

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202813Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 202813/000
Submission Date: 24-MAY-2011
Regulatory: 24-MAR-2012

Action Goal:
District Goal: 24-JAN-2012

Applicant: TEVA BRANDED PHARM
74 NORTHWEST 176TH ST
MIAMI, FL 33169

Brand Name: Beclomethasone Dipropionate Nasal Aerosol
Estab. Name:
Generic Name:

Priority: 3
Org. Code: 570

Product Number; Dosage Form; Ingredient; Strengths
001; AEROSOL; BECLOMETHASONE DIPROPIONATE; 80MCG

Application Comment:

| | | | | |
|----------------------|---------------|-----------------|---------|------------|
| FDA Contacts: | S. PATWARDHAN | Project Manager | (HF-01) | 3017964085 |
| | C. BERTHA | Review Chemist | | 3017961646 |
| | A. SCHROEDER | Team Leader | | 3017961749 |

| | | | | | |
|--------------------------------|------------|----------------|-------------|-----------|------------|
| Overall Recommendation: | ACCEPTABLE | on 03-FEB-2012 | by M. STOCK | (HFD-320) | 3017964753 |
| | PENDING | on 13-JUN-2011 | by EES_PROD | | |

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 2010441 FEI: 2010441
3M DRUG DELIVERY SYSTEMS

19901 NORDHOFF ST
NORTHRIDGE, CA 913243213

DMF No: (b) (4) **AADA:**

Responsibilities: (b) (4)
FINISHED DOSAGE MANUFACTURER

Establishment Comment: 3M SITE LOCATED IN MAPI FWOOD, MN IS RESPONSIBLE FOR QUALITY CONTROL TESTING OF (b) (4)
(on 13-JUN-2011 by S. PATWARDHAN (HF-01) 3017964085)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

| <u>Milestone Name</u> | <u>Milestone Date</u> | <u>Request Type</u> | <u>Planned Completion</u> | <u>Decision</u> | <u>Creator</u> |
|--|-----------------------|---------------------|---------------------------|-----------------|----------------|
| <u>Comment</u> | | | | <u>Reason</u> | |
| SUBMITTED TO OC | 13-JUN-2011 | | | | PATWARDHAN |
| SUBMITTED TO DO | 17-JUN-2011 | 10-Day Letter | | | STOCKM |
| ASSIGNED INSPECTION TO IB | 30-AUG-2011 | Product Specific | | | CEVERLY |
| INSPECTION TO BE PERFORMED DURING PRODUCT SPECIFIC PAI FOR ANOTHER APPLICATION. | | | | | |
| INSPECTION SCHEDULED | (b) (4) | | | | CEVERLY |
| INSPECTION PERFORMED | (b) (4) | | | | CEVERLY |
| DO RECOMMENDATION | 02-FEB-2012 | | | ACCEPTABLE | CEVERLY |
| A PRODUCT SPECIFIC PRE-APPROVAL INSPECTION WAS PERFORMED (b) (4) THE INSPECTION INSPECTION WAS CLASSIFIED VAI. THERE WERE NO OBSERVATIONS SPECIFIC TO THIS PRODUCT/APPLICATION THEREFORE LOS-DO RECOMMENDS THAT THIS SITE IS ACCEPTABLE. | | | | | |
| CARYN MCNAB, PRE-APPROVAL MANAGER | | | | | |
| OC RECOMMENDATION | 03-FEB-2012 | | | ACCEPTABLE | STOCKM |
| DISTRICT RECOMMENDATION | | | | | |

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: (b) (4)

AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment
Comment:

Profile: CONTROL TESTING LABORATORY

OAI Status: NONE

| <u>Milestone Name</u> | <u>Milestone Date</u> | <u>Request Type</u> | <u>Planned Completion</u> | <u>Decision</u> | <u>Creator</u> |
|-----------------------|-----------------------|---------------------|---------------------------|--------------------------------|----------------|
| <u>Comment</u> | | | | <u>Reason</u> | |
| SUBMITTED TO OC | 13-JUN-2011 | | | | PATWARDHAN |
| OC RECOMMENDATION | 17-JUN-2011 | | | ACCEPTABLE BASED ON PROFILE | STOCKM |

