

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022560Orig1s000**

**OTHER REVIEW(S)**

## CLINICAL REVIEW OF SAFETY LABELING/REMS SUPPLEMENT

**NDA:** 022560 / S001 (labeling)  
022560 / S002 (REMS)

**DRUG:** Risedronate sodium delayed-release, Atelvia tablets

**INDICATION:** Treatment of postmenopausal osteoporosis

**COMPANY:** Warner Chilcott

**DATE OF SUBMISSION:** November 12, 2010

**DATE OF REVIEW:** January 14, 2011

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Warner Chilcott has submitted these supplements to the Atelvia NDA in response to the Agency's Safety Labeling Change and Risk Evaluation and Management Strategy (REMS) request. In a letter dated October 13, 2010, the Division requested the addition of language to the product full prescribing information outlining the possible increased risk of atypical fractures and diaphyseal femoral fractures. The Division also requested additional language to the indications section of the full prescribing information outlining the uncertainty regarding long-term use of bisphosphonate medications.

In addition to the product labeling, a REMS (including a Medication Guide and Timetable for Submission of Assessments) was requested in order to ensure the benefits of the drug outweigh the risks of atypical subtrochanteric and diaphyseal femoral fractures in patients using bisphosphonates for the treatment and/or prevention of osteoporosis.

Each section of the product labeling is discussed below, with the Agency's proposed language (in italics) presented first, followed by the Sponsor's proposed language and then this medical officer's discussion of any proposed changes. The Sponsor's submissions have also been reviewed by the Division of Risk Management, the Division of Medication Error Prevention and Analysis, and the Division of Drug Marketing, Advertising and Communications.

### **1) Highlights of Prescribing Information**

#### Recent Major Changes:

FDA proposed:

- *Indications and Usage (insert date)*
- *Warnings and Precautions (insert date)*

The Sponsor accepted the language as proposed.

Indications and Usage:

FDA proposed:

*The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis.*

The Sponsor accepted the language as proposed.

Warnings and Precautions:

FDA proposed:

*Atypical femur fractures have been reported. Patients with new thigh or groin pain should be evaluated to rule out a femoral fracture*

The Sponsor accepted the language as proposed.

**2) Full Prescribing Information**

INDICATIONS AND USAGE:

FDA proposed:

*1.3 Important Limitations of Use*

*The safety and effectiveness of Atelvia for the treatment of osteoporosis are based on clinical data of one year duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.*

The Sponsor accepted the language as proposed.

WARNINGS AND PRECAUTIONS:

FDA proposed:

*Atypical Subtrochanteric and Diaphyseal Femoral Fractures:*

*Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.*

*Atypical femur fractures most commonly occur with minimal or no (b) (4) to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete*

*fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.*

*Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. (b) (4) presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.*

**Reviewer Comment:** The Sponsor accepted the language as proposed. However, after consideration of all labeling comments received from all sponsors, the Division has accepted three changes to the labeling requested. These changes are:

- 1) Changed the word (b) (4) to “trauma” in the first sentence of the second paragraph of the Atypical and Subtrochanteric Femoral Fractures Warning and Precaution.
- 2) Included the term “incomplete” to describe the type of femoral fracture that should be ruled out in patients with thigh or groin pain.
- 3) Changed the word (b) (4) to “Patients” in the second sentence of the third paragraph of the Atypical and Subtrochanteric Femoral Fractures Warning and Precaution.

These changes were conveyed to the Applicant and were accepted. Therefore, the agreed-upon Warning and Precaution language is as follows:

#### 5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures:

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the

contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

In addition to the above requested changes, a review of the Atelvia product label was conducted and the following statement was removed in the Clinical Trials section of the product labeling, with the Sponsor's agreement:



**3) Medication Guide:** The Division, in conjunction with the Division of Risk Management, initially developed a Medication Guide template that was sent to the Sponsor with the October 13, 2010 labeling and REMS request. Multiple comments were conveyed to the Sponsor and were accepted. The to-be approved Medication Guide was submitted on January 10, 2011.

**4) REMS Assessment:** The Sponsor's proposed REMS assessment has been reviewed by the Division of Risk Management. The review of the REMS generated multiple comments which the Sponsor has accepted. Acceptable REMS documents were submitted on January 10, 2011.

**5) Carton and Container Labels:** The Sponsor's revised carton and container labeling were reviewed by the Division of Medication Error Prevention and Analysis and the Division of Drug Marketing, Advertising and Communication. The reviews generated multiple comments, which the Sponsor has accepted.

**Reviewer Recommendations: All product labeling, the Medication Guide, and the REMS documents are acceptable. This reviewer recommends approval of this supplemental New Drug Application which incorporates new label language, a new Medication Guide and a Medication Guide only REMS.**

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/s/  
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THERESA E KEHOE  
01/20/2011

AUDREY L GASSMAN  
01/20/2011

Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology

**PATIENT LABELING REVIEW**

Date: **October 6, 2010**

To: Scott Monroe, MD, Director  
**Division of Reproductive and Urologic Products (DRUP)**

Through: LaShawn Griffiths, RN, MSHS-PH, BSN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

Melissa Hulett, RN, BSN, MSBA  
Patient Labeling Reviewer  
**Division of Risk Management**

Barbara Fuller, RN, MSN, CWOCN  
Patient Labeling Reviewer  
**Division of Risk Management**

From: Robin Duer, MA, BSN, RN  
Patient Labeling Reviewer  
**Division of Risk Management**

Steve L. Morin, RN, BSN  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name), Application Type/Number, and Applicant

- Actonel (risedronate sodium) Tablets, NDA 20-835, Warner Chilcott Co., LLC
- Actonel (risedronate sodium with calcium carbonate) Tablets, NDA 21-823, Warner Chilcott Co., LLC
- Boniva (ibandronate sodium) Tablets, NDA 21-455, Hoffman-LaRoche Inc.
- Boniva (ibandronate sodium) Injection, NDA 21-858, Hoffman-LaRoche Inc.
- Fosamax (alendronate sodium) Tablets, NDA 20-560, Merck & Co., Inc.
- Fosamax (alendronate sodium) Oral solution, NDA 21-575, Merck & Co., Inc.
- Fosamax Plus D (alendronate/cholecalciferol) Tablets, NDA 21-762, Merck & Co., Inc.

- Reclast (zoledronic acid) Injection, NDA 21-817 and NDA 22-080, Novartis Pharmaceuticals Corp.
- Atelvia (risedronate sodium) delayed-release tablets, NDA 22-560, Warner Chilcott, Co., LLC

TSI# 468

Therapeutic Class: Bisphosphonates

OSE RCM #: 2010-2013

## 1 INTRODUCTION

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review proposed Medication Guides (MG) for the oral bisphosphonate products. The currently approved patient labeling for these products will be converted to MGs because DRUP has determined that safety labeling changes are required. DRUP plans to send Prior Approval Supplement requests to the Applicants for the above referenced NDAs requiring safety labeling changes and a Risk Evaluation and Mitigation Strategy (REMS) for these products.

