.
- Other codes indicate why the DMF was not reviewed, as follows:
- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW #8



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Investigation New Drug Application	IND 43,841	Original IND for Nasacort HFA (TAA nasal aerosol)
New Drug Application	NDA 20-468	Nasacort AQ Nasal Spray

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics		05-MAR-2002, for expiry assessment (see p. 51 of CR#5).	Dr. F. Zhou
EES	WITHHOLD ACCEPTABLE ACCEPTABLE (08-Oct-2003)	01-JUN-2000 (requested) 17-MAY-2002 (requested) 28-APR-2003 (requested)	OC OC New sites added.
Pharm/Tox	ACCEPTABLE UNACCEPTABLE ACCEPTABLE	27-JAN-2000 (extractables/leachables) 06-MAR-2002 / resolved through lowering acceptance criterion) 22-OCT-2003 (extractables/leachables & foreign particulates)	Dr. L. Pei Dr. V. Whitehurst Dr. L. Pei
Biopharm			
LNC	N/A		
Methods Validation			Submitted to ONDC 14-JAN-2004 (M. Folkendt) for forwarding to Agency laboratory.
OPDRA	N/A		
EA	ACCEPTABLE – Categorical Exclusion Requested as per 21 CFR 25.31(b)		
Microbiology	RECOMMEND APPROVAL	16-DEC-97	Carol K. Vincent

¹This expiration dating period analysis was based on acceptance criteria limits that were not finalized. See the response to comment 2.e (p.19 of CR#7) for the final granted period of 15 months.

The Chemistry Review for NDA 20-784

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective it is recommended that the application be **approved (AP)**. The action letter should also remind the applicant of the CMC-related agreements that were outlined in their 14-JAN-2004, amendment.

Background Note: The lengthy time-frame required for the recommendation to approve this application in terms of CMC was due, for the most part, to the limited reformulation efforts on the part of the original owner of the application in developing a non-CFC nasal aerosol. Their target was to do a simple "drop-in" replacement of the CFC with the HFA propellant. It is now commonly known that this will not lead to a drug with formulation characteristics with suitable reproducibility in terms of dosing performance as a result of the inherent physicochemical differences between the new HFA propellants and the older CFC propellants. In addition, the methodology (cascade impaction or CI) used to determine and control the aerodynamic particle size distribution (APSD) is uncommon and suspect in terms of the wide variability in the resultant data. The change of ownership that has occurred has impacted on the resolution of the various quality issues as well. Also, responses following the issuance of action letters have been delayed in many cases (e.g., a 2 year gap in their response in 1997 and several year gaps in later responses due to the change in ownership of the application). All of these factors contribute to the apparently long length of time since the original submission (dated 16-Dec-1996).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has made an agreement to develop and institute an improved method for the control of the APSD of the drug product (DP) to replace the current method. The new methodology will utilize the _____ and will be provided by the firm no later than 30-March-2004.

We have agreed to allow the applicant to tighten the acceptance criterion for the _____ extractable from the _____ to reflect the data collected _____ from _____ manufacturing campaigns. This would be done post-approval.

Executive Summary Section

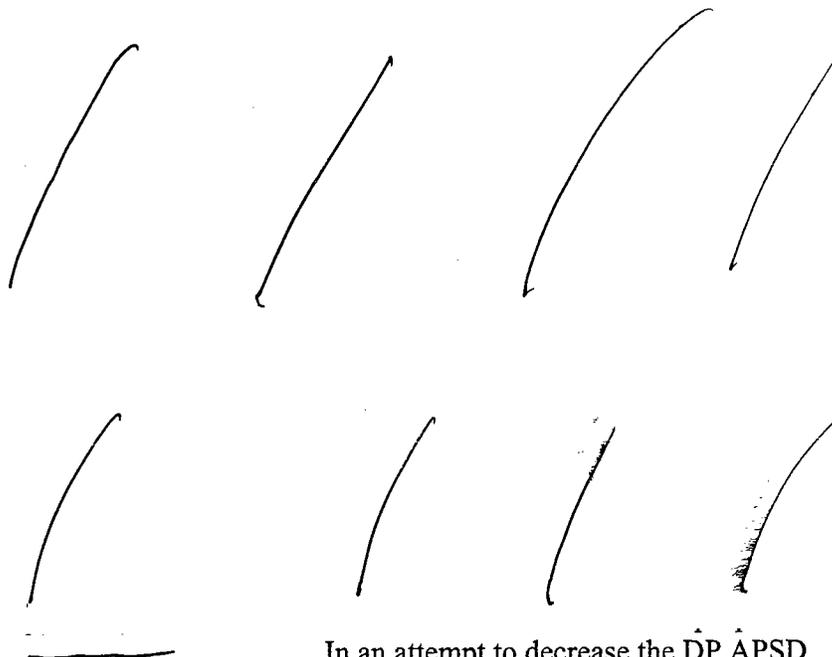
The applicant has agreed to work with the supplier of the actuator to decrease the dimensional tolerance of the orifice diameter from the current allowed limits of — nm. The improvements will be reported in the first annual report for the application. Aventis will be reminded that these improvements in the actuators will need to be reflected in — supporting DMF.

The PM has forwarded the list of agreements by telephone facsimile (as outlined in the draft letter attached to CR#7) on 14-JAN-2004. The applicant has acknowledge these agreements in the 14-JAN-2004, amendment.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The DP for this application is Nasacort® HFA (triamcinolone acetonide) Nasal Aerosol. This drug is intended to be an eventual replacement of the firms approved chlorofluorocarbon based version of a triamcinolone acetonide nasal aerosol (application N19-798). The DP delivers 65.0 mg / .n theory, refer to p. 22 of CR#4) of formulation from the valve, containing a target amount of 100 mcg of triamcinolone acetonide (USAN name abbreviated as TAA), — ethanol and — of 1,2,2,2-tetrafluoroethane propellant (HFA-134a), with a target delivery from the nasal actuator of 55 mcg TAA/actuation. The DP is indicated for the nasal treatment of SAR and PAR. The TAA is a glucocorticosteroid that has an annual schedule period for retesting.



In an attempt to decrease the DP APSD

Executive Summary Section

_____ that became problematic in terms of leakage. The purpose is to prevent these potential problematic units from reaching the marketplace where it is possible that they may encounter similar undesirable storage conditions _____

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose for adults with the Nasacort® HFA Nasal Aerosol product is 220 mcg once a day (two 55 mcg actuations into each nostril). The starting dose may be as high as 440 mcg once daily. After the desired effect is achieved some patients may be maintained on a dose of as little as one spray (55 mcg) in each nostril once a day (total daily dose 110 mcg per day). It is noted that the delivered dose uniformity (DDU) testing is performed with two (2) actuations of the DP per determination (i.e., with a target minimum dose of _____ mcg TAA).

C. Basis for Approvability or Not-Approval Recommendation

- N/A

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Craig M. Bertha, Ph.D., Acting CMC Teamleader
HFD-570/820



Executive Summary Section

C. CC Block

cc:

Orig. NDA 20-784

HFD-570/Division File

HFD-570/CBertha

HFD-570/VShah

HFD-570/CJackson

HFD-570/SBarnes

R/D Init. by B. Rogers: _____

Filename and Location: c:\data\mydocuments\reviews etc\NDA\20784\Review 8 (CB)\04-01-14.rev.doc

4 Page(s) Withheld

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this page is the manifestation of the electronic signature.**

/s/

Craig Bertha
1/16/04 06:50:04 AM
CHEMIST

see hardcopy in your office

Brian Rogers
1/16/04 10:55:18 AM
CHEMIST

NDA 20-784

**NASACORT[®] (triamcinolone acetonide)
HFA Nasal Aerosol**

Aventis Inc.

**Craig M. Bertha, Ph.D.
Division of Pulmonary and Allergy Drug Products (HFD-
570/820)**



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Chemistry Review Data Sheet

1. NDA 20784
2. REVIEW #7:
3. REVIEW DATE: 19-DEC-2003
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
DR Letter (telephone facsimile)	14-NOV-2003
Correspondence	08-OCT-2003
Amendment	06-OCT-2003
Amendment	07-AUG-2003
DR Letter	20-MAY-2003
Amendment	21-MAR-2003
AE Letter	31-MAY-2002
Amendment	28-FEB-2002
Amendment	30-NOV-2001
AE Letter	04-FEB-2000
Amendment	30-JUL-1999
Amendment	09-DEC-1999
Amendment	20-DEC-1999
AE Letter	17-DEC-1997
Amendment	24-OCT-1997
Amendment	01-OCT-1997
Amendment	13-AUG-1997
IR Letter	19-MAY-1997
Amendment	07-APR-1997
Amendment	04-APR-1997
Amendment	21-MAR-1997
Amendment	14-MAR-1997



CHEMISTRY REVIEW #7



Chemistry Review Data Sheet

Amendment	04-MAR-1997
Amendment	28-FEB-1997
Original NDA	16-DEC-1996

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendments (AC)	09-DEC-2003
Amendments (BC)	16-DEC-2003
Amendments (BC)	17-DEC-2003
Amendments (BC)	18-DEC-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Aventis, Inc.
Address:	200 Crossing Boulevard P.O. Box 6890 Bridgewater, NJ 08807-0890
Representative:	Eric A. Floyd, Ph.D.
Telephone:	(908) 231-2474

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Nasacort® HFA Nasal Aerosol
- b) Non-Proprietary Name (USAN): triamcinolone acetonide HFA nasal aerosol
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Glucocorticosteroid for nasal treatment of seasonal and perennial allergic rhinitis (SAR and PAR)

11. DOSAGE FORM: nasal aerosol

12. STRENGTH/POTENCY: 55 mcg of triamcinolone acetonide (TAA)/actuation (ex-actuator) and 100 mcg TAA/act (ex-valve); target valve

Chemistry Review Data Sheet

delivery is 65.0 mg (see discussion of valve delivery on p. 22 of CR#4) of formulation containing w/w TAA, w/w Dehydrated Alcohol, USP, and w/w HFA-134a (1,1,1,2-tetrafluoroethane). There is only one size of the product which is a 100 actuation unit containing a target amount of of formulation (overfill).