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9612162 FEI: 3002807777

IVAX PHARMACEUTICALS IRELAND
UNIT 301 WATERFORD IND. ESTATE
WATERFORD, , IRELAND

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: TEVA PHARMACERUTICALS IRELAND (AKA IVAX PHARMACEUTICALS IRELAND) IS RESPONSIBLE FOR ASSEMBLY OF CANISTER WITH ACTUATOR, FINAL PACKAGING, RELEASE AND STABILITY TESTING. THE FEI NUMBER PROVIDED BY THE APPLICANT IS 3003702580 (on 13-JUN-2011 by S. PATWARDHAN (HF-01) 3017964085)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

| <u>Milestone Name</u> | <u>Milestone Date</u> | <u>Request Type</u> | <u>Planned Completion</u> | <u>Decision</u> | <u>Creator</u> |
|-----------------------|-----------------------|---------------------|---------------------------|--------------------------------|----------------|
| <u>Comment</u> | | | | <u>Reason</u> | |
| SUBMITTED TO OC | 13-JUN-2011 | | | | PATWARDHAN |
| OC RECOMMENDATION | 15-JUN-2011 | | | ACCEPTABLE BASED ON PROFILE | STOCKM |

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: QUALITY CONTROL TESTING OF BULK FILLED CANISTERS (RELEASE AND STABILITY) (on 07-JUN-2011 by S. PATWARDHAN (HF-01) 3017964085)
Profile: CONTROL TESTING LABORATORY OAI Status: NONE

| <u>Milestone Name</u> | <u>Milestone Date</u> | <u>Request Type</u> | <u>Planned Completion</u> | <u>Decision</u> | <u>Creator</u> |
|-----------------------|-----------------------|---------------------|---------------------------|--------------------------------|----------------|
| <u>Comment</u> | | | | <u>Reason</u> | |
| SUBMITTED TO OC | 13-JUN-2011 | | | | PATWARDHAN |
| OC RECOMMENDATION | 15-JUN-2011 | | | ACCEPTABLE BASED ON PROFILE | STOCKM |

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

App No: NDA 202813/000
Orphan #: 570
Priority: 3
Stamp Date: 24-MAY-2011
PDUFA Date: 24-MAR-2012
Action Goal:
District Goal: 24-JAN-2012

Sponsor: TEVA BRANDED PHARM
 74 NORTHWEST 176TH ST
 MIAMI, FL 33169
Brand Name: Beclomethasone Dipropionate Nasal Aerosol
Estab. Name:
Generic Name:
Product Number; Dosage Form; Ingredient; Strengths
 001; AEROSOL; BECLOMETHASONE DIPROPIONATE; 80MCG

| | | | | |
|----------------------|---------------|-----------------|---------|------------|
| FDA Contacts: | S. PATWARDHAN | Project Manager | (HF-01) | 3017964085 |
| | C. BERTHA | Review Chemist | | 3017961646 |
| | A. SCHROEDER | Team Leader | | 3017961749 |

| | | | | | |
|--------------------------------|------------|----------------|-------------|-----------|------------|
| Overall Recommendation: | ACCEPTABLE | on 03-FEB-2012 | by M. STOCK | (HFD-320) | 3017964753 |
| | PENDING | on 13-JUN-2011 | by EES_PROD | | |

Establishment: **CFN:** 2010441 **FEI:** 2010441
 3M DRUG DELIVERY SYSTEMS

DMF No: NORTHBRIDGE, , UNITED STATES 913243213
 (b) (4)

AADA:

Responsibilities: (b) (4)
 FINISHED DOSAGE MANUFACTURER

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-FEB-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: [REDACTED] **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-JUN-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: 9612162 FEI: 3002807777

IVAX PHARMACEUTICALS IRELAND
UNIT 301 WATERFORD IND. ESTATE
WATERFORD, , IRELAND

DMF No: [REDACTED] **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-JUN-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: [REDACTED] **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-JUN-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

E: ment: **CFN:** 9610201 **FEI:** 3002808174

SICOR S.P.A. (SOCIETA ITALIANA CORTICOSTEROIDI)
VIA TERRAZZANO 77

DMF No: RHO (MILAN), , ITALY **AADA:**
4871

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-JUN-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC
HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 06-FEB-2012

TO: N202813 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

THROUGH: Prasad Peri, Ph.D.
Branch Chief
ONDQA, Division III, Branch VIII



SUBJECT: Consult Status, EES Status, and Final CMC recommendation

SUMMARY: The 09-NOV-2011, review of N202813 concluded that the application was recommended for approval. However, at that time there was an outstanding consult for the foreign particulate risk assessment with the pharmacology/toxicology team. And in addition, the recommendation from the Office of Compliance in the Establishment Evaluation System was pending. Thus, the CMC recommendation did not incorporate any potential facility inspection issues.