## 2 MATERIAL REVIEWED

- Draft MGs proposed by DRUP and accessed by DRISK from the DRUP eRoom on October 5, 2010:
  - Actonel (risedronate sodium) Tablets
  - Actonel (risedronate sodium with calcium carbonate) Tablets
  - Boniva (ibandronate sodium) Tablets
  - Boniva (ibandronate sodium) Injection
  - Fosamax (alendronate sodium) Tablets and Fosamax (alendronate sodium) Oral solution
  - Fosamax Plus D (alendronate/cholecalciferol) tablets
  - Reclast (zoledronic acid) Injection
  - Atelvia (risedronate sodium) delayed-release tablets
- Prescribing information (PI) accessed by DRISK from DRUP eRoom on October 5, 2010:
  - Actonel (risedronate sodium) Tablets
  - Actonel (risedronate sodium with calcium carbonate) Tablets
  - Boniva (ibandronate sodium) Tablets
  - Boniva (ibandronate sodium) Injection
  - Fosamax (alendronate sodium) Tablets and Fosamax (alendronate sodium) Oral solution
  - Fosamax Plus D (alendronate/cholecalciferol) tablets
  - Reclast (zoledronic acid) Injection

- Atelvia (risedronate sodium) delayed-release tablets

### 3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG\_document using the Verdana font, size 11.

In our review of the MG

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- rearranged information where applicable due to PLR format
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

### 4 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MGs are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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STEVE L MORIN  
10/06/2010

LASHAWN M GRIFFITHS  
10/06/2010

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 2, 2010

To: Scott Monroe MD, Director  
Division of Reproductive and Urologic Products

Through: Melina Griffis RPh, Team Leader  
Carol Holquist RPh, Director  
Division of Medication Error Prevention and Analysis

From: Richard Abate, RPh, MS, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Actonel (Risedronate Sodium) Tablets  
Actonel with Calcium (Risedronate Sodium tablets with Calcium Carbonate Tablets, USP)  
Atelvia (Risedronate Sodium) Delayed-release Tablets  
Boniva (Ibandronate Sodium) Tablets and Injection  
Fosamax (Alendronate Sodium) Tablets  
Fosamax Plus D (Alendronate Sodium and Cholecalciferol) Tablets  
Reclast (Zolendronic Acid) Injection

Application Type/Number: NDA 020835/S-042 (Actonel)  
NDA 021823/S-007 (Actonel with Calcium)  
NDA 022560/S-001 (Atelvia)  
NDA 021455/S-011 (Boniva Tablets)  
NDA 021858/S-009 (Boniva Injection)  
NDA 020560/S-060 (Fosamax Tablets)  
NDA 021762/S-013 (Fosamax Plus D Tablets)  
NDA 021817/S-009 (Reclast Injection)

Applicant: Hoffman-La Roche (NDAs 021455 and 21858)  
Merck and Company, Inc (NDAs 020560 and 021762)  
Novartis Pharmaceuticals (NDA 021817)  
Warner Chilcott (NDAs 020835, 021823, and 022560)

OSE RCM #: 2010-2447

## 1 INTRODUCTION

This review evaluates only the placement and readability of the Medication Guide statements to the container labels and carton labeling of approved bisphosphonate products. The labeling changes are part of safety supplements requiring the introduction of a Medication Guide alerting patients and practitioners of serious risks associated with the use of these products.

## 2 MATERIAL REVIEWED

DMEPA reviewed the labels and labeling submitted with the following supplements:

- NDA 021455/S-011 (Boniva Tablets) November 12, 2010.
- NDA 021858/S-009 (Boniva Injection) November 12, 2010.
- NDA 021817/S-009 (Reclast Injection) November 11, 2010.
- NDA 022560/S-001 (Atelvia) November 11, 2010.
- NDA 021823/S-007 (Actonel with Calcium) November 12, 2010.
- NDA 020835/S-042 (Actonel) November 11, 2010.
- NDA 020560/S-060 (Fosamax Tablets) November 29, 2010.
- NDA 021762/S-013 (Fosamax Plus D Tablets) November 29, 2010.

See Appendices A through K for samples.

## 3 RECOMMENDATIONS

Our evaluation found the presentations of the medication guide statements lack prominence and therefore may be overlooked by healthcare providers on many of the labels. We provide recommendations below in Sections 3.1 through 3.4 on the labels that require improvement with respect to the prominence and readability of the medication guide statements. All others were determined to be acceptable, (b) (4)

If you have further questions or need clarifications, please contact Maria Wasilik, project manager, at 301-796-0567.

(b) (4)

**3.3.2 Atelvia Delayed-release Tablets (NDA 022560/S-001)**

A. Dosepack Labeling – 35 mg tablets (Four count)

The Medication Guide statement lacks prominence. Revise and relocate the Medication Guide statement to increase prominence and readability. Position the statement on the principal display panel beneath the proprietary name, established name and strength using the same color and a font at least that of the “Once a Week” statement.

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/s/  
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RICHARD A ABATE  
12/02/2010

MELINA N GRIFFIS  
12/02/2010

CAROL A HOLQUIST  
12/02/2010

## MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### \*\*\*PRE-DECISIONAL AGENCY MEMO\*\*\*

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Date: November 30, 2010

To: Meredith Alpert  
Acting Safety Project Manager  
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: DDMAC comments for:

<b>NDA 020560</b>	Fosamax® (alendronate sodium) tablets and oral solution
<b>021575</b>	Fosamax® (alendronate sodium) tablets and oral solution
<b>020835</b>	Actonel® (risedronate sodium) tablets
<b>021455</b>	Boniva® (ibandronate sodium) Tablets
<b>021762</b>	Fosamax Plus D (alendronate sodium/cholecalciferol) tablets
<b>021817</b>	Reclast® (zoledronic acid) Injection
<b>021823</b>	Actonel® with Calcium (risedronate sodium tablets with calcium carbonate tablets)
<b>021858</b>	Boniva® (ibandronate sodium) Injection
<b>022560</b>	Altevia™ (risedronate sodium) delayed-release tablets

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### Background

This consult is in response to DRUP's November 16, 2010, request for DDMAC's review on sponsors' submissions to DRUP's requested safety updates to the approved product labeling (PI) for all bisphosphonate drug products regarding a possible increased risk of atypical fractures and diaphyseal femoral fractures. The sponsors' submissions include revised PIs, revised proposed Med Guides, proposed Risk Evaluation and Mitigation Strategy (REMS), proposed REMS Supporting Documents, and proposed carton and container labeling.

This consult provides comments on the following revised proposed PIs and carton and container labeling submissions:

- Fosamax® (alendronate sodium) tablets and oral solution
- Fosamax® (alendronate sodium) tablets and oral solution
- Actonel® (risedronate sodium) tablets

- Boniva® (ibandronate sodium) Tablets
- Fosamax Plus D (alendronate sodium/cholecalciferol) tablets
- Reclast® (zoledronic acid) Injection
- Actonel® with Calcium (risedronate sodium tablets with calcium carbonate tablets)
- Boniva® (ibandronate sodium) Injection
- Altevia™ (risedronate sodium) delayed-release tablets.

Reference is made to DDMAC's comments dated September 24, 2010, on the proposed standard safety language to be included in the bisphosphonate PIs. Reference is also made to the following DDMAC reviews: proposed Fosamax Med Guide (September 29, 2010) and proposed Actonel, Boniva Tablets, Boniva Injection, Fosamax Plus D, and Reclast Med Guides (October 1, 2010). Finally, reference is made to the Division of Risk Management's (DRISK) review of the above proposed Med Guides on October 6, 2010.

We offer the following comments:

(b) (4)



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## **NDA 022560 - Altevia™ (risedronate sodium) delayed-release tablets**

PI

### ▪ **5.2 Upper Gastrointestinal Adverse Reactions**

“Atelvia, (b) (4) may cause local irritation of the upper gastrointestinal mucosa” (emphasis added).

- We recommend deleting the phrase, (b) (4) (b) (4) ” as it minimizes the risk of upper gastrointestinal mucosa irritation associated with Atelvia.

### ▪ **5.6 Atypical Subtrochanteric and Diaphyseal Femoral Fractures**

(b) (4)

- DDMAC is concerned that this statement minimizes the consequences of femoral fractures. We recommend deleting this statement.