13. ROUTE OF ADMINISTRATION: intranasal

14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) :

 SPOTS product – Form Completed

 X Not a SPOTS product

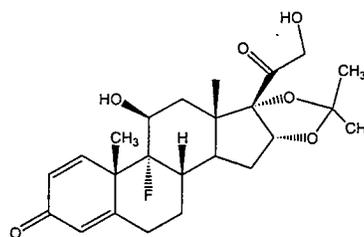
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: (11 β ,16 α)-9-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)is(oxy)]-pregna-1,4-diene-3,20-dione

Molecular Formula: C₂₄H₃₁FO₆

Molecular Wt: 434.51

CAS Reg. No.: 5611-51-8



Triamcinolone Acetonide (TAA)

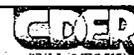
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
2				1,4	Adequate	17-DEC-2003	See review #14 of DMF and evaluation below on p. 14
3				1	Adequate	20-FEB-2002	Response to DMF — def. Letter submitted to DMF



CHEMISTRY REVIEW #7



Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	3		/	1	Adequate	21-FEB-2002	
/	3		/	1	Adequate	22-FEB-2002	
/	3		/	1	Adequate	21-FEB-2002	
/	5		/	7	Adequate	28-SEP-1994	See Pharm/Tox review
/	3		/	3	Adequate	18-SEP-1998	28-MAY-1999 update revealed no change from 09-APR-1998 amendment reviewed on 18-SEP-1998
/	3		/	7	NA	NA	/
/	3		/	1	Adequate	28FEB-2002	
/	3		/	3	Adequate	31-OCT-2000	Reviewed for inhalation aerosol DPs
/	3		/	3	Adequate	02-MAR-1997	
		schaft	copolymer				

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

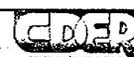
6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW #7



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Investigation New Drug Application	IND 43,841	Original IND for Nasacort HFA (TAA nasal aerosol)
New Drug Application	NDA 20-468	Nasacort AQ Nasal Spray

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	///	05-MAR-2002, for expiry assessment (see p. 51 of CR#5).	Dr. F. Zhou
EES	WITHHOLD ACCEPTABLE ACCEPTABLE (08-Oct-2003)	01-JUN-2000 (requested) 17-MAY-2002 (requested) 28-APR-2003 (requested)	OC OC New sites added.
Pharm/Tox	ACCEPTABLE UNACCEPTABLE ACCEPTABLE	27-JAN-2000 (extractables/leachables) 06-MAR-2002 (resolved through lowering acceptance criterion) 22-OCT-2003 (extractables/leachables & foreign particulates)	Dr. L. Pei Dr. V. Whitehurst Dr. L. Pei
Biopharm			
LNC	N/A		
Methods Validation			Will be submitted to ONDC (M. Folkendt) for forwarding to Agency laboratory.
OPDRA	N/A		
EA	ACCEPTABLE – Categorical Exclusion Requested as per 21 CFR 25.31(b)		
Microbiology	RECOMMEND APPROVAL	16-DEC-97	Carol K. Vincent

¹This expiration dating period analysis was based on acceptance criteria limits that were not finalized. See the response to comment 2.e below (p. 19) for the final granted period of 15 months.

The Chemistry Review for NDA 20-784

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective it is recommended that the application be **approved (AP)**. The PM should forward the comments in the draft letter to the applicant prior to approval to confirm their agreement with the content.

The lengthy time-frame required for the recommendation to approve this application in terms of CMC was due, for the most part, to the limited reformulation efforts on the part of the original owner of the application in developing a non-CFC nasal aerosol. Their target was to do a simple "drop-in" replacement of the CFC with the HFA propellant. It is now commonly known that this will not lead to a drug with formulation characteristics with suitable reproducibility in terms of dosing performance as a result of the inherent physicochemical differences between the new HFA propellants and the older CFC propellants. In addition, the methodology (cascade impaction or CI) used to determine and control the aerodynamic particle size distribution (APSD) is uncommon and suspect in terms of the wide variability in the resultant data. The change of ownership that has occurred has impacted on the resolution of the various quality issues as well. Also, responses following the issuance of action letters have been delayed in many cases (e.g., a 2 year gap in their response in 1997 and several year gaps in later responses due to the change in ownership of the application). All of these factors contribute to the apparently long length of time since the original submission (16-Dec-1996).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has made an agreement to develop and institute an improved method for the control of the APSD of the drug product (DP) to replace the current method. The new methodology will utilize the _____ and will be provided by the firm no later than 30-March-2004.

We have agreed to allow the applicant to tighten the acceptance criterion for the _____) extractable from the _____ reflect the data collected on _____ from _____ manufacturing campaigns. This would be done post-approval.

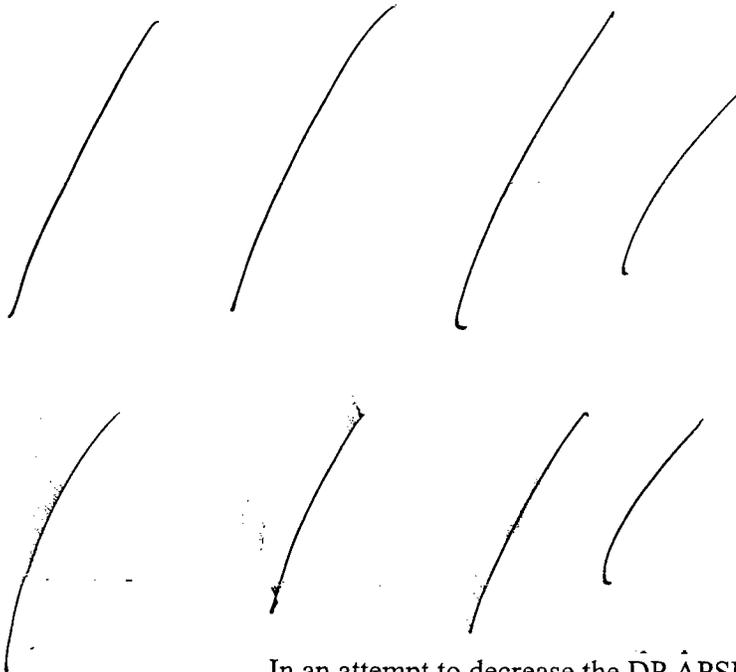
Executive Summary Section

The applicant has agreed to work with the supplier of the actuator _____, to decrease the dimensional tolerance of the orifice diameter from the current allowed limits of _____ mm. The improvements will be reported in the first annual report for the application. Aventis will be reminded that these improvements in the actuators will need to be reflected in _____ supporting DMF.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The DP for this application is Nasacort® HFA (triamcinolone acetonide) Nasal Aerosol. This drug is intended to be an eventual replacement of the firms approved chlorofluorocarbon based version of a triamcinolone acetonide nasal aerosol (application N19-798). The DP delivers 65.0 mg _____ .ng in theory, refer to p. 22 of CR#4) of formulation from the valve, containing a target amount of 100 mcg of triamcinolone acetonide (USAN name abbreviated as TAA), _____ ethanol and _____ of 1,2,2,2-tetrafluoroethane propellant (HFA-134a), with a target delivery from the nasal actuator of 55 mcg TAA/actuation. The DP is indicated for the nasal treatment of SAR and PAR. The TAA is a glucocorticosteroid that has an annual schedule period for retesting.



In an attempt to decrease the DP APSD variability, the applicant has instituted additional controls, _____ during the manufacturing process (see response and evaluation of comment 9.a beginning on p. 33 of CR#5).

Executive Summary Section

There were no comparability issues with regard to the formulations in moving from pre-clinical to clinical to primary stability batch production in the original application. However, during the time after the original submission of the application to the Agency on 17-DEC-1996, the applicant has withdrawn a

In addition, changes to the composition of various valve components of the product resulted in the need for the applicant to place on stability three additional batches of DP, which had _____ of long term data collected and submitted. The biometrics team had assessed the proposed _____ expiration dating period relative to long term stability data from the 05-MAR-2002, consult but the DP specification limits for APSD were not finalized at that time. Note that the applicant has agreed to implement an **expiration dating period of 15 months** based on the relatively limited data from the intended commercial production site. See review of the response to 2.e below on p. 19.