On 10-NOV-2011, the pharmacology/toxicology team filed a consult review regarding the foreign particulate risk assessment provided by the applicant. Based on information already reviewed in support of the applicant's QVAR inhalation aerosol drug product, and considering that the same canister/valve/formulation for that application is being used for the QNASL nasal aerosol drug product, the pharmacology/toxicology team deemed it unnecessary to conduct any additional review regarding foreign particulates.

On 03-FEB-2012, the Office of Compliance updated the EES with a recommendation of ACCEPTABLE for the application.

RECOMMENDATION: From the CMC perspective, it is recommended that the application be approved.

Craig M. Bertha, Ph.D.
Chemist

cc:

OND/DPARP/CHill

ONDQA/DIV 3/CBertha/2/6/12

ONDQA/DIV 3/PPeri

ONDQA/DIV3/ASchroeder

ONDQA/DIV/SSuarez

ONDQA/DIV 3/SPatwardhan

OND/DPARP/XWang

OCP/DCPII/AAgrawal

OND/DPARP/LPei

OTS/OB/DBII/KHamilton

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/s/

CRAIG M BERTHA
02/06/2012

PRASAD PERI
02/06/2012
I concur

NDA 202813

QNASL™ (beclomethasone dipropionate) Nasal Aerosol

Teva Branded Pharmaceutical Products R&D, Inc.

Craig M. Bertha, Ph.D.
ONDQA/DNDQA III/Branch VIII for
Division of Pulmonary, Allergy, and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA 202813
2. REVIEW #: 2
3. REVIEW DATE: 07-NOV-2011
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

| <u>Previous Documents</u> | <u>Document Date</u> |
|---------------------------|--|
| Original | 24-MAY-2011 (assigned 27-MAY-2011) |
| Amendment | 02-AUG-2011 (requested drug product samples) |
| Amendment | 04-AUG-2011 (response to 12-JUL-2011, IR) |

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|-------------------------------|--|
| Amendment | 15-SEP-2011 (18 month stability update) |
| Amendment | 06-OCT-2011 (acknowledgement of (b) (4) amendment) |
| Amendment | 27-OCT-2011 (response to DR of 09-SEP-2011) |

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Branded Pharmaceutical Products R&D, Inc.
Address: 74 NW 176th Street
Miami, FL 33169
Representative: William Kiddell, Sr., Manager, Regulatory Affairs, GRR&D
Telephone: (305)-575-6284

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

- a) Proprietary Name: QNASL
b) Non-Proprietary Name (USAN): beclomethasone dipropionate
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: glucocorticosteroid

11. DOSAGE FORM: nasal aerosol

12. STRENGTH/POTENCY: 80 mcg/actuation

13. ROUTE OF ADMINISTRATION: nasal inhalation

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

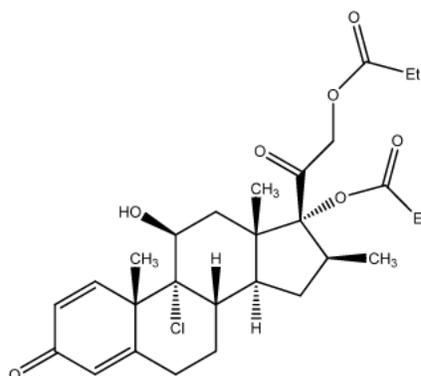
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular Formula: C₂₈H₃₇ClO₇

Molecular Weight: 521.05 g/mol

Chemistry Review Data Sheet



Beclomethasone Dipropionate

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS ³ |
|---------|------|------------|-----------------|-------------------|---------------------|-----------------------|---|
| (b) (4) | 2 | [REDACTED] | (b) (4) | 3 | Adequate | 27-AUG-2010 | |
| | 3 | | | 4 | | | Reference to approved S-019 of applicant's NDA 20911 (identical canister) |
| | 3 | | | 1 | Adequate | 23-AUG-2011 | |
| | 3 | | | 1 | Adequate | 23-AUG-2011 | |
| | 3 | | | 1 | | 13-JUL-2011 | |
| | | | | | Adequate | 03-NOV-2011 | |
| | 4 | | | 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 is enough data in the application, therefore the DMF did not need to be reviewed)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Chemistry Review Data Sheet

