# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022560Orig1s000

# <u>CHEMISTRY REVIEW(S)</u>

# Memorandum

To: CMC Review # 1 of NDA 22-560

From: Caroline Strasinger, Ph.D.
DNDQA II/ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Branch Chief/DNDQA II/ONDQA

Date: 23-Jul-2010

Re: Updating packaging and manufacturer information

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The applicant has submitted amendment 0021 on 19-JUL-2010 regarding packaging and manufacturing information.

(b) (4)

- The distribution center for the drug product has been changed to:
  (b) (4)

- The following alternate testing facility has been removed:
  (b) (4)

**This amendment does not require any changes in EES and does not affect the previous CMC recommendation of "Approval" noted in the Review #1 dated 28-JUN-2010.**

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22560 | ORIG-1 | WARNER CHILCOTT CO LLC | (b) (4) |

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/s/

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CAROLINE STRASINGER
07/28/2010

MOO JHONG RHEE
07/28/2010
Chief, Branch IV

# Memorandum

To: CMC Review # 1 of NDA 22-560

From: Caroline Strasinger, Ph.D.
DNDQA II/ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Branch Chief/DNDQA II/ONDQA

Date: 07-Jul-2010

Re: Updated Labeling

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The applicant has submitted amendment 0018 on 29-JUN-2010, in response to the 74-day letter regarding NDC numbers as well as a change in the proprietary name from (b) (4) to ATELVIA. In the 74-day letter it was requested that the sponsor update the container labels with NDC numbers and ensure that they correspond with NDC numbers listed in the package insert. The sponsor responded that all labeling artwork would be updated during the review of the application to contain the NDC numbers. Additionally, the originally proposed name (b) (4) was not accepted by DMEPA, and as such was revised to ATELVIA. The updated carton with the accepted name of ATELVIA was presented in this amendment. (b) (4) ; only the 1 count sample and 4 count trade dosepack are to be utilized commercially.

The carton has been updated with the correct NDC numbers, and the new artwork featuring the name ATELVIA is acceptable. The updated carton and the trade and sample dosepacks can be seen below.

**This updated labeling information does not affect the previous CMC recommendation of "Approval" noted in the Review #1 dated 28-JUN-2010.**

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22560 | ORIG-1 | WARNER CHILCOTT CO LLC | (b) (4) |

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CAROLINE STRASINGER
07/07/2010

MOO JHONG RHEE
07/07/2010
Chief, Branch IV

# NDA 22-560

## ATELVIA
## (risedronate sodium) delayed-release tablet

## Procter & Gamble Pharmaceuticals, Inc.

**Caroline Strasinger, Ph.D.**
**Branch IV**
**DNDQA II/ONDQA**

## CMC Review for
## Division of Reproductive and Urological Products

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# Chemistry Review Data Sheet

1. NDA 22-560

2. REVIEW #: #1

3. REVIEW DATE: 28-JUN-2010

4. REVIEWER: Caroline Strasinger, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| N/A | |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 24-SEP-2009 |
| Amendment 0006 | 8-FEB-2010 |
| Amendment 0007 | 11-FEB-2010 |
| Amendment 0008 | 25-FEB-2010 |
| Amendment 0010 | 23-APR-2010 |
| Amendment 0015 | 28-MAY-2010 |
| Amendment 0016 | 22-JUN-2010 |

7. NAME & ADDRESS OF APPLICANT:

Name: Warner Chilcott Pharmaceuticals Inc. (Formerly Proctor & Gamble Pharmaceuticals Inc.)

Address: Mason Business Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Representative: Gary F Galletta PharmD

Telephone: 513-622-4952

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ATELVIA
b) Non-Proprietary Name (USAN): (risedronate sodium) delayed-release tablets
c) Code Name/#: NE-58095
d) Chem. Type/Submission Priority:
- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: For treatment [redacted] (b) (4) of postmenopausal osteoporosis [redacted] (b) (4)

11. DOSAGE FORM: delayed-release tablet

12. STRENGTH/POTENCY: 35mg risedronate sodium per tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

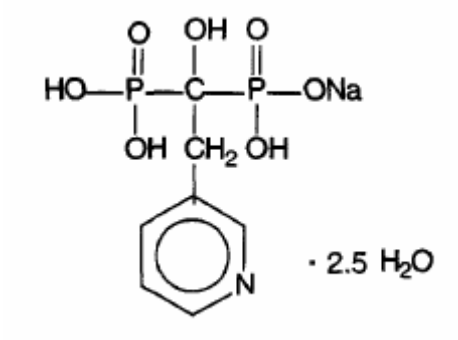
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