Note that two of the three primary stability batches from Manati (15-34A-1, -2, and -3) were prepared with the to-be-marketed actuator manufactured by _____ but that the third was prepared with an actuator unit manufactured by _____. As a result of CR#3 the applicant was given the option of providing certain comparative performance data for the product that would have demonstrated the interchangeable nature of the two actuators or the option to withdraw one of them from the application. The applicant has, as of the 30-NOV-2001, amendment, *withdrawn* the _____ nasal actuator from the application. As a result, the stability data from the batch 15-34A-3, which used the *withdrawn* _____ actuator, were considered supportive and no longer a primary stability batch. In fact, after the proposal of a new DP manufacturing site at Holmes Chapel, UK in the 21-MAR-2003, amendment, the Manati site was *withdrawn* (see EES system under site CFN 2650125) from the application as a production site of this product, and various "improvements" to the manufacturing process were introduced at Holmes Chapel to attempt to lessen product variability in measured APSD (see p. 33 of CR#5). Thus, these Manati stability data (15-34A-1, -2, and -3) are certainly considered more as supportive under these circumstances and the Agency must relied more heavily on the analysis of the available _____ stability data from the three batches from Holmes Chapel (PM/066/02, PM/067/02, and PM/073/02). Evaluation of these limited data were included in CR#6.

The applicant has also instituted _____ testing for the product (see of CR#5) which has the purpose of _____, thus allowing the subsequent culling, _____ those canisters _____ that became problematic in terms of leakage. The purpose is to prevent these potential problematic units from reaching the marketplace where it is possible that they may encounter similar undesirable storage conditions _____



Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose for adults with the Nasacort® HFA Nasal Aerosol product is 220 mcg once a day (two 55 mcg actuations into each nostril). The starting dose may be as high as 440 mcg once daily. After the desired effect is achieved some patients may be maintained on a dose of as little as one spray (55 mcg) in each nostril once a day (total daily dose 110 mcg per day). It is noted that the delivered dose uniformity (DDU) testing is performed with two (2) actuations of the DP per determination (i.e., with a target minimum dose of mcg TAA).

C. Basis for Approvability or Not-Approval Recommendation

- N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., Acting CMC Teamleader
HFD-570/820



Executive Summary Section

C. CC Block

cc:

Orig. NDA 20-784

HFD-570/Division File

HFD-570/CBertha

HFD-570/VShah

HFD-570/CJackson

HFD-570/SBarnes

R/D Init. by B. Rogers: _____

Filename and Location: c:\data\mydocuments\reviews etc\NDA\20784\Review 7 (CB)\03-12-09.rev.doc

33 Page(s) Withheld

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/s/

Craig Bertha
12/19/03 03:19:10 PM
CHEMIST

Brian Rogers
12/19/03 03:27:55 PM
CHEMIST
Signed for Craig Bertha



NDA 20-784

**NASACORT[®] (triamcinolone acetonide)
HFA Nasal Aerosol**

Aventis Inc.

**Craig M. Bertha, Ph.D.
Division of Pulmonary and Allergy Drug Products (HFD-
570/820)**

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Chemistry Review Data Sheet

1. NDA 20784
2. REVIEW #6:
3. REVIEW DATE: 08-OCT-2003
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
DR Letter	20-MAY-2003
Amendment	21-MAR-2003
AE Letter	31-MAY-2002
Amendment	28-FEB-2002
Amendment	30-NOV-2001
AE Letter	04-FEB-2000
Amendment	30-JUL-1999
Amendment	09-DEC-1999
Amendment	20-DEC-1999
AE Letter	17-DEC-1997
Amendment	24-OCT-1997
Amendment	01-OCT-1997
Amendment	13-AUG-1997
IR Letter	19-MAY-1997
Amendment	07-APR-1997
Amendment	04-APR-1997
Amendment	21-MAR-1997
Amendment	14-MAR-1997
Amendment	04-MAR-1997
Amendment	28-FEB-1997
Original NDA	16-DEC-1996



CHEMISTRY REVIEW #6



Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Amendments/Correspondences

07-AUG-2003 AC (assigned 14-AUG-2003)

06-OCT-2003 AC (stamp 07-OCT-2003)

08-OCT-2003 C (site withdrawal)

7. NAME & ADDRESS OF APPLICANT:

Name:

Aventis, Inc.

Address:

200 Crossing Boulevard
P.O. Box 6890
Bridgewater, NJ 08807-0890

Representative:

Eric A. Floyd, Ph.D.

Telephone:

(908) 231-2474

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Nasacort® HFA Nasal Aerosol
- b) Non-Proprietary Name (USAN): triamcinolone acetonide HFA nasal aerosol
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Glucocorticosteroid for nasal treatment of seasonal and perennial allergic rhinitis (SAR and PAR)

11. DOSAGE FORM: nasal aerosol

12. STRENGTH/POTENCY: 55 mcg of triamcinolone acetonide (TAA)/actuation (ex-actuator) and 100 mcg TAA/act (ex-valve); target valve delivery is 65.0 mg (see discussion of valve delivery on p. 22 of CR#4) of formulation containing — w/w TAA, — w/w Dehydrated Alcohol, USP,

Chemistry Review Data Sheet

and _____ w/w HFA-134a (1,1,1,2-tetrafluoroethane). There is only one size of the product which is a 100 actuation unit containing a target amount of _____ of formulation (_____ overfill).

13. ROUTE OF ADMINISTRATION: intranasal

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

Not a SPOTS product

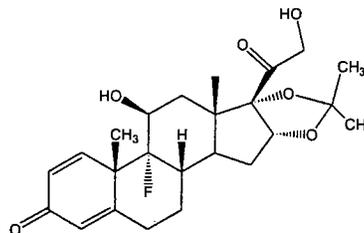
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: (11 β ,16 α)-9-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)is(oxy)]-pregna-1,4-diene-3,20-dione

Molecular Formula: C₂₄H₃₁FO₆

Molecular Wt: 434.51

CAS Reg. No.:



Triamcinolone Acetonide (TAA)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	2	/	/	1	Inadequate	30-SEP-2003	Deficiency letter to be issued
/	3			1	Adequate	20-FEB-2002	Response to DMF
/	3						ef. letter submitted to DMF



CHEMISTRY REVIEW #6



Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	3		/	1	Adequate	21-FEB-2002	
/	3			1	Adequate	22-FEB-2002	
/	3			1	Adequate	21-FEB-2002	
/	5			7	Adequate	28-SEP-1994	See Pharm/Tox review
/	3			3	Adequate	18-SEP-1998	28-MAY-1999 update revealed no change from 09-APR-1998 amendment reviewed on 18-SEP-1998
/	3			7	NA	NA	/
/	3			1	Adequate	28FEB-2002	
/	3			3	Adequate	31-OCT-2000	Reviewed for inhalation aerosol DPs
/	3			3	Adequate	02-MAR-1997	

¹ Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)

**CHEMISTRY REVIEW #6**

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Investigation New Drug Application	IND 43,841	Original IND for Nasacort HFA (TAA nasal aerosol)
New Drug Application	NDA 20-468	Nasacort AQ Nasal Spray

18. STATUS:

ONDC:

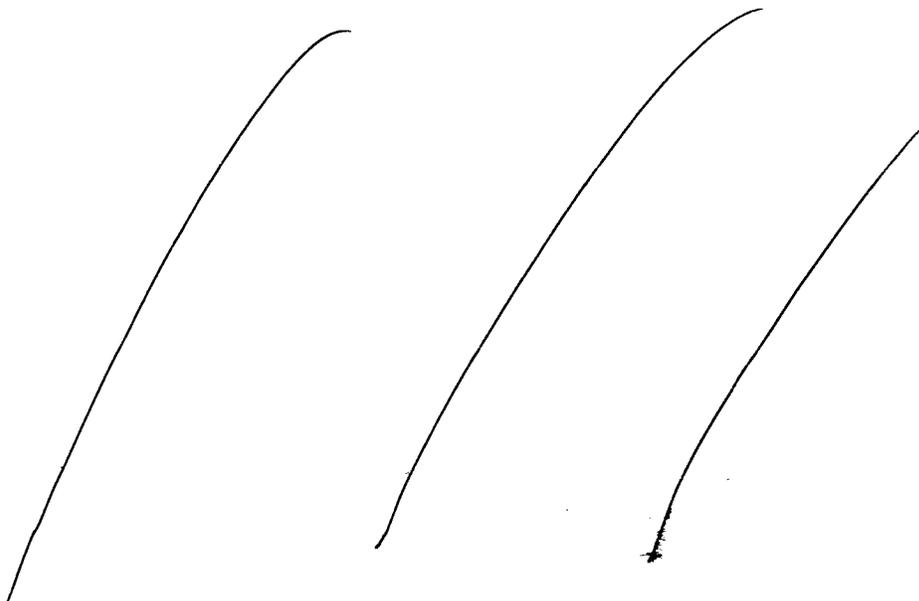
CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	/	05-MAR-2002, for expiry assessment (see p. 51 of CR#5).	Dr. F. Zhou
EES	WITHHOLD ACCEPTABLE ACCEPTABLE (08-Oct-2003)	01-JUN-2000 (requested) 17-MAY-2002 (requested) 28-APR-2003 (requested)	OC OC New sites added.
Pharm/Tox	ACCEPTABLE UNACCEPTABLE UNACCEPTABLE (see comment 3 of 23-Sep-2003 AE)	27-JAN-2000 (extractables/leachables) 06-MAR-2002 / — 21-APR-2003 (extractables/leachables)	Dr. L. Pei Dr. V. Whitehurst Dr. L. Pei
Biopharm			
LNC	N/A		
Methods Validation			Will be submitted upon applicant submission of MV packages. See comment in draft letter.
OPDRA	N/A		
EA	ACCEPTABLE – Categorical Exclusion Requested as per 21 CFR 25.31(b)		
Microbiology	RECOMMEND APPROVAL	16-DEC-97	Carol K. Vincent

¹This expiration dating period analysis was based on acceptance criteria limits that are not finalized so that the final expiration dating period recommendation may need to be adjusted. See p. 45 of this review.