| Doc # | OWNER | ITEM REFERENCED | STATUS | DATE REVIEW COMPLETED | COMMENTS |
|------------------|---|---|----------|-----------------------|------------------------------|
| NDA 20911, S-019 | Teva Branded Pharmaceutical Products R&D Inc. | The formulation, canister, valve, and manufacturing process and controls are the same for the current nasal aerosol as for the analogous components of the applicants QVAR Inhalation Aerosol of NDA 20911 ¹ | Approved | 29-NOV-2010 | Approval granted 03-DEC-2010 |
| | | | | | |
| | | | | | |

C. Related Documents:

| DOCUMENT | APPLICATION NUMBER | OWNER | DESCRIPTION/COMMENT |
|----------|--------------------|---------------------------------------|--|
| IND | 101639 | Teva Branded Pharmaceuticals R&D Inc. | beclomethasone dipropionate nasal aerosol for seasonal and perennial allergic rhinitis |
| | | | |
| | | | |
| | | | |

18. CONSULTS/CMC-RELATED REVIEWS:

| CONSULTS | SUBJECT | DATE FORWARDED | STATUS/ REVIEWER | COMMENTS |
|--------------------|---|----------------|-----------------------|---|
| Biometrics | N/A | | | |
| EES | | 13-JUN-2011 | Pending | |
| Pharm/Tox | Foreign Particulate acceptance criteria | 07-NOV-2011 | Pending/L. Pei, Ph.D. | New toxicological review and risk assessment of particulate matter provided in 27-OCT-2011, amendment |
| LNC | N/A | | | |
| Methods Validation | N/A | | | |
| OPDRA | N/A | | | |
| EA | N/A | | | |
| Microbiology | N/A | | | |

¹ Teva provides authorization to cross reference the QVAR® Inhalation Aerosol application of NDA 20911 for the review of NDA 202813.

The Chemistry Review for NDA 202813

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval. However, there is currently an outstanding consult for the foreign particulate risk assessment with the pharmacology/toxicology team. Depending on the outcome of that consult, there may need to be additional CMC related changes regarding drug product foreign particulate controls. In addition, the current recommendation from the Office of Compliance in the Establishment Evaluation System is pending. Thus, the CMC recommendation does not incorporate any potential facility inspection issues.

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

None at this time.

II. Summary of Chemistry Assessments

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

The drug product QNASL (beclomethasone dipropionate) Nasal Aerosol delivers 80 mcg of drug in 59 mg of formulation per actuation. The drug product is a non-sterile, solution nasal aerosol propelled with HFA-134a propellant and includes (b) (4) ethanol (b) (4) for the beclomethasone dipropionate (BDP). It is designed to deliver 120 actuations and has a target fill of (b) (4). The nasal actuator incorporates a counter which counts down from 120 to 0 after four priming actuations (initial counter reading 124). The drug product does not include any additional protective packaging. The drug product filled canisters are manufactured using the same formulation, manufacturing process, and at the same facility, with the same canister and valve as that for the currently marketed product, QVAR of NDA 20911. The drug product is intended to be indicated for the treatment of seasonal and perennial allergic rhinitis.

The BDP drug substance is a glucocorticosteroid that has a retest date of (b) (4). As the drug product formulation is a solution, the physical properties of the drug substance play a limited role in the performance of the drug product. The solution formulation is (b) (4).

Twelve months of long

term stability data have been provided for three batches of the 120 count drug product which supports the proposed **24 month expiration dating period**. It is noted that the related approved QVAR application currently has a 24 month expiration dating period. The clinical trials were carried out with the 120 count product, but there was also a 100 count version (only difference is lower fill volume) that was also used. Stability data have been provided for the 100 count product as well as a bioequivalence report that is said to demonstrate comparability with the to-be-marketed 120 count version (bioequivalence study report under review by the ONDQA biopharmaceutics reviewer).

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

The recommended dose for children 12 years and older and adults is 2 sprays (80 mcg BDP each) in each nostril once a day, for a total daily dose of 320 mcg. Thus, the 120 count drug product can be expected to be used for a maximum of 30 days (less for SAR where repriming may be necessary).

C. Basis for Approvability or Not-Approval Recommendation

N/A, see caveats in I.A above.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./Date: 07-NOV-2011
Prasad Peri, Ph.D.