(b) (4)

(b) (4)

Carton/Container Labeling

- Sample Carton Label
  - DDMAC has no comments on the Sample Carton Label at this time.
- Trade Carton Label
  - DDMAC has no comments on the Trade Carton Label at this time.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)  
(301) 796-3821, or [janice.maniwang@fda.hhs.gov](mailto:janice.maniwang@fda.hhs.gov)

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/s/  
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JANICE L MANIWANG  
11/30/2010

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**PATIENT LABELING REVIEW**

Date: November 23, 2010

To: Scott Monroe, MD, Director  
**Division of Reproductive and Urologic Products (DRUP)**

Through: LaShawn Griffiths, RN, MSHS-PH, BSN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**  
Barbara Fuller, RN, MSN, CWOCN  
Patient Labeling Reviewer  
**Division of Risk Management**  
Melissa Hulett, RN, BSN, MSBA  
Patient Labeling Reviewer  
**Division of Risk Management**

From: Robin Duer, MA, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Risk Management**  
Steve L. Morin, RN, BSN  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guides)

Drug Name (established name), Application Type/Number, and Applicant

- Actonel (risedronate sodium) Tablets, NDA 20-835, Warner Chilcott Co., LLC
- Actonel (risedronate sodium with calcium carbonate) Tablets, NDA 21-823, Warner Chilcott Co., LLC
- Atelvia (risedronate sodium) delayed-release tablets, NDA 22-560, Warner Chilcott, Co., LLC
- Boniva (ibandronate sodium) Tablets, NDA 21-455, Hoffman-LaRoche Inc.
- Boniva (ibandronate sodium) Injection, NDA 21-858, Hoffman-LaRoche Inc.
- Fosamax (alendronate sodium) Tablets, NDA 20-560, Merck & Co., Inc.
- Fosamax (alendronate sodium) Oral solution, NDA 21-575, Merck & Co., Inc.
- Fosamax Plus D (alendronate/cholecalciferol) Tablets, NDA 21-762, Merck & Co., Inc.
- Reclast (zoledronic acid) Injection, NDA 21-817, Novartis Pharmaceuticals Corp.

Therapeutic Class: Bisphosphonates

OSE RCM #: 2010-2435

## 1 INTRODUCTION

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the Applicants' proposed Medication Guides (MGs) and Risk Evaluation and Mitigation Strategies (REMS) for the bisphosphonate products. The currently approved patient labeling for these products were converted to MGs because DRUP determined that safety labeling changes were required.

DRISK provided comprehensive MG reviews of the bisphosphonate products on October 6, 2010. DRUP forwarded DRISK's comments to the respective Applicants in Prior Approval Supplements (PAS)/REMS letters on October 13, 2010. The Applicants were advised to submit:

- Prior Approval Supplements for the above referenced NDAs to include the safety class labeling changes in the MG attached to the Agency's October 13, 2010 letter.
- Proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS supporting document.

The REMS reviews for these products will be provided by DRISK under separate cover.

## 2 MATERIAL REVIEWED

- Draft MGs and professional labeling submitted to the Agency by the Applicants on November 12, 2010 for:
  - Actonel (risedronate sodium) Tablets
  - Actonel (risedronate sodium with calcium carbonate) Tablets
  - Atelvia (risedronate sodium) Delayed-Release Tablets
  - Fosamax (alendronate sodium) Tablets and Fosamax (alendronate sodium) Oral Solution
  - Fosamax Plus D (alendronate/cholecalciferol) Tablets
  - Reclast (zoledronic acid) Injection
- Draft MGs and professional labeling submitted to the Agency by the Applicant on November 15, 2010 for:
  - Boniva (ibandronate sodium) Tablets
  - Boniva (ibandronate sodium) Injection
- Prior Approval Supplements (PAS)/REMS letters sent to the respective Applicants on October 13, 2010 for:
  - Actonel (risedronate sodium) Tablets
  - Actonel (risedronate sodium with calcium carbonate) Tablets
  - Atelvia (risedronate sodium) Delayed-Release Tablets
  - Boniva (ibandronate sodium) Tablets
  - Boniva (ibandronate sodium) Injection
  - Fosamax (alendronate sodium) Tablets and Fosamax (alendronate sodium) Oral Solution

- Fosamax Plus D (alendronate/cholecalciferol) Tablets
- Reclast (zoledronic acid) Injection

### 3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG\_document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- compared the Applicants' proposed MG language to the FDA proposed MG language sent to the Applicants in the Agency's PAS/REMS request letters dated October 13, 2010

### 4 COMMENTS

The MGs listed below are not acceptable, and DRISK reiterates their comments from the Agency's October 13, 2010 PAS/REMS request letters.

[Redacted] (b) (4)

- NDA 22-560 (Atelvia): Warner Chilcott, Co. made minor changes to the MG. Warner Chilcott, Co.'s language is not acceptable.

[Redacted] (b) (4)

## 5 RECOMMENDATIONS

- DRISK reiterates their comments from their October 6, 2010 review for the Actonel, Actonel with Calcium, Atelvia, Fosamax, Fosamax Plus D, Boniva Tablets, Boniva Injection and Reclast Injection MGs found not to be acceptable. Our annotated versions of the MGs are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.
- Please send these comments to the Applicants and copy DRISK on the correspondences.

Please let us know if you have any questions.

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/s/  
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ROBIN E DUER  
11/23/2010

LASHAWN M GRIFFITHS  
11/23/2010

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** November 19, 2010

**To:** Meredith Alpert – Acting Safety Regulatory Project Manager  
Division of Reproductive and Urologic Products (DRUP)

**From:** Michelle Safarik, MSPAS, PA-C – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Subject:** DDMAC comments on revised proposed bisphosphonate  
Medication Guides (Med Guide)  
TSI 468

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This consult is in response to DRUP's November 16, 2010, request for DDMAC to review sponsors' submissions to DRUP's requested safety updates to the approved product labeling (PI) for all bisphosphonate drug products regarding a possible increased risk of atypical fractures and diaphyseal femoral fractures. The sponsors' submissions include revised proposed PIs, revised proposed Med Guides, proposed Risk Evaluation and Mitigation Strategy (REMS), proposed REMS Supporting Documents, and proposed carton and container labeling.

This consult provides comments on the following revised proposed Med Guides:

- Actonel (NDA 020835)
- Actonel with Calcium (NDA 021823)
- Atelvia (NDA 022560)
- Boniva Tablets (NDA 021455)
- Boniva Injection (NDA 021858)
- Fosamax Tablets (NDA 020560)
- Fosamax Oral Solution (NDA 021575)
- Fosamax Plus D (NDA 021762)
- Reclast (NDA 021817)

Reference is made to DDMAC's comments dated September 24, 2010, on the proposed standard safety language to be included in the bisphosphonate PIs. Reference is also made to the following DDMAC reviews: proposed Fosamax Med Guide (September 29, 2010) and proposed Actonel, Boniva Tablets, Boniva

Injection, Fosamax Plus D, and Reclast Med Guides (October 1, 2010). Finally, reference is made to the Division of Risk Management's (DRISK) review of the above proposed Med Guides on October 6, 2010.

Our comments are provided directly in the attached versions of the sponsors' revised proposed Med Guides. DDMAC appreciates the opportunity to provide comments. If you have any questions, please contact Michelle Safarik at 301-796-0620 or [michelle.safarik@fda.hhs.gov](mailto:michelle.safarik@fda.hhs.gov).