Executive Summary Section

A. Description of the Drug Product(s) and Drug Substance(s)

The DP for this application is Nasacort® HFA (triamcinolone acetonide) Nasal Aerosol. This drug is intended to be an eventual replacement of the firms approved chlorofluorocarbon based version of a triamcinolone acetonide nasal aerosol (application N19-798). The DP delivers 65.0 mg, ~~mg~~ in theory, refer to p. 22 of CR#4) of formulation from the valve, containing a target amount of 100 mcg of triamcinolone acetonide (USAN name abbreviated as TAA), ethanol and ~~g~~, of 1,2,2,2-tetrafluoroethane propellant (HFA-134a), with a target delivery from the nasal actuator of 55 mcg TAA/actuation. The DP is indicated for the nasal treatment of SAR and PAR. The TAA is a glucocorticosteroid that has an annual schedule period for retesting.



~~_____~~. In an attempt to decrease the DP APSD variability, the applicant has instituted additional controls, during the manufacturing process (see response and evaluation of comment 9.a beginning on p. 33 of CR#5).

There were no comparability issues with regard to the formulations in moving from pre-clinical to clinical to primary stability batch production in the original application. However, during the time after the original submission of the application to the Agency on 17-DEC-1996, the applicant has withdrawn a

Executive Summary Section

In addition, changes to the composition of various valve components of the product resulted in the need for the applicant to place on stability three additional batches of DP, which had _____ of long term data collected and submitted. The biometrics team had assessed the proposed _____ expiration dating period relative to long term stability data from the 05-MAR-2002, consult but the DP specification limits for APSD were not and are still not finalized. See review of the response to comment 2.h below beginning on p. 45.

Note that two of the three primary stability batches from Manati (15-34A-1, -2, and -3) were prepared with the to-be-marketed actuator manufactured by _____ but that the third was prepared with an actuator unit manufactured by _____. As a result of CR#3 the applicant was given the option of providing certain comparative performance data for the product that would have demonstrated the interchangeable nature of the two actuators or the option to withdraw one of them from the application. The applicant has, as of the 30-NOV-2001, amendment, *withdrawn* the _____ nasal actuator from the application. As a result, the stability data from the batch 15-34A-3, which used the *withdrawn* _____ actuator, are considered supportive and no longer a primary stability batch. In fact, after the proposal of a new DP manufacturing site at Holmes Chapel, UK in the 21-MAR-2003, amendment, the Manati site was *withdrawn* (see EES system under site CFN 2650125) from the application as a production site of this product, and various "improvements" to the manufacturing process were introduced at Holmes Chapel to attempt to lessen product variability in measured APSD (see p. 33 of CR#5). Thus, these Manati stability data (15-34A-1, -2, and -3) are certainly considered more as supportive under these circumstances and the Agency must rely more heavily on the analysis of the available _____ stability data from the three batches from Holmes Chapel (PM/066/02, PM/067/02, and PM/073/02). Evaluation of these limited data are included in this current review (CR#6).

The applicant has also _____ testing for the product (see of CR#5) which has the purpose of _____ thus allowing the subsequent culling, _____ those canisters _____ that became problematic in terms of leakage. The purpose is to prevent these potential problematic units from reaching the marketplace where it is possible that they may encounter similar undesirable storage conditions _____

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose for adults with the Nasacort® HFA Nasal Aerosol product is 220 mcg once a day (two 55 mcg actuations into each nostril). The starting dose may be as high as 440 mcg once daily. After the desired effect is achieved some patients may be maintained on a dose of as little as one spray (55 mcg) in each nostril once a day (total daily dose 110 mcg per day). It is noted that the delivered dose uniformity (DDU) testing is performed with two (2)

Executive Summary Section

actuations of the DP per determination (i.e., with a target minimum dose of _____ mcg TAA).

C. Basis for Approvability or Not-Approval Recommendation

Currently the application, in terms of the CMC portion, is considered to be **approvable** pending revision as outlined in the attached draft letter. In summary, the remaining comments to be addressed involve the following issues:

- Supporting DMF _____ is currently inadequate and the holder will be notified of the deficiencies.
- The acceptance criteria for control of the _____ are unacceptably permissive and this is expected to impact negatively on the resultant APSD of the delivered drug. The applicant is asked to base their acceptance criteria on data from _____ where data are seen to be much less variable. _____
- The acceptance criteria for the dosing uniformity¹ were previously agreed upon (see CR#4) but the applicant claimed in the 21-Mar-2003, submission that they would not be able to meet these criteria. After our discussion of this issue with the applicant at the 18-Jul-2003, meeting, the applicant has tightened their proposed acceptance criteria somewhat. The data collected under the routine storage conditions indicate that further tightening, closer to the dosing standards expected by the Agency for nasal aerosol products, is possible and our counterproposal is included in the comments in the draft letter. See review of the response to comment 2.a below on p. 22.
- Aerodynamic PSD data (_____ cascade impaction) are variable and, as requested by the Agency during the 18-Jul-2003, meeting, the applicant has tightened, to some extent, the acceptance criteria. For details and remaining deficiencies, see the response and review for comment 2.f beginning on p. 31. The applicant will also be reminded of their agreement to replace the _____ methodology for determination of the aerodynamic PSD with methodology that provides a more thorough characterization of the entire dose to be received by patients.

¹ Dose uniformity is termed Unit Spray Content or USC by the applicant and Dose Content Uniformity or DCU or Delivered Dose Uniformity or DDU by the Agency.

Executive Summary Section

- Certain issues are pending related to the control and possibly the identity of the foreign particulates and the applicant will be informed that further comments regarding this may be forthcoming as a result of a pending consult to our pharmacology/toxicology team. The consult was forwarded on 24-Sep-2003. It is also noted that the resent 07-Sep-2003, AE letter included comment 3 from our pharm/tox team. The applicant indicated in their 06-Oct-2003, complete response that the response to comment 3 was included in the 02-Sep-2003, submission. This comment dealt with the presence and limits for _____ extractables _____.
- Based on the currently limited stability data on the product manufactured at the intended commercial site and with the intended conditions of manufacturing (_____ the expiration dating period proposed as _____ by the applicant should be revised to _____.
- Lastly, the applicant will be requested to submit multiple copies of the method validation package for forwarding to Agency laboratories for their assessment of the controlling methodology for both the DP, once specifications are finalized.

Note that three new sites were added to the EES request which was submitted to OC on 28-Apr-2003 and 30-Apr-2003. The Office of Compliance recommended WITHHOLD for the application on 29-Sep-2003 but with the clarifications provided by the applicant in the 08-Oct-2003, correspondence withdrawing the Collegeville, PA site, the recommendation was changed to ACCEPTABLE.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., Review Chemist
HFD-570/820



Executive Summary Section

C. CC Block

cc:

Orig. NDA 20-784

HFD-570/Division File

HFD-570/CBertha

HFD-570/GPoochikian

HFD-570/VShah

HFD-570/CJackson

HFD-570/SBarnes

R/D Init. by: GPoochikian

Filename and Location: c:\data\mydocuments\reviews etc\NDA\20784\Review 6 (CB)\03-08-07.rev.doc

58 Page(s) Withheld

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Draft Labeling

Deliberative Process



NDA 20-784

**NASACORT[®] (triamcinolone acetonide)
HFA Nasal Aerosol**

Aventis Inc. (Quintiles, Inc. authorized US Agent)

**Craig M. Bertha, Ph.D.
Division of Pulmonary and Allergy Drug Products (HF-570)**

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Chemistry Review Data Sheet

1. NDA 20784
2. REVIEW #5:
3. REVIEW DATE: 06-MAY-2003
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
AE Letter	31-MAY-2002
Amendment	28-Feb-2002
Amendment	30-Nov-2001
AE Letter	04-FEB-2000
Amendment	30-JUL-1999
Amendment	09-DEC-1999
Amendment	20-DEC-1999
AE Letter	17-DEC-1997
Amendment	24-OCT-1997
Amendment	01-OCT-1997
Amendment	13-AUG-1997
IR Letter	19-MAY-1997
Amendment	07-APR-1997
Amendment	04-APR-1997
Amendment	21-MAR-1997
Amendment	14-MAR-1997
Amendment	04-MAR-1997
Amendment	28-FEB-1997
Original NDA	16-DEC-1996

6. SUBMISSION(S) BEING REVIEWED:



Chemistry Review Data Sheet

Submission(s) ReviewedDocument Date

Amendments

21-Mar-2003 AC (assigned 01-
Apr-2003)
05-May-2003 BM

7. NAME & ADDRESS OF APPLICANT:

Name: Aventis, Inc. (US Agent, Quintiles, Inc.)
Address: P.O. Box 9708
Kansas City, MO 64134-0708
Representative: Wayne F. Vallee, MBA, R.Ph.
Telephone: (816) 767-6466

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Nasacort® HFA Nasal Inhaler
- b) Non-Proprietary Name (USAN): triamcinolone acetate HFA nasal aerosol
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Glucocorticosteroid for nasal treatment of seasonal and perennial allergic rhinitis (SAR and PAR)

11. DOSAGE FORM: nasal aerosol

12. STRENGTH/POTENCY: 55 mcg of triamcinolone acetate (TAA)/actuation (ex-actuator) and 100 mcg TAA/act (ex-valve); target valve delivery is 65.0 mg (see discussion of valve delivery on p. 22 of CR#4) of formulation containing — w/w TAA, — w/w Dehydrated Alcohol, USP, and — w/w HFA-134a (1,1,1,2-tetrafluoroethane). There is only one size of the product which is a 100 actuation unit containing a target amount of — of formulation (— overfill).