**Risedronate sodium:**
[1-hydroxy-2-(3-pyridinyl)[ethylidene]bis[phosphonic acid] monosodium salt
MW = 305.10 g/mole (anhydrous), MW =350.13 (hemi-pentahydrate), MW = 323.11 g/mole (monohydrate)




## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| (b) (4) | III | (b) (4) | (b) (4) | 3 | Adequate | 12/07/2009 | Dr. Y. Tang for (b) (4) |
| | III | (b) (4) | | 3 | Adequate | 02/18/2010 | Dr. C. Strasinger for NDA 22-560 |
| | III | (b) (4) | | 3 | Adequate | 03/13/2008 | Dr. H. Jung for (b) (4) |

[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)

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| IND | 31,029 | ACTONEL Capsule |
| IND | 74,086 | (b) (4) |
| IND | (b) (4) | |
| NDA | 20-835 | ACTONEL |

## 18. STATUS:

**ONDQA:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | N/A | | |
| EES | Acceptable | 5/1/10 | Office of Compliance |
| Pharm/Tox | N/A | | |
| Biopharm | Dissolution specification is satisfactorily revised. | 4/12/10 | Sandra Suarez |
| LNC | N/A | | |
| Methods Validation | To be done per ONDQA's policy | | |
| DMEPA | N/A | | |
| EA | Claim for categorical exclusion is granted | 4/6/10 | |
| Microbiology | N/A | | |

# The Chemistry Review for NDA 22-560

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

An overall "Acceptable" recommendation has been made by the Office of Compliance.

All labels and labeling(Description and How Supplied sections) have the required information

Therefore, from the CMC perspective, this NDA is recommended for approval.

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

None

## II. Summary of Chemistry Assessments

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

**Drug product:**
ATELVIA (risedronate sodium) is a yellow, delayed-release, enteric coated tablet containing 35mg of drug substance on an anhydrous basis (equivalent to 32.48 mg of risedronic acid). It is oval in shape with one face engraved with "EC 35." The tablets are manufactured by **Norwich Pharmaceuticals in North Norwich, NY** while **Proctor and Gamble Pharmaceuticals Inc.** is responsible for the final release of the product. Several additional companies have been listed as excipient testing and packaging facilities, all of which are domestic.

The delayed release tablet is formulated to minimize the interaction of risedronate sodium with [redacted] (b) (4), found in food. Drug release is controlled with a 5.5 pH trigger methacrylic acid copolymer [redacted] (b) (4). An additional competitive chelating agent [redacted] (b) (4) EDTA) [redacted] (b) (4)

The quality of the tablets is controlled by tests for description, identification of risedronate sodium, content uniformity, assay, dissolution and degradation

products. No impurity specification has been set for the product. This is consistent with the currently approved ACTONEL immediate release tablet. Process impurities are monitored in the drug substance and no degradants have been observed under normal handling and storage. Degradation is monitored for stability, however, not at release because the substance is very stable and the product is manufactured in a way in which it is unlikely to cause formation of degradants.

The tablets are packaged in (b) (4) clear (b) (4) blister with aluminum foil lidding. Each package will contain either one, four (b) (4) tablets. The Applicant is requesting 36 months of expiration dating period, and it is granted after further stability data were updated

**Drug substance:**
No information has been submitted in the application for the drug substance as the drug substance information is unchanged from that previously provided in the approved ACTONEL NDA 20-835. This was previously discussed and agreed upon by the FDA in the Pre-NDA meeting dated May 20, 2009.

For the commercial product, all risedronate sodium drug substance will be sourced from the (b) (4). Annual reports indicate that the drug substance is stable for 48 months, and a 60 month time point for testing has been committed to.

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

ALTEVIA 35mg (risedronate sodium) is an extended-release tablet for once-weekly oral administration. ATELVIA should be taken with water (b) (4) The subject should not lie down for 30 minutes after taking ATELVIA. The product should be stored at room temperature.

## C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for the drug substance and drug product for assuring product quality of drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure the strength, purity and quality of the drug product during the expiration dating period.

An "Acceptable" site recommendation from the Office of Compliance has been made. A minor issue on trade name and labeling is pending (see below), however since the trade name is not CMC purview, this NDA is recommended for APPROVAL.