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/s/  
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MICHELLE L SAFARIK  
11/19/2010



3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMC is a clinical drug interaction (between a PPI and risedronate sodium DR) trial.
--

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
    - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

In vivo drug-drug interaction trial

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

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CELIA R PEACOCK  
10/08/2010

AUDREY L GASSMAN  
10/08/2010

MEMORANDUM

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

DATE: July 21, 2010

TO: Scott Monroe, M.D.  
Director  
Division of Reproductive and Urologic Products (DRUP)

FROM: Xikui Chen, Ph.D.  
Chemist  
Martin K. Yau, Ph.D.  
Pharmacologist  
Division of Scientific Investigations (DSI)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 7/21/10*  
Acting Team Leader - Bioequivalence  
GLP & Bioequivalence Branch  
Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-560, (b)(4)  
(Risedronate Sodium, Delayed-Release Tablets), 35 mg,  
sponsored by Procter and Gamble Pharmaceuticals, Inc.,  
Mason, OH

At the request of DRUP, DSI audited the clinical and analytical portions of the following bioequivalence study:

**Study # 2008119**

**Title:** "A multi-Center, Randomized, Double-Blind, Two-Treatment, Two-Period, Two-Sequence, Crossover Study to Assess the Bioequivalence of the Phase II and Commercial Risedronate 35 mg Delayed-release Formulations in Healthy Male and Female Subjects"

The inspections of the clinical portion were conducted at the following 5 sites: (1) Comprehensive Phase One Miramar, Miramar, FL (site number: 104970) from March 8 to 12, 2010, (2) Covance CRU San Diego, San Diego, CA (site number: 104972) from February 2 to 5, 2010, (3) Covance CRU Dallas, Dallas, TX (site number: 104973), from March 23 to April 1, 2010, (4) Covance CRU Austin, Austin, TX (site number: 104974) from March 15 to 22, 2010, and (5) Comprehensive Phase One Ft. Myers, Ft. Myers, FL (site number: 104975) from March 22 to 26, 2010. No Form FDA-483 was

issued at Comprehensive Phase One Miramar, Covance CRU San Diego, and Comprehensive Phase One Ft. Myers. Form FDA-483 was issued at Covance CRU Dallas and Covance CRU Austin (see Attachments 1 and 2). The response from Covance CRU Dallas (dated April 21, 2010) was available in Attachment 3. The inspection of the analytical portion of the study was conducted at (b) (4)

Form FDA 483 was issued to (b) (4) following the inspection (see Attachment 4). The response from (b) (4) was available in Attachment 5. Our evaluation of the inspectional findings and 483 responses follows:

Clinical Site - Covance CRU Dallas, 1341 W. Mockingbird Lane, Dallas, TX 75247 (site number 104973)

An investigation was not conducted in accordance with the investigational plan. Specifically, for P&G Protocol 2008119, Covance Research Study # 8200-239:

1. Numerous blood draw events deviated from the scheduled blood collection time points and procedures per protocol for the subjects' PK serum sample assessments during Study Day 1 of treatment period.

Subject	Period	Time Point	Deviation from Protocol	Reason for Deviation
4062	1	5 hour	sample not collected	difficult blood draw
4062	1	6.5 hour	sample not collected	difficult blood draw
4062	2	6.5 hour	sample not collected	difficult blood draw
4070	1	3.5 hour	sample not collected	difficult blood draw
4070	2	20 hour	sample not collected	difficult blood draw
4047	1	9 hour	sample not collected	difficult blood draw
4051	1	5 hour	sample not collected	adverse event of "felt faint"
4100	2	8 hour	sample drawn was short 1 mL of serum	staff error
4070	2	6.5 hour	sample drawn was short 1 mL of serum	staff error
4046	1	3 hour	sample drawn was short 0.5 mL of serum	staff error
4090	2	7 hour	sample drawn was short 0.5 mL of serum	staff error
4084	2	6.5 hour	sample drawn was short 0.25 mL of serum	staff error
4062	1	8 hour	collected 24 minutes late	difficult blood draw
4046	1	5 hour	collected 16 minutes late	difficult blood draw
4070	2	6 hour	collected 11 minutes late	difficult blood draw
4101	2	7 hour	collected 11 minutes late	difficult blood draw
4077	1	4.5 hour	collected 11 minutes late	difficult blood draw
4010	1	2.25 hour	collected 10 minutes early	technician error
4065	1	5 hour	collected 9 minutes late	staff error
4059	1	6 hour	collected 9 minutes late	difficult blood draw
4062	2	2.25 hour	collected 8 minutes late	subject late to event
4077	2	7 hour	collected 8 minutes late	difficult blood draw
4070	1	2.25 hour	collected 8 minutes late	difficult blood draw
4100	2	4.5 hour	collected 7 minutes late	subject late to event
4062	1	2.25 hour	collected 7 minutes late	difficult blood draw

4062	2	6 hour	collected 7 minutes late	difficult blood draw
4059	1	2.25 hour	collected 7 minutes late	difficult blood draw
4077	2	5 hour	collected 6 minutes late	difficult blood draw
4090	2	7 hour	collected 6 minutes late	difficult blood draw
4056	1	8 hour	collected 6 minutes late	difficult blood draw
4016	2	6.5 hour	collected 6 minutes late	difficult blood draw
4062	1	7 hour	collected 6 minutes late	difficult blood draw
4046	1	5.5. hour	collected 6 minutes late	difficult blood draw
4090	1	3.5 hour	collected 6 minutes late	difficult blood draw
4080	1	2.25 hour	collected 6 minutes late	difficult blood draw
4071	1	2.25 hour	collected 6 minutes late	staff error
4070	1	6 hour	collected 6 minutes late	difficult blood draw
4068	2	7 hour	collected 6 minutes late	redrawn due to previous insufficient blood drawn

In their response, Covance CRU Dallas explained that their staff had difficulties in drawing blood samples and thus in collecting adequate quantities of blood for some subjects. The OCP reviewer should confirm that the actual collection times for serum samples with late blood draw (see listing in the above table) be used in the bioequivalence determination.

2. A number of total urine volume measurements deviated from the urine interval collection procedures per protocol for the subjects' pooled PK urine sample assessments during treatment period. The total volume for collection intervals of some subjects was incomplete.

Subject	Treatment Period	Interval	Reason for Incomplete Total Volume Deviation
4013	1	24-48 hour	cross-contamination with Subject 4017's urine
4017	1	24-48 hour	cross-contamination with Subject 4013's urine
4087	2	0-24 hour	cross-contamination with Subject 4088's urine
4088	2	0-24 hour	cross-contamination with Subject 4087's urine
4003	2	-12-0 hour	failure to catch 1 void in the urine collection hat
4093	1	0-24 hour	failure to catch 1 void in the urine collection hat
4093	1	24-48 hour	failure to catch 1 void in the urine collection hat
4047	1	24-48 hour	partial spillage of 1 void from the urine collection hat

In their response, Covance CRU Dallas said that the staff will be trained properly on urine collection procedures to avoid the same mistakes from occurring again in future studies. However, due to cross-contamination or failure to collect urine samples properly, the urine samples listed in the above table should be excluded from the urine data analysis.

Clinical Site - Covance CRU Austin, 313 East Anderson Lane, Austin, TX 78752 (site number 104974)

An investigation was not conducted in accordance with the investigational plan.

Specifically, for 43 subject records reviewed, deviations from the protocol were observed as described:

1. Protocol Section 3.4.5.1. Pharmacokinetic Sample Collection, specifies that "Blood samples for serum risedronate PK analysis will be collected at: 0 (pre-dose) and 0.75, 1.5, 2.25, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 20, 24 and 30 hours after study drug administration."