13. ROUTE OF ADMINISTRATION: intranasal

Chemistry Review Data Sheet

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

[Note22]: SPOTS product – Form Completed Not a SPOTS product

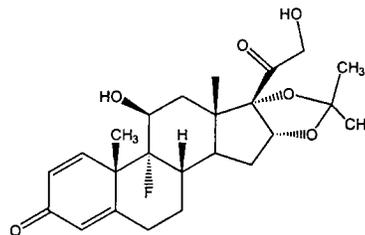
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: (11 β ,16 α)-9-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)is(oxy)]-pregna-1,4-diene-3,20-dione

Molecular Formula: C₂₄H₃₁FO₆

Molecular Wt: 434.51

CAS Reg. No.:



Triamcinolone Acetonide (TAA)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	2	/	/	1	Inadequate	11-APR-2003	Deficiency letter issued
—	3			1	Adequate	20-FEB-2002	Response to DMF — def. letter submitted to DMF
—	3			1	Adequate	21-FEB-2002	
—	3			1	Adequate	22-FEB-2002	



CHEMISTRY REVIEW #5



Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	3	/	/	1	Adequate	21-FEB-2002	
/	5			7	Adequate	28-SEP-1994	See Pharm/Tox review
/	3			3	Adequate	18-SEP-1998	28-MAY-1999 update revealed no change from 09-APR-1998 amendment reviewed on 18-SEP-1998
/	3			7	NA	NA	
/	3			1	Adequate	28FEB-2002	
/	3			3	Adequate	31-OCT-2000	Reviewed for inhalation aerosol DPs
/	3			3	Adequate	02-MAR-1997	
/	3						

¹ Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Investigation New Drug Application	IND 43,841	Original IND for Nasacort HFA (TAA nasal aerosol)
New Drug Application	NDA 20-468	Nasacort AQ Nasal Spray



CHEMISTRY REVIEW #5



Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	/ / /	05-MAR-2002, for expiry assess (see p. 51 of CR#5).	Dr. F. Zhou
EES	WITHHOLD ACCEPTABLE Pending	01-JUN-2000 17-MAY-2002 28-APR-2003	OC OC New sites added.
Pharm/Tox	ACCEPTABLE UNACCEPTABLE PENDING	27-JAN-2000 (extractables/leachables) 06-MAR-2002 21-APR-2003 (extractables/leachables)	Dr. L. Pei Dr. V. Whitehurst Dr. L. Pei
Biopharm			
LNC	N/A		
Methods Validation			Will be submitted upon applicant submission of MV packages (see def. comment 2.1 in draft letter).
OPDRA	N/A		
EA	ACCEPTABLE – Categorical Exclusion Requested as per 21 CFR 25.31(b)		
Microbiology	RECOMMEND APPROVAL	16-DEC-97	Carol K. Vincent

¹This expiration dating period analysis was based on acceptance criteria limits that are not finalized so that the final expiration dating period recommendation may need to be adjusted.

The Chemistry Review for NDA 20-784

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommended action for this application from the CMC perspective is **approvable (AE)**.

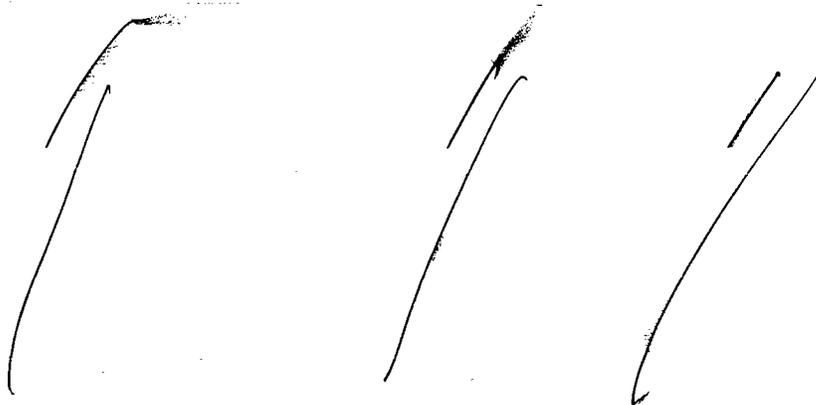
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product for this application is Nasacort® HFA (triamcinolone acetonide) Nasal Aerosol. This drug is intended to be an eventual replacement of the firm's approved chlorofluorocarbon based version of a triamcinolone acetonide nasal aerosol (application N19-798). The drug product delivers 65.0 mg (in theory, refer to p. 22 of CR#4) of formulation from the valve, containing a target amount of 100 mcg of triamcinolone acetonide (USAN name abbreviated as TAA), ethanol and 1,2,2,2-tetrafluoroethane propellant, with a target delivery from the nasal actuator of 55 mcg TAA/actuation. The drug product is indicated for the nasal treatment of SAR and PAR. The TAA is a glucocorticosteroid that has an annual schedule period for retesting.



Executive Summary Section

_____ In order to improve DP aerodynamic particle size distribution (APSD) variability, the applicant has instituted additional controls, _____ during the manufacturing process (see response and evaluation of comment 9.a beginning on p. 33 below).

There were no comparability issues with regard to the formulations in moving from pre-clinical to clinical to primary stability batch production in the original application. However, during the time after the original submission of the application to the Agency on 17-DEC-1996, the applicant has withdrawn a _____

In addition, changes to the composition of various valve components of the product resulted in the need for the applicant to place on stability three additional batches of drug product, which now have _____ of long term data collected and submitted. (The biometrics team had assessed the proposed _____ expiration dating period relative to long term stability data from the 05-MAR-2002, consult but the DP specification limits for APSD were not and are still not finalized: see review and evaluation of comment 9.a response below starting on p. 33).

Note that two of the three new primary stability batches from Manati (15-34A-1, -2, and -3) were prepared with the to-be-marketed actuator manufactured by _____ but that the third was prepared with an actuator unit manufactured by _____. As a result of CR#3 the applicant was given the option of providing certain comparative performance data for the product that would have demonstrated the interchangeable nature of the two actuators or to withdraw one of them from the application. The applicant has, as of the 30-NOV-2001, amendment, *withdrawn* the _____ nasal actuator from the application. As a result, the stability data from the batch 15-34A-3, which used the *withdrawn* _____ actuator, are considered supportive and no longer a primary stability batch. A new DP manufacturing site is proposed at Holmes Chapel, UK in the 21-MAR-2003, amendment and _____ stability data from three batches are included (PM/066/02, PM/067/02, and PM/073/02).

It is also notable that for both sites, manufacturing "improvements" noted above have been implemented subsequent to the preparation of the _____ primary stability batches from Manati, in an attempt to lessen the variability in the

Executive Summary Section

in vitro aerodynamic PSD for the product (see review of response to comment 9.a beginning on p. 33).

The applicant has also instituted _____ testing for the product (see p. 25 of this review) which has the purpose of _____, thus allowing the subsequent culling _____ those canisters _____ that became problematic in terms of leakage. The purpose is to prevent these potential problematic units from reaching the marketplace where it is possible that they may encounter similar undesirable storage conditions _____.

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose for adults with the Nasacort® HFA Nasal Aerosol product is 220 mcg once a day (two 55 mcg actuations into each nostril). The starting dose may be as high as 440 mcg once daily. After the desired effect is achieved some patients may be maintained on a dose of as little as one spray (55 mcg) in each nostril once a day (total daily dose 110 mcg per day). It is noted that the dose content uniformity (DCU) testing is performed with two (2) actuations of the DP per determination (i.e., with a target minimum dose of _____ mcg TAA).

C. Basis for Approvability or Not-Approval Recommendation

Currently the application, in terms of the CMC portion, is considered to be **approvable** pending revision as outlined in the attached draft letter. In summary:

- Supporting DMF _____ is currently inadequate and the holder has been notified of the deficiencies.
- Clarity is sought on the current acceptance criteria for both the DS and the DP for the _____ toxicological qualification data is needed from the applicant.
- The _____ and the acceptance criteria for the resultant APSD are currently unacceptably permissive.
- The acceptance criteria for the dosing uniformity¹ were previously agreed upon (see CR#4) but the applicant now claims that they will not be able to meet these criteria and have widened them.

¹ Dose uniformity is termed Unit Spray Content or USC by the applicant and Dose Content Uniformity or DCU or Dose Delivery Uniformity or DDU by the Agency.

Executive Summary Section

- Aerodynamic PSD data (cascade impaction) are variable and the current proposed controls, already presented by the applicant in Dec-2002 and discussed in the 10-Feb-2003 telephone conference, are viewed by the Agency as too wide for quality control and thus, unacceptable. Interim specifications for APSD of the emitted plume from acutated DP by methodology have associated acceptable criteria that should be tightened. The applicant commits to replace the methodology for determination of the aerodynamic PSD with methodology that provides a more thorough characterization of the entire dose to be received by patients. The applicant is being asked to provide a commitment to the exact date by which this methodology can be put in place (see evaluation of response to comment 9.c on p. 50).
- Certain issues are pending related to levels and controls for extractables, leachables (i.e., _____) and foreign particulates and the applicant will be informed that further comments regarding the levels of leachables and extractables in CCS components may come as a result of a pending consult to our pharmacology/toxicology team.
- Lastly, the applicant will be requested to submit multiple copies of the method validation package for forwarding to Agency laboratories for their assessment of the controlling methodology for both the drug product, once specifications are finalized.