C. CC Block

OND/DPARP/XWang
OCP/DCPII/AAgrawal
OND/DPARP/LPei
OND/DPARP/CHill
ONDQA/SPatwardhan
ONDQA/Biopharm/SSuarez
ONDQA/DNDCAIII/ASchroeder
OTS/OB/DBII/KHamilton

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/s/

CRAIG M BERTHA
11/07/2011

PRASAD PERI
11/09/2011
I concur

NDA 202813

QNASL™ (beclomethasone dipropionate) Nasal Aerosol

Teva Branded Pharmaceutical Products R&D, Inc.

Craig M. Bertha, Ph.D.
ONDQA/DNDQA III/Branch VIII for
Division of Pulmonary, Allergy, and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA 202813
2. REVIEW #: 1
3. REVIEW DATE: 23-AUG-2011
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

| <u>Previous Documents</u> | <u>Document Date</u> |
|---------------------------|----------------------|
| N/A | |

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|-------------------------------|--|
| Original | 24-MAY-2011 (assigned 27-MAY-2011) |
| Amendment | 02-AUG-2011 (requested drug product samples) |
| Amendment | 04-AUG-2011 (response to 12-JUL-2011, IR) |

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Branded Pharmaceutical Products R&D, Inc.
Address: 74 NW 176th Street
Miami, FL 33169
Representative: William Kiddell, Sr., Manager, Regulatory Affairs, GRR&D
Telephone: (305)-575-6284

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: QNASL
- b) Non-Proprietary Name (USAN): beclomethasone dipropionate

Chemistry Review Data Sheet

- c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: glucocorticosteroid

11. DOSAGE FORM: nasal aerosol

12. STRENGTH/POTENCY: 80 mcg/actuation

13. ROUTE OF ADMINISTRATION: nasal inhalation

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

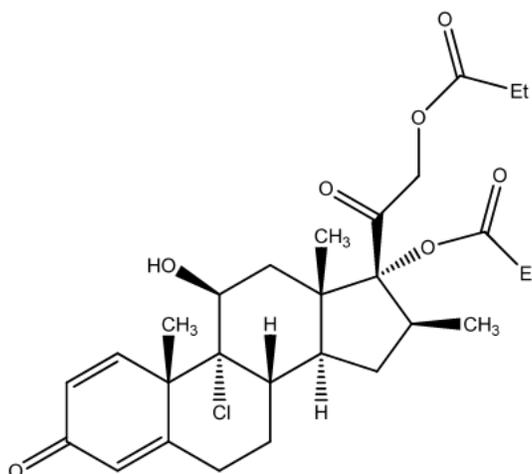
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular Formula: C₂₈H₃₇ClO₇

Molecular Weight: 521.05 g/mol

Chemistry Review Data Sheet



Beclomethasone Dipropionate

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS ³ |
|---------|------|--------|-----------------|-------------------|---------------------|-----------------------|---|
| (b) (4) | 2 | | (b) (4) | 3 | Adequate | 27-AUG-2010 | |
| | 3 | | | 4 | | | Reference to approved S-019 of applicant's NDA 20911 (identical canister) |
| | 3 | | | 1 | Adequate | 23-AUG-2011 | |
| | 3 | | | 1 | Adequate | 23-AUG-2011 | |
| | 3 | | | 1 | Inadequate | 13-JUL-2011 | |
| | 4 | | | | | | |
| | | | | | 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 is enough data in the application, therefore the DMF did not need to be reviewed)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Chemistry Review Data Sheet

| Doc # | OWNER | ITEM REFERENCED | STATUS | DATE REVIEW COMPLETED | COMMENTS |
|------------------|---|---|----------|-----------------------|------------------------------|
| NDA 20911, S-019 | Teva Branded Pharmaceutical Products R&D Inc. | The formulation, canister, valve, and manufacturing process and controls are the same for the current nasal aerosol as for the analogous components of the applicants QVAR Inhalation Aerosol of NDA 20911 ¹ | Approved | 29-NOV-2010 | Approval granted 03-DEC-2010 |
| | | | | | |
| | | | | | |

C. Related Documents:

| DOCUMENT | APPLICATION NUMBER | OWNER | DESCRIPTION/COMMENT |
|----------|--------------------|---------------------------------------|--|
| IND | 101639 | Teva Branded Pharmaceuticals R&D Inc. | beclomethasone dipropionate nasal aerosol for seasonal and perennial allergic rhinitis |
| | | | |
| | | | |
| | | | |