Serum samples were collected more than 5 minutes after the specified timepoints for at least 20 of 43 subjects. For example:

- a. Subject 5002, Period 2, 5.5 hour sample due 13:33 was performed 13:40 (7 minutes late)
  - b. Subject 5010, Period 1, 1.5 hour sample due 09:57 was performed 10:08 (9 minutes late)
  - c. Subject 5025, Period 1, 24 hour sample due 09:12 was performed 09:30 (18 minutes late)
  - d. Subject 5037, Period 1, 10 hour sample due 18:27 was performed 18:39 (12 minutes late)
  - e. Subject 5063, Period 2, .75 hour sample due 09:09 was performed 09:15 (6 minutes late)
  - f. Subject 5071, Period 1, 6.5 hour sample due 15:18 was performed 15:30 (12 minutes late)
- (See Attachment 6 for complete listing)

The OCP reviewer should confirm that the actual collection times for serum samples listed in the above 483 observation be used in the bioequivalence determination (see Attachment 6 for complete listing).

2. Protocol Section 3.4.5.1., Pharmacokinetic Sample Collection, specifies that "Pooled urine samples for risedronate PK analysis will be collected from -12 to 0 hours prior to administration of study drug on Day 1, and then 3 consecutive 24-hour pooled urine samples will be collected starting immediately prior to study drug administration (i.e., 0 to 24 hours [Day 1 though Day 2], 24 to 48 hours [Day 2 though Day 3], and 48 to 72 hour [Day 3 though Day 4] relative to dosing)."

Urine samples were not collected and retained for all collection periods as described in the protocol for at least 4 of 43 subjects reviewed.

- a. The first urine void for subject 5023 during Period 1, 48-72 hour collection period, was poured into the pooled collection container for subject 5001. The pooled urine collection for

subjects 5001 and 5023 was discarded, and a new collection for the period was started for both subjects. All pharmacokinetic urine aliquots for subjects 5001 and 5023 for this period were taken from the new urine collection for each subject, respectively.

- b. Subject 5032 did not collect urine samples according to the protocol during the -12 to 0 hour urine collection. Staff members observed during review of the subject's source documentation that the subject had only two urine voids during the collection period. The matter was discussed with the subject, and staff members learned that a bathroom door in the facility had been propped open, and the subject was using that facility rather than the collecting urine specimens.
- c. Urine aliquots from the pooled urine collection for subject 5013's period 2, 48-72 hour collection could not be located for shipment to the sponsor.

Due to the improper urine sample collections, the urine samples for subjects 5001 and 5023 during Period 1 at 48-72 hours should be excluded from the urine data analysis.

3. Protocol Section 3.4.1.7 Exit Procedures, states that, at the time of study withdrawal or on Treatment Period 2 Day 4, the following procedures will be performed: update medical and medication history; complete a brief physical examination; record vital signs (pulse, respiratory rate, blood pressure, and oral body temperature) after 5 minutes sitting; assess Adverse Events. Subject 5014 was discharged on Period 2 Day 1 due to positive urine drug screen without having their exit physical examination performed.

Covance CRU Austin should follow the Protocol Exit Procedures. As Subject 5014 was discharged, data of the subject were not collected in period 2 for the Bioequivalence determination. The discharge without conducting proper exit procedures should not have a significant effect on the bioequivalence evaluation.

Analytical Site - (b) (4)

1. Failure to assure accuracy of the urine data generated in Study 2008119. Specifically, an in-house investigation was conducted to evaluate an Incurred Samples Reproducibility (ISR) failure in a different (b) (4) study. The investigation

concluded that there is ISR issues in the urine method (b)(4) (b)(4) used to analyze all urine samples collected in Study 2008119. An improved procedure (b)(4) was subsequently developed to resolve the ISR problem, but the urine samples in Study 2008119 were not re-analyzed.

(b)(4) should have re-analyzed all urine samples obtained in Study 2008119 using the improved procedure documented in (b)(4) (b)(4) because accuracy of the reported urine data (generated using the procedure documented in (b)(4)) is questionable.

In their written response (see Attachment 5), (b)(4) claimed that the ISR failure cited in Item 1 of the Form FDA-483 was observed in a different (b)(4) study (Study 92058) and Study 92058 was a multisite study including 7 different clinical sites. Only samples collected from subjects enrolled in clinical site # 1000 exhibited ISR problem. However, in their investigation report, (b)(4) acknowledged that the exact root cause of the ISR problem was not identified, but an unidentified urine component might bind to risedronic acid and decrease its recovery. The investigation report further said that "urine collected after lunch and after one freeze/thaw (F/T) cycle might influence the recovery of risedronic acid in the assay. Centrifugation of the samples prior to extraction may give irreproducible results from day to day. The addition of internal standard to the study samples followed by one F/T cycle, coupled with no centrifugation prior to analysis achieved assay reproducibility". Thus, based on the (b)(4) investigation report, the ISR problem potentially can occur in any risedronic acid studies when urine samples were analyzed using (b)(4) (b)(4). In the written response, (b)(4) also argues that comparison between risedronate concentration values obtained from the reanalysis of urine samples from Study 92058 using procedure in (b)(4) (the improved procedure) and original risedronate concentration values generated using procedure in (b)(4) showed that overall 85.45% of the reanalyzed concentration values confirmed the original concentration values. (b)(4) however, did not focus the comparison on samples collected in clinical site #1000. Thus, the 85.45% cited above might not present a clear picture of the problem identified in the urine assay. Overall, DSI is of the opinion that accuracy of the reported urine data in Study 2008119 is questionable. All urine samples obtained in this

study should be re-analyzed using the improved urine assay that can generate more accurate urine data.

**2. Failure to conduct ISR experiments using sufficient subject serum samples in Study 2008119. Only 0.5% (n=20) of urine samples and 1.45% (n=300) of serum samples were used.**

In light of the ISR issue in the urine assay (see analytical 483 Item 1 above), the ISR experiment conducted by (b)(4) for Study 2008119 is not acceptable, as only 20 incurred urine samples were used. (b)(4) should conduct a new ISR experiment using (1) 5% of the study urine samples and (2) the improved urine assay procedure documented in (b)(4)

Regarding the serum assay, DSI is of the opinion that the existing ISR data can be accepted because (1) 78.7% of the tested incurred serum samples met the ISR acceptance criteria, (2) a larger (n=300) number of serum samples were used, and (3) no similar ISR issue as in the urine assay was found. (b)(4) also said that they have revised their ISR SOP to require 5-10% of incurred study samples to be used in future ISR experiments.

**3. Failure to accurately described and report experimental results in serum method validation report 77077QTP.**

**For example:**

**a. Precision and accuracy data generated from Run (b)(4) and (b)(4) with poor results were excluded without valid reasons.**

In their written response, (b)(4) said they have revised their SOP. Currently, data generated in validation runs with acceptable calibration curves will not be excluded. (b)(4) also updated the assay precision and accuracy table to include data from Runs (b)(4) and (b)(4) and showed that except for precision (17.7%) at the low QC (0.6 ng/ml), the precision and accuracy of the serum assay is adequate.

**b. The autosampler stability experiment (Run (b)(4)) was not conducted according to the procedure described in the report.**

In the written response, (b)(4) explained that the auto-sampler stability experiment of the serum assay was conducted according to the sponsor's procedure which is different from

(b)(4) procedure. DSI is of the opinion that (b)(4) should have conducted the experiment according to (b)(4) procedure.

**c. The short term stability data of risedronic acid in solution at room temperature (Table 18) were not reliable, as 4 out of 6 (67%) QC2 level samples in Run (b)(4) failed.**

The short term stability experiment of risedronic acid in solution at room temperature was repeated by (b)(4) following the FDA inspection. The results were found acceptable and were included in the written response.