Note that three new sites have been added to the EES request which was submitted to OC on 28-Apr-2003 and 30-Apr-2003. A decision from the Office of Compliance is currently pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., Review Chemist
HFD-570/820



Executive Summary Section

C. CC Block

cc:

Orig. NDA 20-784

HFD-570/Division File

HFD-570/CBertha

HFD-570/GPoochikian

HFD-570/VShah

HFD-570/CJackson

HFD-570/SBarnes

R/D Init. by: GPoochikian

Filename and Location: c:\data\mydocuments\reviews etc\NDA\20784\Review 5 (CB)\03-03-21.rev.doc

69 Page(s) Withheld

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this page is the manifestation of the electronic signature.**

/s/

Craig Bertha
5/13/03 02:48:33 PM
CHEMIST

Guiragos Poochikian
5/13/03 03:09:44 PM
CHEMIST



NDA 20-784

**NASACORT® (triamcinolone acetonide)
HFA Nasal Aerosol**

Aventis Inc. (Quintiles, Inc. authorized US Agent)

**Craig M. Bertha, Ph.D.
Division of Pulmonary and Allergy Drug Products (HF-570)**

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Chemistry Review Data Sheet

1. NDA 20784
2. REVIEW #4:
3. REVIEW DATE: 04-APR-2002
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

AE Letter
Amendment
Amendment
Amendment
AE Letter
Amendment
Amendment
Amendment
IR Letter
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment
Original NDA

Document Date

04-FEB-2000
30-JUL-1999
09-DEC-1999
20-DEC-1999
17-DEC-1997
24-OCT-1997
01-OCT-1997
13-AUG-1997
19-MAY-1997
07-APR-1997
04-APR-1997
21-MAR-1997
14-MAR-1997
04-MAR-1997
28-FEB-1997
16-DEC-1996

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment
Amendment

Document Date

30-NOV-2001 (assigned 05-FEB-2002)
28-FEB-2002 (assigned 01-MAR-2002)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Aventis, Inc. (US Agent, Quintiles, Inc.)
Address: P.O. Box 9708
Kansas City, MO 64134-0708
Representative: Wayne F. Vallee, MBA, R.Ph.
Telephone: (816) 767-6466

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Nasacort® HFA Nasal Inhaler
b) Non-Proprietary Name (USAN): triamcinolone acetonide HFA nasal aerosol
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Glucocorticosteroid for nasal treatment of seasonal and perennial allergic rhinitis (SAR and PAR)

11. DOSAGE FORM: nasal aerosol

12. STRENGTH/POTENCY: 55 mcg of triamcinolone acetonide (TAA)/actuation (ex-actuator) and 100 mcg TAA/act (ex-valve); target valve delivery is 65.0 mg (see discussion of valve delivery on p. 22 of review) of formulation containing — w/w TAA, — w/w Dehydrated Alcohol, USP, and — w/w HFA-134a (1,1,1,2-tetrafluoroethane)

13. ROUTE OF ADMINISTRATION: intranasal

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

[Note22]:

SPOTS product – Form Completed

Not a SPOTS product



CHEMISTRY REVIEW

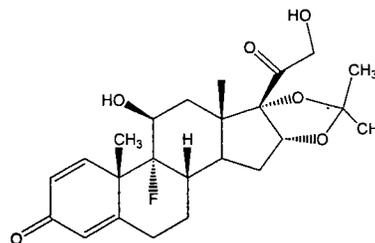


Chemistry Review Data Sheet

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

Chemical Names: (11 β ,16 α)-9-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione

Molecular Formula: C₂₄H₃₁FO₆
Molecular Wt: 434.51
CAS Reg. No.:



Triamcinolone Acetonide (TAA)

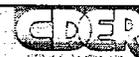
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	2			1	Inadequate	06-MAR-2002	Deficiency letter issued 4/2/02
—	3			1	Adequate	20-FEB-2002	Response to DMF def. letter submitted to DMF
—	3			1	Adequate	21-FEB-2002	
—	3			1	Adequate	22-FEB-2002	
—	3			1	Adequate	21-FEB-2002	
—	5			7	Adequate	28-SEP-1994	See Pharm/Tox review
—	3			3	Adequate	18-SEP-1998	28-MAY-1999 update revealed no change from 09-APR-1998 amendment



CHEMISTRY REVIEW



Chemistry Review Data Sheet

						reviewed on 18-SEP-1998
	3		7	NA	NA	
	3		1	Adequate	28FEB-2002	
	3		3	Adequate	31-OCT-2000	Reviewed for inhalation aerosol DPs
	3		3	Adequate	02-MAR-1997	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Investigation New Drug Application	IND 43,841	Original IND for Nasacort HFA (TAA nasal aerosol)
New Drug Application	NDA 20-468	Nasacort AQ Nasal Spray

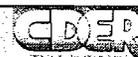
18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending	05-MAR-2002, for expiry assess (see pp. 37, 51 of review).	
EES	WITHHOLD	01-JUN-2000	OC
Pharm/Tox	ACCEPTABLE	27-JAN-2000	Dr. L. Pei
	UNACCEPTABLE	06-MAR-2002	Dr. V. Whitehurst
Biopharm			
LNC	N/A		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Methods Validation			Will be submitted upon applicant submission of MV packages (see comment in draft letter).
OPDRA	N/A		
EA	ACCEPTABLE – Categorical Exclusion Requested as per 21 CFR 25.31(b)		
Microbiology	RECOMMEND APPROVAL	16-DEC-97	Carol K. Vincent

The Chemistry Review for NDA 20-784

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommended action for this application from the CMC perspective is approvable (AE).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product for this application is Nasacort® HFA (triamcinolone acetonide) Nasal Aerosol. This drug is intended to be an eventual replacement of the firm's approved chlorofluorocarbon based version of a triamcinolone acetonide nasal aerosol (application N19-798). The drug product delivers 65.0 mg (in theory, refer to p. 22) of formulation from the valve, containing a target amount of 100 mcg of triamcinolone acetonide (USAN name abbreviated as TAA), ethanol and of 1,2,2,2-tetrafluoroethane propellant, with a target delivery from the nasal actuator of 55 mcg TAA/actuation. The drug product is indicated for the nasal treatment of SAR and PAR. The TAA is a glucocorticosteroid that has an annual schedule period for retesting.

Executive Summary Section

There were no comparability issues with regard to the formulations in moving from pre-clinical to clinical to primary stability batch production in the original application. However, during the time after the original submission of the application to the Agency on 17-DEC-1996, the applicant has withdrawn a

_____. In addition, changes to the composition of various valve components of the product resulted in the need for the applicant to place on stability three additional batches of drug product, which now have _____ of long term data collected and submitted. (The biometrics team is currently assessing the proposed _____ expiration dating period relative to long term stability data from the 05-MAR-2002, consult). Note that two of the three new primary stability batches were prepared with the to-be-marketed actuator manufactured by _____ out that the third was prepared with an actuator unit manufactured by _____. As a result of CR#3 the applicant was given the option of providing certain comparative performance data for the product that would have demonstrated the interchangeable nature of the two actuators or to withdraw one of them from the application. The applicant has, as of the 30-NOV-2001, amendment, withdrawn the _____ nasal actuator from the application. As a result, the stability data from the batch 15-34A-3, which used the *withdrawn* _____ actuator, are considered supportive and no longer a primary stability batch. It is also notable that manufacturing "improvements" have been implemented subsequent to the preparation of the primary stability batches in an attempt to lessen the variability in the *in vitro* aerodynamic PSD for the product.

The applicant has also instituted _____ testing for the product _____, which has the purpose of allowing the culling _____ those canisters _____ that might have become problematic in terms of leakage once reaching the marketplace and upon exposure to undesirable storage conditions _____. There are questions regarding the _____ and full validation data for this process are yet to be provided (see draft letter comment 3).

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose for adults with the Nasacort® HFA Nasal Aerosol product is 220 mcg once a day (two 55 mcg actuations into each nostril).

Executive Summary Section

The starting dose may be as high as 440 mcg once daily. After the desired effect is achieved some patients may be maintained on a dose of as little as one spray (55 mcg) in each nostril once a day (total daily dose 110 mcg per day). It is noted that the dose content uniformity (DCU) testing is performed with two (2) actuations of the DP per determination (i.e., with a target dose of — , TAA).

C. Basis for Approvability or Not-Approval Recommendation

Currently the application, in terms of the CMC portion, is considered to be **approvable** pending revision as outlined in the attached draft letter. Supporting DMF (—————) is currently inadequate and the holder has been notified of the deficiencies. Additional data are requested from the applicant in support of the ————— testing as well as certain extractables limits set for incoming container/closure components. Aerodynamic PSD data (————— cascade impaction) are quite variable for the product and the applicant will be asked to correct this and subsequently tighten the associated acceptance criteria. In addition the applicant will be asked to tighten the ————— specification for the ————— excipient and to revise the drug product stability protocol to increase the number of annual stability batches relative to the production rate and to revise the withdrawal protocol in the event of a stability failure. Lastly, the applicant will be requested to submit multiple copies of the method validation package for forwarding to Agency laboratories for their assessment of both the controlling methodology for both the drug substance and product. As a result of the pharm/tox consult for the ————— that is a potential DS and DP impurity, the applicant will need to tighten the acceptance limit or provide the appropriate toxicological data for qualification.