18. CONSULTS/CMC-RELATED REVIEWS:

| CONSULTS | SUBJECT | DATE FORWARDED | STATUS/ REVIEWER | COMMENTS |
|--------------------|---------|----------------|------------------|----------|
| Biometrics | N/A | | | |
| EES | | 13-JUN-2011 | Pending | |
| Pharm/Tox | N/A | | | |
| LNC | N/A | | | |
| Methods Validation | N/A | | | |
| OPDRA | N/A | | | |
| EA | N/A | | | |
| Microbiology | N/A | | | |

¹ Teva provides authorization to cross reference the QVAR® Inhalation Aerosol application of NDA 20911 for the review of NDA 202813.

The Chemistry Review for NDA 202813

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is **approvable**. The deficiencies outlined in the attached draft letter need to be addressed and resolved by the application before an approval recommendation can be made. **It is requested that the PM send the comments in the attached draft letter in a CMC discipline review letter.**

A request for methods validation for the Agency laboratories will not be made for this application. It is also noted that an establishment evaluation request has been forwarded to the Office of Compliance and currently the recommendation is PENDING.

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

None at this time.

II. Summary of Chemistry Assessments

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

The drug product QNASL (beclomethasone dipropionate) Nasal Aerosol delivers 80 mcg of drug in 59 mg of formulation per actuation. The drug product is a non-sterile, solution nasal aerosol propelled with HFA-134a propellant and includes (b) (4) ethanol (b) (4) for the beclomethasone dipropionate (BDP). It is designed to deliver 120 actuations and has a target fill of (b) (4). The nasal actuator incorporates a counter which counts down from 120 to 0 after four priming actuations (initial counter reading 124). The drug product does not include any additional protective packaging. The drug product filled canisters are manufactured using the same formulation, manufacturing process, and at the same facility, with the same canister and valve as that for the currently marketed product, QVAR of NDA 20911. The drug product is intended to be indicated for the treatment of seasonal and perennial allergic rhinitis.

The BDP drug substance is a glucocorticosteroid that has a retest date of (b) (4). As the drug product formulation is a solution, the physical properties of the drug substance play a limited role in the performance of the drug product. The solution formulation is (b) (4).

(b) (4)

Twelve months of long term stability data have been provided for three batches of the 120 count drug product which supports the proposed (b) (4) expiration dating period proposed. It is noted that the related approved QVAR application currently has a 24 month expiration dating period. The clinical trials were carried out with the 120 count product, but there was also a 100 count version (only difference is lower fill volume) that was also used. Stability data have been provided for the 100 count product as well as a bioequivalence report that is said to demonstrate comparability with the to-be-marketed 120 count version (bioequivalence study report under review by the ONDQA biopharmaceutics reviewer).

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

The recommended dose for children 12 years and older and adults is 2 sprays (80 mcg BDP each) in each nostril once a day, for a total daily dose of 320 mcg. Thus, the 120 count drug product can be expected to be used for a maximum of 30 days (less for SAR where repriming may be necessary).

C. Basis for Approvability or Not-Approval Recommendation

The application is currently not recommended for approval based on the deficiency comments outlined in the attached letter. It is expected that the applicant will be able to address and resolve these deficiencies such that an approval recommendation can be made in the future.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./Date: 23-AUG-2011
Prasad Peri, Ph.D.

C. CC Block

OND/DPARP/XWang
OCP/DCPII/AAgrawal
OND/DPARP/LPei
OND/DPARP/CHill
ONDQA/SPatwardhan
ONDQA/Biopharm/SSuarez
ONDQA/DNDCAIII/ASchroeder
OTS/OB/DBII/KHamilton

101 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CRAIG M BERTHA
08/23/2011

PRASAD PERI
08/30/2011
I concur

**MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC
HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 28-JUN-2011

TO: N202813 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

THROUGH: Prasad Peri, Ph.D.
Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: CMC filing memorandum