**d. The process stability data in Table 16 (Original Run # 1 (b)(4), Reinjection Run # (b)(4)) are not meaningful as calibration standards and QCs were both stored in room temperature for 88 hours and then reinjected. The QCs samples were not back calculated using a fresh or original standard curve.**

The process stability experiment cited above was repeated by (b)(4) following the FDA inspection. The repeated experiment was conducted according to (b)(4) validation SOP, and concentrations of QCs that have been stored at room temperature are compared to concentrations of QCs freshly prepared. The results were found acceptable and were included in the written response.

### **Conclusions:**

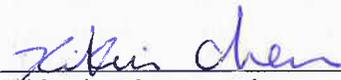
Following inspections of the clinical and analytical portions of Study 2008119, DSI recommends the following:

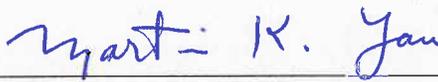
1. At Covance CRU Dallas and Covance CRU Austin, blood draws in some study subjects were delayed due to technical difficulties, and urine samples from several subjects were not collected properly. The identity of these serum and urine samples were listed in the 483 observations issued at these two clinical sites. The OCP reviewer should (1) confirm that the actual blood sample collection times were used by the sponsor in the bioequivalence determination and (2) exclude the urine samples that were not collected properly from the urine data analysis (see discussion under clinical 483 observations for more details)
2. Accuracy of the reported urine data in Study 2008119 is questionable. If the urine data are needed to support approval of the NDA application, (b)(4) should re-analyze all the study

urine samples using the improved procedure documented in (b) (4). In addition, (b) (4) should conduct a new ISR experiment using (1) 5% of the study urine samples and (2) the improved urine assay procedure (see discussion under analytical 483 Items 1 and 2 for more details). DSI also recommends that all risedronate urine data reported in other (b) (4) studies be re-analyzed if the urine data were generated using the (b) (4) urine assay as documented in (b) (4).

3. The risedronate serum data from Study 2008119 can be accepted for review if actual blood sampling times were used by the sponsor in the bioequivalence determination.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

  
\_\_\_\_\_  
Xikui Chen, Ph.D.

  
\_\_\_\_\_  
Martin K. Yau, Ph.D.

**Final Classification:**

VAI - (b) (4)  
VAI - Covance CRU Dallas, Dallas, TX  
VAI - Covance CRU Austin, Austin, TX  
NAI - Comprehensive Phase One Ft. Myers, Ft. Myers, FL  
NAI - Comprehensive Phase One Miramar, Miramar, FL  
NAI - Covance CRU San Diego, San Diego, CA

cc: DARRTS  
DSI/Ball/Haidar  
DSI/Yau/Rivera-Lopez/CF  
OND/DRUP/Scott Monroe/Karl Stiller  
OTS/OCF/Doanh Tran/Myong-Jin Kim  
HFR-SE250/Brunilda Torres  
HFR-PA2535/Courtney Long  
HFR-SW150/Leighton Ngai  
HFR-SW1575/Karen Daugherty  
HFR-SE2585/Bill Tackett  
Draft: XC 7/19/10; MKY 7/19/10  
Edit: MKY 7/19/10, 7/20/10  
DSI: (b) (4)  
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FACTS: (b) (4)

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Application  
Type/Number

Submission  
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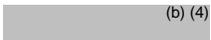
Submitter Name

Product Name

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NDA-22560

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ORIG-1

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WARNER  
CHILCOTT CO LLC

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 (b) (4)

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/s/  
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XIKUI CHEN  
07/21/2010

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-Decisional Agency Information\*\*\***

## Memorandum

**Date:** July 16, 2010

**To:** Karl Stiller  
Regulatory Project Manager  
Division of Reproductive and Urologic Products (DRUP)

**From:** Michelle Safarik, PA-C- Regulatory Review Officer  
Carrie Newcomer, PharmD - Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Subject:** TRADENAME (risedronate sodium) delayed-release tablets  
NDA 022560  
Comments on draft product labeling

---

DDMAC has reviewed the proposed product labeling (Package Insert (PI) and Patient Package Insert (PPI)) dated July 6, 2010, and the proposed carton and container labeling dated September 24, 2009, for TRADENAME (risedronate sodium) delayed-release tablets (TRADENAME), submitted for consult on October 14, 2009.

DDMAC acknowledges that this NDA provides for a delayed-release/once-weekly formulation (b) (4)

DDMAC's comments are provided directly in the attached document (please see below).

DDMAC notes that DRISK provided comments on the draft PPI for NDA 022560 on July 15, 2010. DDMAC agrees with DRISK's comments and has provided additional comments directly on DRISK's review of the PPI (please see attached document below).

Thank you for your consult.

If you have any questions on the comments for the proposed PI or proposed carton and container labeling, please contact Michelle Safarik at 301.796.0620 or [michelle.safarik@fda.hhs.gov](mailto:michelle.safarik@fda.hhs.gov).

If you have any questions on the comments for the proposed PPI, please contact Carrie Newcomer at 301.796.1233 or [carrie.newcomer@fda.hhs.gov](mailto:carrie.newcomer@fda.hhs.gov).

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22560

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ORIG-1

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WARNER  
CHILCOTT CO LLC

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 (b) (4)

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/s/  
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CARRIE A NEWCOMER  
07/16/2010

MICHELLE L SAFARIK  
07/16/2010



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: July 15, 2010

To: Scott Monroe, MD, Director  
Division of Reproductive and Urologic Drug Products

Through: Zachary Oleszczuk, PharmD, Acting Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Cathy A. Miller, MPH, BSN, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Atelvia (Risedronate Sodium) Delayed-release Tablets  
35 mg

Application Type/Number: NDA 022560

Applicant/sponsor: Warner Chilcott

OSE RCM #: 2009-2049

## 1 INTRODUCTION

This review responds to a request from the Division of Reproductive and Urologic Products (DRUP) for the Division of Medication Error Prevention and Analysis (DMEPA) medication error review of the labels and labeling for Atelvia (Risedronate Sodium) Delayed-release tablets, NDA 022560. The labels and labeling were submitted as part of the Applicant's request for review of proprietary name, Atelvia, in their submission dated April 9, 2010. DMEPA found the proprietary name acceptable in OSE Review #2010-808 dated June 21, 2010.

## 2 PRODUCT INFORMATION

Risedronate Sodium is currently marketed as an immediate release formulation tablet in 5 mg, 30 mg, 35 mg and 150 mg strengths marketed under the proprietary name Actonel. A 75 mg strength was previously marketed but was discontinued in June 2009. Actonel With Calcium (Risedronate Sodium and Calcium Carbonate) is also available as an immediate release formulation containing 35 mg Risedronate Sodium and 1250 mg Calcium Carbonate strength tablets. Actonel and Actonel With Calcium are indicated for the treatment and prevention of Postmenopausal Osteoporosis. Actonel is additionally indicated for the treatment to increase bone mass in men with Osteoporosis, treatment and prevention of Glucocorticoid-induced osteoporosis, and the treatment of Paget's disease. The recommended dose for Actonel and Actonel With Calcium varies according to indication including 5 mg daily, 30 mg daily for two months, 35 mg once a week, 75 mg two consecutive days per month of 150 mg once a month. Both Actonel and Actonel With Calcium must be taken with plain water (6 to 8 ounces) at least thirty minutes before the first food or drink of the day and patients cannot lie down for thirty minutes.

Atelvia (Risedronate Sodium) Delayed-release 35 mg tablet is proposed for the indication of treatment of postmenopausal osteoporosis (b) (4)

(b) (4) Dosing for Atelvia is one 35 mg tablet once weekly administered immediately after breakfast with at least four ounces of plain water. Atelvia will be supplied in 4-count (one month supply) (b) (4) dose packs.