Note that current Office of Compliance 01-JUN-2000 recommendation for the associated sites for the application is WITHHOLD (as of 04-APR-2002).

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Craig M. Bertha, Ph.D., Review Chemist
HFD-570/820



Executive Summary Section

C. CC Block

cc:

Orig. NDA 20-784

HFD-570/Division File

HFD-570/CBertha

HFD-570/GPoochikian

HFD-570/VShah

HFD-570/CJackson

HFD-570/SBarnes

R/D Init. by: GPoochikian

Filename and Location: c:\data\mydocuments\reviews etc\NDA\20784\Review 4 (CB)\01-11-30.rev.doc

47 Page(s) Withheld

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this page is the manifestation of the electronic signature.

/s/

Craig Bertha
4/10/02 02:15:59 PM
CHEMIST

Guiragos Poochikian
4/10/02 02:28:58 PM
CHEMIST

Division of Pulmonary Drug Products
Chemist NDA Review
Review of Chemistry Manufacturing & Controls

NDA #: N 20784

CHEM. REVIEW: 3

REVIEW COMPLETION DATE: February 03, 2000

REVIEW CHEMIST: Vibhakar Shah, Ph.D.

<u>SUBMISSION TYPE</u>		<u>DOC. DATE</u>	<u>CDER DATE</u>	<u>RECEIPT DATE</u>	<u>REMARKS</u>
Amendment*	AZ	30-JUL-1999	02-AUG-1999	13-SEP-1999	* Subject of this Review
Amendment*	BC	09-DEC-1999	10-DEC-1999	10-DEC-1999	
Amendment*	BC	20-DEC-1999	21-DEC-1999	21-DEC-1999	
Amendment	AC	24-OCT-1997	24-OCT-1997	11-NOV-1997	
Amendment	BC	01-OCT-1997	03-OCT-1997	08-OCT-1997	
Amendment	BC	13-AUG-1997	14-AUG-1997	18-AUG-1997	Chem. Rev. 2
Amendment	BC	07-APR-1997	09-APR-1997	21-APR-1997	
Amendment	BC	04-APR-1997	09-APR-1997	21-APR-1997	
Amendment	BZ	21-MAR-1997	25-MAR-1997	31-MAR-1997	
Amendment	BC	14-MAR-1997	17-MAR-1997	19-MAR-1997	
Amendment	BC	04-MAR-1997	05-MAR-1997	12-MAR-1997	Chem. Rev. 1
Amendment	BC	28-FEB-1997	03-MAR-1997	07-MAR-1997	
Original NDA		16-DEC-1996	17-DEC-1996	06-JAN-1997	

NAME & ADDRESS OF APPLICANT:

Applicant:
Rhone-Poulenc Rorer Pharmaceuticals Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

U.S. Agent (if any):
None

DRUG PRODUCT NAME:

Proprietary: NASACORT™ HFA-134a Nasal
Nonproprietary/USAN: Triamcinolone acetonide nasal inhalation aerosol
Code Name: Not applicable
Chemical Type/Therapeutic Class: 3S

PHARMACOLOGICAL CATEGORY:

Indication: Glucocorticosteroid/nasal inhaler for the nasal treatment of seasonal and perennial allergic rhinitis
Dosage Form: Metered dose inhaler (suspension)
Strengths: 55 mcg of Triamcinolone acetonide (TAA) per actuation ex-actuator (— mg Dehydrated Alcohol, USP/actuation — — HFA-134a (1,1,1,2-tetrafluoroethane)/actuation); 100 mcg of TAA ex valve;

— 100 actuations per canister, 15 mg TAA/canister,

Route of Administration:

Dispensed:

Rx: X **OTC:**

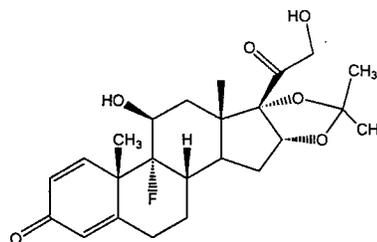
Special Products:

Yes: **No:** X

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

Chemical Names: (11β,16α)-9-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione

Molecular Formula: C₂₄H₃₁FO₆
Molecular Wt: 434.51
CAS Reg. No.:



Triamcinolone Acetonide (TAA)

SUPPORTING DOCUMENTS:

A. DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference
— Type II	/	/	Adequate ¹	4/12/96	Chem. NDA Rev-1, p 7
— Type III			Inadequate ²	01/22/2000	Chem. DMF Review 4. See p.63 of this review
— Type III			Inadequate ²		See p. 63 of this review
— Type I, III			Inadequate ³	01/22/2000	See p. 62 of this review
— Type III			Inadequate ³	01/22/2000	See p. 63 of this review
— Type III			Adequate	1/17/97	Chem. NDA Rev-1, p 16 See p 9 of this review
— Type V			Adequate	9/28/94	Reviewed by Pharmacologist Misoon Chun, HFD-570
— Type III			Adequate ⁴	09/21/1998	Chem. DMF Rev-2 See p.98 of this review
— Type III			Adequate	10/4/96	Chem. NDA Rev-1, p 55
— Type III			er Adequate	2/19/97	Chem. NDA Rev-1, p 55

¹DMF — reviewed by B. Rogers, Ph.D. of HFD-570 and found to be adequate for support of the applicant's aqueous nasal spray suspension, Nasacort AQ (triamcinolone acetonide) Nasal Spray.

²DMF — reviewed by B. Rogers, Ph.D., HFD-570 and found to be inadequate for — . DMF — is supporting document for DMF —

³DMF — reviewed by C. Bertha, Ph.D., HFD-570 and found to be inadequate for —

³DMF — reviewed by C. Bertha, Ph.D., HFD-570 and found to be inadequate for —

⁴DMF — reviewed by G. Kang, HFD-627 and found adequate for —

B. INDs/NDAs:

Following INDs and NDAs has been specified by the applicant in support of this application

NDA 18-117	Azmacort® Oral Inhaler
IND 26,171	Nasacort® Nasal Inhaler
IND 39,306	Nasacort® AQ Nasal Spray
IND 43,841	Nasacort® HFA Nasal
NDA 19-798	Nasacort® Nasal Inhaler
NDA 20-468	Nasacort® AQ Nasal Spray

RELATED DOCUMENTS (if applicable): None

CONSULTS:

CONSULT	Forward Date	Status	Comments
1. Establishment Evaluation (EER)	November 16, 1999	Withhold Feb. 01, 2000	RPR drug product manufacturing facility at Manati, PR has been found unacceptable by OC due to inadequate QA function.
2. Microbiology (HFD-160)	-	-	None required.
3. Pharmacology: Extractables and Leachables specifications	Jan. 20, 2000	Acceptable Jan. 27, 2000	See Pharmacologist Rev-4 dated January 27, 2000. See p 64 of this review.
4. Biometrics	-	-	Deferred pending resolution of acceptance criteria for the drug product.
5. Methods Validation	-	pending	Will be forwarded to FDA Labs. once all the pending issues as outlined in this review pertaining to drug product specifications are resolved.
6. Labeling & Nomenclature	-	-	A final trade Name is not proposed yet by the applicant.
7. Environmental Assessment	-	-	Applicant should be reminded to claim Categorical exclusion under CFR §25.15 (d)/(e)

REMARKS/COMMENTS: See attached Review Notes.

CONCLUSIONS & RECOMMENDATIONS:

The application as amended is **not approvable** from the standpoint of chemistry, manufacturing, and controls. Deficiencies (CMC) are summarized in the attached draft letter to the applicant. These deficiencies should be forwarded to the applicant.

Additionally, as indicted on p 2 of this review, the drug master files, amended in support of the _____ for this application are found deficient. The holders of DMFs _____ have been notified of appropriate comments respective to their products.

Currently, the manufacturing facility for the drug product has been found inadequate by Office of Compliance. An acceptable EER should be received prior to the approval of this application.

Vibhakar J. Shah, Ph.D.
Review Chemist for DPADP (HFD-570)
DNDC-II (HFD-820), Office of New Drug Chemistry
OPS, Center for Drug Evaluation and Research

cc:

Org. NDA 20784
HFD-570/Division File
HFD-570/Chemist/Vshah
HFD-570/Chemist/CBertha
HFD-570/CSO/SBarnes
HFD-570/TL/GPoochikian

R/D Init. by: GPoochikian

Document: N20784CMCRev3.doc

File Location: E:\CDERDocs\DPADP570\NDAs\N20784\N20784DFS\N20784CMCRev3.doc

NOT APPROVABLE

136 Page(s) Withheld

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

NDA #: 20-784 **CHEM. REVIEW #** 2 **REVIEW DATE:** 11/26/97

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	12/16/96	12/17/96	1/6/97
AMENDMENT (BC)	2/28/97	3/3/97	3/7/97
AMENDMENT (BC)	3/4/97	3/5/97	3/12/97
AMENDMENT (BC)	3/14/97	3/17/97	3/19/97
AMENDMENT (BZ)	3/21/97	3/25/97	3/31/97
AMENDMENT (BC)*	4/4/97	4/9/97	4/21/97
AMENDMENT (BC)*	4/7/97	4/9/97	4/21/97
AMENDMENT (BC)*	8/13/97	8/14/97	8/18/97
AMENDMENT (BC)*	10/1/97	10/3/97	10/8/97
AMENDMENT (BC)*	10/24/97	10/24/97	11/3/97

*Subject of this review.