# III. Administrative

## A. Reviewer's Signature

## B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

## C. CC Block



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| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22560 | ORIG-1 | WARNER CHILCOTT CO LLC | (b) (4) |

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/s/

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CAROLINE STRASINGER
06/28/2010

MOO JHONG RHEE
06/28/2010
Chief, Branch IV

# Initial Quality Assessment
# Branch III
# Pre-Marketing Assessment Division II

| | |
|---|---|
| **OND Division:** | Division of Reproductive and Urologic Products |
| **NDA:** | 22-560 |
| **Applicant:** | Procter & Gamble |
| **Stamp Date:** | 23-Sep-2009 |
| **PDUFA Date:** | 24-Jul-2010 |
| **Trademark:** | (b) (4) |
| **Established Name:** | Risedronate sodium |
| **Dosage Form:** | Delayed release tablet |
| **Route of Administration:** | Oral |
| **Indications:** | Treatment (b) (4) of post-menopausal osteoporosis (b) (4) |
| **PAL:** | Donna F. Christner, Ph.D. |

| | YES | NO |
|---|---|---|
| **ONDQA Fileability:** | X | ☐ |
| **Comments for 74-Day Letter** | X | ☐ |

**Summary and Critical Issues:**

**A. Summary**

The drug product is a yellow, oval-shaped, enteric coated tablet containing 35 mg of risedronate sodium on an anhydrous basis which is equivalent to 32.48 mg of risedronic acid. The tablet is engraved with "EC 35" on one side only. Tablets are packaged in blisters and are available in blister packs of 4 tablets (b) (4) A 36 month expiration dating period is requested.

**B. Critical issues for review**

*For drug substance, the reviewer should consult the reviews dated 27-Feb-2006 by Elsbeth Chikhale and 16-Mar-2007 by Janice Brown to see what changes were agreed to in the referenced supplements.*

*For Microbial Quality, the sponsor has provided data to support the exclusion of this as a routine test. This will require careful review.*

*For Impurities/Degradation products, in addition to review of the submitted data, it may be valuable to see if this test has been deleted on release for the approved NDA 20-835.*

*The sponsor states that the requested 36 month expiry is based on statistical analysis of the submitted data. As per the* ***Guidance for Industry: Q1E Evaluation of Stability Data****, extrapolation of expiration dating period is allowed, but the available data may not be sufficient to allow extrapolation from 18 months to 36 months, especially taking into account the manufacturing site change. The 36 month expiry request will require careful evaluation.*

*In order to qualify the change in manufacturing site, the sponsor has followed the* ***Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changed: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation*** *which recommends at least three months of stability data, a multipoint dissolution comparison of drug product manufactured at the two sites, and a bioequivalence study to be performed. The sponsor has provided the necessary data for review to qualify the site change. The ONDQA Biopharmaceutics group should evaluate the adequacy of the comparative dissolution data to qualify the site change.*

## C. Comments for 74-Day Letter

*We acknowledge that agreement was made in a meeting held on 20-May-2009 that all information on the drug substance could be included in the current NDA by cross-reference to NDA 20-835. However, for the reviewer's convenience and for completeness of the NDA review, we request that a specification table for the drug substance be submitted to NDA 22-560.*

*For Residual Solvents, you state that the tablets have been assessed as per USP/NF <467> Residual Solvents and levels were found to be below the permitted daily exposure. Provide data in support of this conclusion.*

*Update the specification and acceptance criteria for APPEARANCE to identify the imprint used on the tablet.*

*Update the container labels with the NDC numbers. Ensure that it corresponds with the NDC number listed on the Physician's Insert*

*Ensure that the established name on the container/carton labels is at least ½ the size of the proprietary as per 21 CFR 201.10(g)(1).*

*The labeling includes a* (b) (4) *as a manufacturing site, while the application lists only the Norwich Pharmaceutical site. Explain the discrepancy and either remove the* (b) (4) *site from the labeling or add the site to the NDA as a manufacturing site available for inspection.*

*As per 21 CFR 314.50(d)(1)(ii)(c), provide a copy of the proposed Master Batch Record*

## D. Recommendation:

This NDA is fileable from a CMC perspective. There are 7 comments to be conveyed in the 74-day letter. A single reviewer, Caroline Strasinger, Ph.D, has been assigned.

_____

Donna F. Christner, Ph.D.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22560 | ORIG-1 | PROCTER AND GAMBLE PHARMACEUTICALS INC | (b) (4) |

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DONNA F CHRISTNER
12/03/2009

MOO JHONG RHEE
12/04/2009
Chief, Branch III