## 3 METHODS AND MATERIALS

For this review, DMEPA searched the FDA Adverse Event Reporting System (AERS) database and reviewed proposed container labels and carton labeling.

### 3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Since Risedronate Sodium is a currently marketed product under the tradename 'Actonel' and 'Actonel with Calcium', the Division of Medication Error Prevention and Analysis searched the Adverse Events Reporting System (AERS) database for any medication errors related to the product. Because the currently U.S. marketed product is available in multiple strengths with multiple frequency of administration instructions, DMEPA limited our search to the overlapping 35 mg strengths to identify errors that may be indicative of this product once marketed.

For this review, DMEPA performed an AERS search on June 7, 2010 for medication errors submitted for this product. The following criteria was used: active ingredient “Risedronate”, Trade name “Actonel”, and the verbatim terms “Risedronate%” and “Actonel%”; and the MedDRA reactions “Medication Errors” (HLGT) and “Product Quality Issues” (HLGT) to identify medication errors that would be relevant to this review.

The reports were manually reviewed to determine if a medication error occurred. If an error occurred, the staff reviewed the reports to determine if the root cause could be associated with the labels or labeling of the product, and thus pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors unrelated to labeling such as patient non-adherence, intentional overdose, adverse events, drug use with concomitant medications, etc.) were excluded from further analysis. Duplicate reports were combined into cases. The cases that described the medication errors were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to medication errors.

### **3.2 LABELS AND LABELING**

Using the principles of Human Factors and Failure Mode and Effects Analysis (FMEA)<sup>1</sup> the Division of Medication Error Prevention and Analysis (DMEPA) evaluates the labels and labeling of products. This review focuses on those submitted on April 9, 2010 (see Appendix A).

## **4 RESULTS AND DISCUSSION**

The following summarizes our findings from the AERS search and review of the proposed container labels and carton labeling.

### **4.1 AERS RESULTS**

The AERS search retrieved a total of 109 reports. Eighty-four (n=84) of the reports were deemed not relevant to our evaluation of Atelvia labels and labeling for the reasons listed below.

Fifty-three (n=53) reports cited adverse events with Risedronate Sodium use alone or along with other medications cited in the reports.

Seventeen (17) of the reports wrong drug medication errors of which and were deemed not relevant to our Atelvia review since the error involved confusion with the proprietary name Actonel rather than the name Atelvia and our evaluation did not find significant orthographic or phonetic similarities between the drugs cited and the name Atelvia. These errors included wrong drug medication errors between Actonel versus Actos (n=11), Actonel versus Actanol (n=1), Actonel versus Atenolol (n=2), Actonel versus Ambien (n=1), Actonel versus Fosamax (n=1), for which the reporter also complained of wrong drug medication errors between several other products in a select pharmacy, and one

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

error (n=1) where the reported cited that a patient prescribed Actonel 5 mg (yellow tablet) was dispensed a ‘unspecified white tablet’ instead.

Six (n=6) of the reports did not include any reference to ‘Actonel’ or ‘Risedronate Sodium’ in the report.

One (n=1) report cited an accidental exposure of Actonel by a ten year old however, no details were provided about how the exposure occurred.

Seven (n=7) of the reports cited wrong dose or wrong strength medication errors with various strengths of Actonel. Because Atelvia will be available in only on 35 mg strength, with one dose regimen of one tablet per week, our evaluation deemed these types of errors not relevant to our review of Atelvia labels and labeling.

The remaining 25 cases were deemed relevant to our evaluation of Atelvia labels and labeling including three (n=3) cases of maladministration, one (n=1) case involving wrong drug medication errors between the established name Risedronate and Alendronate and, twenty-one (n=21) cases involving wrong frequency medication errors. These cases are discussed further below.

#### Actonel Maladministration Medication Errors (n=3)

Three of the 25 cases retrieved involve maladministration of Actonel. Two of the three cases (ISR #6190914 dated 5/13/09 and 6190954 dated 5/13/09) involved the maladministration of Actonel in a non-fasting state, along with failure to remain upright for thirty minutes in one case. Neither of the two cases included information about why the non-fasting and failure to remain upright maladministrations occurred. Our review of insert labeling and carton labeling for Actonel confirms that the instructions “Do not take with food” and “Do not lie down, eat, drink or take other medications for 30 minutes” are included in the carton labeling, as well as the Dosage and Administration and Patient Information section of the insert labeling. Additionally, the carton labeling includes an illustration of a plate of food with a red ‘X’ through it, beside the administration instructions. DMEPA believes the labeling provides adequate directives regarding Actonel administration in a fasting state and remaining upright for thirty minutes following administration. None of the cases included information indicating that the pictograms adjacent to the instructions created confusion. DMEPA’s assessment of the carton labeling and the illustrations provided with the narrative instructions found that they appear to be clear in their intended communication to take with plain water and take without food.

In the third case (ISR #3841281 dated 11/30/01), the reporter stated that a patient who was having gastritis symptoms after two to three weeks of administration of Actonel 5 mg was advised by a technician performing a bone mineral density test on his wife to dissolve the pill in water before administration. The patient dissolved his Actonel in a shot glass full of water before administration as advised, followed by a full glass of water. The patient did not experience further gastritis symptoms and no further information was reported. A review of the insert labeling and carton labeling confirmed that administration instructions are provided to “swallow one tablet whole in the morning with at least four ounces of plain water” as well as a warning no to “chew, cut or crush the tablet” as well as an illustration of a glass of water with a tablet placed beside it

adjacent to the administration instructions on the carton labeling. DMEPA believes that labeling provides adequate directives regarding administration of the product. (See Appendix C for case details)

#### Wrong Drug Medication Errors - Risedronate Sodium versus Alendronate Sodium (n=1)

One of the 25 cases (ISR #4421810 dated 8/9/04) cited wrong drug confusion between established name Risedronate Sodium and Alendronate Sodium in the 35 mg strength. The case cited “a couple of mix ups” but the report did not include an exact number of errors, nor did the report state where the errors occurred during prescribing or dispensing of the medication. The case cited that suspected contributing factors for the wrong drug medication errors include similarity in the established names, overlapping 35 mg strength and dose availability for both products, and similar packaging configurations in a four count pack with the same color (yellow) tablets, along with the same indications of use (osteoporosis).

DMEPA evaluated orthographic similarities between Risedronate and Alendronate, in conjunction with other similarities in product characteristics to determine whether errors of this type were likely to reoccur in the clinical setting and result in future medication errors of this type. DMEPA acknowledges the orthographic similarities in the name including ‘R’ can appear like ‘A’, and both names end with ‘dronate’ and ‘Sodium’. We also acknowledge that the 35 mg overlap in strength and dose, as well as similar packaging configurations and indication of use create additional similarities in product characteristics. Product characteristic variations include the established name for Atelvia is Risedronate Sodium Delayed-release versus Risedronate Sodium for Actonel, and administration instructions specify “take immediately following breakfast with at least four ounces of water” which is included on the carton labeling and insert labeling dosage and administration section. This case was reported in 2004 and our AERS search did not uncover any additional wrong drug medication error cases between Risedronate versus Alendronate. DMEPA understands that the potential exists for errors of this type to occur in the future and will, therefore, continue monitoring these types of errors through our routine postmarketing surveillance efforts. (See Appendix D for case details).