SUMMARY: The application from Teva Branded Pharmaceuticals R&D Inc. is for QNASL (beclomethasone dipropionate) Nasal Aerosol to be used for the treatment of seasonal and perennial allergic rhinitis. The nasal aerosol has a target or label claim delivery of 80 mcg of drug substance per actuation. The formulation, canister, valve, and the manufacturing process and controls for the filled canisters are identical to that for the 80 mcg/actuation 120 count QVAR (beclomethasone dipropionate) Inhalation Aerosol as recently approved in S-019 of NDA 20911. Note that Teva Branded Pharmaceutical Products R&D, Inc., has all rights to NDA 20911 as they are now the holder of that application. Therefore, the majority of the CMC review of NDA 202813, will involve the evaluation of the container closure components specifically associated with the nasal aerosol, and the performance associated with its combination with the filled canisters. (b) (4)

Furthermore, the approval of the 120 count QVAR Inhalation Aerosol via S-019 of NDA 20911 involved a comparison to the 80 mcg/actuation 100 count QVAR Inhalation Aerosol, which is important as the current phase 3 clinical studies used both of these canister fills. See P.2 for a detailed evaluation of the progression of the product configuration during the development and the studies provided for bridging. The bridging studies provided follow the approach outlined in the Agency draft biopharmaceutics guidance for establishment of BA/BE for nasal sprays and nasal aerosols.¹ The ONDQA biopharmaceutics team has been made aware of these studies which are intended to support a bridge of the 100 count and the to-be-marketed 120 count drug product versions used in the phase 3 studies.

The NDA 202813 is in eCTD format. The majority of the information for the drug substance is referenced to DMF (b) (4) (LOA provided) and this has recently been reviewed in support of the applicant's approved NDA 20911 for QVAR Inhalation Aerosol. The ONDQA PM has

¹ See draft *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003).

submitted the EES request on 13-JUN-2011, for all of the sites to the Office of Compliance, and the recommendation is PENDING.

Teva is requesting a categorical exclusion from the requirement for submitting an environmental assessment. Approval of the application will increase the use of the active moiety, but the applicant claims that they have performed calculations that estimate the concentration of the drug in the aquatic environment due to both QVAR and the QNASL products to be below 1 ppb, so that the preparation and inclusion of an environmental assessment is not required.

The application includes a complete section for the drug product in the CTD format, as well as letters of authorization to allow the Agency to review type III and IV DMFs for the container closure system and formulation components, respectively.

| | Parameter | Yes | No | Comment |
|----|---|------------|-----------|---|
| 1 | On its face, is the section organized adequately? | X | | eCTD format |
| 2 | Is the section indexed and paginated adequately? | X | | |
| 3 | On its face, is the section legible? | X | | |
| 4 | Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs? | X | | |
| 5 | Is a statement provided that all facilities are ready for GMP inspection? | | X | PM has submitted EES request to OC on 13-JUN-2011 |
| 6 | Has an environmental assessment report or categorical exclusion been provided? | X | | |
| 7 | Does the section contain controls for the drug substance? | X | | Majority of drug substance information provided by reference to DMF (b) (4) and NDA 20911 |
| 8 | Does the section contain controls for the drug product? | X | | |
| 9 | Have stability data and analysis been provided to support the requested expiration date? | X | | Twelve months long term and 6 months accelerated data provided for 3 batches; Note that product does not include protective packaging |
| 10 | Has all information requested during the IND phase, and at the pre-NDA meetings been included? | X | | Note that the applicant has not included the (b) (4) of the drug in the current application as originally planned |
| 11 | Have draft container labels been provided? | X | | The proposed trademark (Qnasl) is not yet included on the labels |
| 12 | Has the draft package insert been provided? | X | | |
| 13 | Has an investigational formulations section been provided? | | X | Drug product formulation development is outlined in P.2, however |
| 14 | Is there a Methods Validation package? | X | | |
| 15 | Is a separate microbiological section included? | | X | There is a discussion of the microbiological aspects in P.2 |
| 16 | Have all DMF References been identified? | X | | |

RECOMMENDATION: From the CMC perspective, the application is sufficiently complete to recommend that it be filed. There are no comments from the CMC team for the 74 day letter.

COMMENTS FOR 74-DAY LETTER:

N/A

Craig M. Bertha, Ph.D.
Chemist

cc:
OND/DPARP/CHill
ONDQA/DIV 3/CBertha/28-JUN-2011
ONDQA/DIV 3/PPeri
ONDQA/DIV3/ASchroeder
ONDQA/DIV/SSuarez
ONDQA/DIV 3/SPatwardhan

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CRAIG M BERTHA
06/28/2011

PRASAD PERI
06/28/2011
I concur