NAME & ADDRESS OF APPLICANT:

Rhône-Poulenc Rorer Pharmaceuticals Inc.
 500 Arcola Road
 P.O. Box 1200
 Collegeville, PA 19426-0107

DRUG PRODUCT NAME

Proprietary:

NASACORT® HFA-134a Nasal

Nonproprietary/USAN:

triamcinolone acetonide nasal
 aerosol

Code Name/#:

CAS-76-25-5 or RG 5029T

Chem.Type/Ther.Class:

3S

PHARMACOL. CATEGORY/INDICATION: glucocorticosteroid/nasal inhaler for the nasal treatment of seasonal and perennial allergic rhinitis

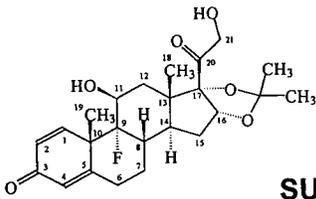
DOSAGE FORM: Metered dose inhaler (suspension)

STRENGTHS: 55 µg of triamcinolone acetonide (TAA) per actuation ex-actuator
 — mg Dehydrated Alcohol, USP/actuation, — HFA-134a
 (1,1,1,2-tetrafluoroethane)/actuation); 100 µg of TAA ex valve;
 100 actuations per canister, 15 mg TAA/canister,
 — r. Theoretical valve shot
 weight is — mg.

ROUTE OF ADMINISTRATION: nasal inhalation

DISPENSED: Rx OTC

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



Triamcinolone Acetonide

(11β, 16α)-9-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione

Molecular Formula: C₂₄H₃₁FO₆ Molecular Weight: 434.51

SUPPORTING DOCUMENTS:

Drug Master Files:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in chemistry review #
— Type II	/	/	Adequate ¹	4/12/96	See p. 7 of CR #1
— Type III			Inadequate	2/26/97 (Stamp 3/6/97)	See p. 55 of CR #1
— Type III			inadequate	11/6/97	See p. 45 of CR #2
—			Inadequate	11/6/97	See p. 45 of CR #2
— Type I, III			Inadequate ²	2/21/97	See p. 54 of CR #1
— Type III			Adequate	1/17/97	See p. 16 of CR #1
— Type V			Adequate	9/28/94	Reviewed by Pharmacologist Misoon Chun.
885 Type III			Inadequate ²	2/19/97	See p. 54 of CR #1
— Type III			Adequate	10/4/96	See p. 55 of CR #1
— Type III			Adequate	2/19/97	See p. 55 of CR #1

¹DMF — reviewed by B. Rogers, Ph.D of HFD-570 and found to be adequate for support of the applicant's aqueous nasal spray suspension, Nasacort AQ (triamcinolone acetonide) Nasal Spray.

²No response received as of 11/25/97.

RELATED DOCUMENTS:

- NDA 18-117 Azmacort® Oral Inhaler
- IND 26,171 Nasacort® Nasal Inhaler
- IND 39,306 Nasacort® AQ Nasal Spray
- IND 43,841 Nasacort® HFA Nasal —
- NDA 19-798 Nasacort® Nasal Inhaler
- NDA 20-468 Nasacort® AQ Nasal Spray

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	1/18/97	Pending	Note: Once the alternate testing site for the HFA-134a propellant is identified, a request for inspection will be forwarded.
Microbiology	a). 2/19/97 b). 8/29/97	a). Pending b). Pending	a). For evaluation of the microbiological test methods. b). For evaluation of applicant's response to comment 2.e.
Biometrics	Not forwarded		
Pharmacology: a) drug product impurities; b) CCS extractives levels and specifications.	a) 2/19/97 b) Not forwarded	a) Complete	a) Total impurities limited to limit for qualification of individuals (ICH). b) Pending submission of complete data from applicant (see response to comment 6.p below).
Methods Validation	Not forwarded to agency labs.		Pending resolution of method issues by the firm.
Environmental Assessment	Not forwarded for concurrence.		PM has recommended that firm withdraw EA as per Federal Register final rule.
Labeling & Nomenclature	Not forwarded.		A final tradename has not been proposed yet (see v4.2, p. 2-304).

REMARKS/COMMENTS: For remarks and comments, see p. 5.

CONCLUSIONS & RECOMMENDATIONS: The application as amended is not **approvable** from the standpoint of chemistry, manufacturing, and controls. Deficiencies (CMC) are detailed in the accompanying review notes and summarized in the attached draft letter to the applicant. These deficiencies should be forwarded to the applicant.

cc:
 Orig. NDA 20-784
 HFD-570/Division File
 HFD-570/CBertha/11/26/97
 HFD-570/SBarnes
 HFD-570/GPoochikian
 HFD-570/RNicklas
 HFD-570/LPei
 HFD-570/T-MChen
 R/D Init by: *CB* 12/2/97
 filename: 97-10-24.rev.doc



 Craig M. Bertha, Ph.D.
 Review Chemist

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APR 9 1997

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

NDA #: 20-784 **CHEM. REVIEW #** 1 **REVIEW DATE:** 4/3/97

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	12/16/96	12/17/96	1/6/97
AMENDMENT (BC)	2/28/97	3/3/97	3/7/97
AMENDMENT (BC)	3/4/97	3/5/97	3/12/97
AMENDMENT (BC)	3/14/97	3/17/97	3/19/97
AMENDMENT (BZ)	3/21/97	3/25/97	3/31/97

NAME & ADDRESS OF APPLICANT: Rhône-Poulenc Rorer Pharmaceuticals Inc.
 500 Arcola Road
 P.O. Box 1200
 Collegeville, PA 19426-0107

DRUG PRODUCT NAME

Proprietary: NASACORT® HFA-134a Nasal
Nonproprietary/USAN: triamcinolone acetonide nasal
Code Name/#: CAS-76-25-5 or RG 5029T
Chem.Type/Ther.Class: 3S

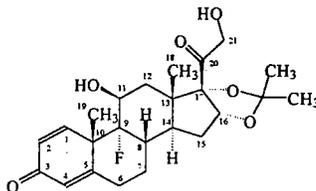
PHARMACOL. CATEGORY/INDICATION: glucocorticosteroid/nasal inhaler for the nasal treatment of seasonal and perennial allergic rhinitis

DOSAGE FORM:**STRENGTHS:**

Metered dose inhaler (suspension)
 55 µg of triamcinolone acetonide (TAA) per actuation ex-actuator Dehydrated Alcohol, USP/actuation, HFA-134a (1,1,1,2-tetrafluoroethane)/actuation); 100 µg of TAA ex valve. 100 actuations per canister, 15 mg TAA/canister,

ROUTE OF ADMINISTRATION:**DISPENSED:**

nasal inhalation
 Rx OTC

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

Triamcinolone Acetonide

(11β,16α)-9-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione

Molecular Formula: C₂₄H₃₁FO₆ Molecular Weight: 434.51

SUPPORTING DOCUMENTS:

Drug Master Files:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review
Type II			Adequate	4/12/96	p. 7
Type III			Inadequate	2/26/97 (Stamp 3/6/97)	p. 55
Type I, III			Inadequate	2/21/97	p. 54
Type III			Adequate	1/17/97	p. 16
Type V				not reviewed	
Type III			Inadequate	2/19/97	p. 54
Type III			Adequate	10/4/96	p. 55
Type III			Adequate	2/19/97	p. 55

RELATED DOCUMENTS:

- NDA 18-117 Azmacort® Oral Inhaler
- IND 26,171 Nasacort® Nasal Inhaler
- IND 39,306 Nasacort® AQ Nasal Spray
- IND 43,841 Nasacort® HFA Nasal
- NDA 19-798 Nasacort® Nasal Inhaler
- NDA 20-468 Nasacort® AQ Nasal Spray

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	1/18/97	Pending	
Microbiology	2/19/97	Pending	For evaluation of the microbiological test methods.
Biometrics	Not forwarded		Pending updated stability data from firm.
Pharmacology: a) drug product impurities; b) CCS extractives levels and specifications.	a) 2/19/97 b) Not forwarded	a) Pending	a) For evaluation of drug product impurities. b) Pending submission of data from applicant (see pp. 69, 70 of review)
Methods Validation	Not forwarded to agency labs.		Pending resolution of method issues by the firm.
Environmental Assessment	Not forwarded for concurrence.		EA review will be done separately and comments will be forwarded to firm at a later time (see p. 104).
Labeling & Nomenclature	Not forwarded.		A final tradename has not been proposed yet (see v1.7, p. 4-1-516).

REMARKS/COMMENTS: For remarks and comments, see p. 5

CONCLUSIONS & RECOMMENDATIONS: The application as amended is not approvable from the standpoint of chemistry, manufacturing, and controls. Deficiencies (CMC) are detailed in the accompanying review notes and summarized in the attached draft letter to the applicant. These deficiencies should be promptly forwarded to the applicant.

cc:

Orig. NDA 20-784
 HFD-570/Division File
 HFD-570/CBertha/4/3/97
 HFD-570/SBarnes
 HFD-570/GPoochikian
 HFD-570/CKwong
 HFD-570/VWhitehurst
 HFD-570/T-MChen
 R/D Init by: SRV/9/97
 filename: 96-12-16.kev


 Craig M. Bertha, Ph.D. Review Chemist

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Deliberative Process