#### Actonel Wrong Frequency Medication Errors (n=21)

Twenty-one (n=21) cases involved wrong frequency medication errors with Actonel. Three (n=3) of the cases cited errors that occurred because healthcare staff administered Actonel to the patient at the wrong frequency during hospital admission. Six (6) cases cited errors where the prescription was written correctly but transcribed incorrectly with the wrong frequency. Nine (n=9) of the cases cited errors that occurred because the patient administered Actonel at the wrong frequency but none of the reports cited reasons for the patients’ wrong frequency administration errors. Three (n=3) of the cases cited errors in frequency of administration that occurred during prescribing of the medication, including one case where the prescription was written correctly but the healthcare provider gave instructions to ‘take daily’. In all 21 cases, the wrong frequency medication errors reached the patient. (See Appendix E for case details)

Our evaluation of the wrong frequency medication errors found that the errors occurred across a variety of strengths and dose regimens of Actonel, and in nine of the cases, the wrong frequency medication errors involved Actonel 35 mg strength tablets. We

consider these findings significant since Atelvia will also be available in a 35 mg strength tablet with once weekly dosing. The errors identified in our search occurred between 11/2001 through 12/2009. DMEPA understands that there is a potential for wrong frequency of administration errors inherent to Actonel use, since the product is available in multiple strengths with multiple dosing regimens with varying frequency of administrations. We also acknowledge that the potential exists for similar errors to occur with Atelvia. However, Atelvia is available in only one strength with one (once weekly) frequency of administration dosing regimen, and we believe that the unique proprietary name ‘Atelvia’ may help provide differentiation to healthcare practitioners and patients, and might help minimize wrong frequency medication errors. DMEPA will continue monitoring the potential for these types of medication errors through our routine postmarketing surveillance efforts.

## **4.2 LABELS AND LABELING**

The proposed carton labeling does not accurately reflect the most current administration instruction (take immediately following breakfast with at least four ounces of plain water). The DRUP review team provided the most current insert labeling to DMEPA on June 29, 2010, including revisions to the administration instructions originally proposed by the Applicant that read [REDACTED] <sup>(b) (4)</sup> Based on DRUP revisions to the insert labeling, Atelvia should be administered immediately following breakfast with at least four ounces of plain, therefore, the carton labeling administration instructions should be revised to align with these directives to assure the correct administration of Atelvia. Although DMEPA identified three cases of maladministration of Actonel in our AERS searches, we did not find that the graphic pictures displayed on the Actonel carton labeling were a contributing factor to these errors. Therefore, we do not anticipate that the graphics will contribute to similar maladministration medication errors with Atelvia.

## **5 CONCLUSION AND RECOMMENDATIONS**

We find that the proposed carton labeling does not align with administration instructions to “take immediately following breakfast with at least four ounces of plain water.” We have provided recommendations for revisions to carton labeling in Section 4.1 and request that these recommendations be communicated to the Applicant prior to approval. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Maria Wasilik at 301-796-0567.

### **5.1 COMMENTS TO THE APPLICANT**

Revise the carton labeling administration instructions that currently state [REDACTED] <sup>(b) (4)</sup> [REDACTED] on the principal display panel and on the inside flap of the Atelvia carton labeling, so that they align with the revised administration instructions to “take immediately following breakfast with at least four ounces of water.”

## REFERENCES

### Previous OSE Reviews:

Miller, C.A., OSE Review #2010-808 Proprietary Name Review for Atelvia dated June 17, 2010.

#### *1. Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

**Appendix B:** AERS Cases deemed not relevant to review of Atelvia labels and labeling (n=85)

Fifty-three (n=53) reports cited adverse events with Risedronate Sodium use alone or along with other medications cited in the reports.

Eighteen (n=18) of the reports wrong drug medication errors of which, sixteen (17) reports were deemed not relevant to our Atelvia review since the errors involved confusion with the proprietary name Actonel rather than the name Atelvia and our evaluation did not find significant orthographic or phonetic similarities between the drugs cited and the name Atelvia. These errors included wrong drug medication errors between Actonel versus Actos (n=11), Actonel versus Actanol (n=1), Actonel versus Atenolol (n=2), Actonel versus Ambien (n=1), Actonel versus Fosamax, for which the reporter also complained of wrong drug medication errors between several other products in a select pharmacy (n=1), and one error (n=1) where the reported cited that a patient prescribed Actonel 5 mg (yellow tablet) was dispensed a ‘unspecified white tablet’ instead.

Six (n=6) of the reports did not include any reference to ‘Actonel’ or ‘Risedronate Sodium’ in the report.

One (n=1) report cited an accidental of exposure of Actonel by a ten year old however, no details were provided about how the exposure occurred.

Seven (n=7) of the reports cited wrong dose or wrong strength medication errors with various strengths of Actonel. Because Atelvia will be available in only on 35 mg strength, with one dose regimen of one tablet per week, however, our evaluation deemed these types of errors not relevant to our review of Atelvia labels and labeling.

**Appendix C:** Actonel Maladministration Medication Errors (n=3)

ISR NUM	RECV DATE	Narratives	Error Type
3841281	11/30/01	<p>12 April2001: The wife of a 70 year old patient reported that her husband started taking Actonel 5 mg daily about 6 weeks ago to treat osteoporosis and compression fractures of the spine; experienced gastric upset nausea stomach trouble was not feeling good and didn't want any food and dissolved the Actonel tablets in water. He had taken Actonel according to directions for 2 to 3 weeks and began experiencing gastric upset and nausea The patient had not experienced these symptoms previously. When the patient's wife underwent a bone mineral density BMD test the technician suggested that her husband should dissolve the tablet in water and drink it. The technician stated that several doctors had recommended that if patients were having problems. The patient dissolved his Actonel in a shot glass full of water and then followed it with a full glass of water. He felt fine no longer had any gastric upset or nausea, felt better and was eating again. Except for swallowing the tablet whole he was still taking the medication according to the directions. Actonel had not been discontinued and the patient recovered.</p>	Maladministration Dissolved in water
6190954	5/13/09	<p>Intestinal subocclusion [Intestinal obstruction] malaise [Malaise] Gastrointestinal pain [Gastrointestinal pain] drug administration error [Drug administration error]            Case Description: (b) (6) A physician reported that a female patient who was receiving Actonel (risedronate sodium) 75 mg twice per month for prophylaxis against menopausal osteoporosis, experienced intestinal subocclusion, malaise and gastrointestinal pain on an unspecified date. The patient was hospitalized. The patient had a large breakfast without waiting 30 min to take Actonel. The action taken with Actonel was unknown. The outcome of this event was unknown. MEDICAL HISTORY/ALLERGIES: None reported. CONCOMITANT MEDICATIONS: None reported. ADDITIONAL INFORMATION: 05-MAY-2009: The physician reported that the 65 year old patient (48 kg/148 cm) was receiving Actonel since JAN-2009 for osteoporosis. Actonel was maintained. The outcome of these events was recovered. CONCOMITANT MEDICATIONS: CACIT D3 (CALCIUM CARBONATE/COLECALCIFEROL). MEDICAL HISTORY: Colon cancer (operated).</p>	Maladministration Non-fasting

ISR NUM	RECV DATE	Narratives	Error Type
6190914	5/13/09	<p>fat embolism (secondary to tibia fracture following a fall) [Fat embolism] 3 fractures on tibia (secondary to fall) [Tibia fracture] other unspecified bone fractures [Fracture] fall [Fall] coma (secondary to embolism) [Coma] hemiparalysis (secondary to embolism) [Hemiparesis] dysphagia (secondary to left hemiparalysis) [Dysphagia] aggravation of gastritis [Gastritis] nausea [Nausea] heartburn [Dyspepsia] did not take Actonel in fasting and did not remain standing up for 1 hour [Wrong technique in drug usage process] SGOT increased [Aspartate aminotransferase increased] SGPT increased [Alanine aminotransferase increased] Gamma-GT increased [Gamma-glutamyltransferase increased] osteoporosis (worsened during therapy with Actonel) [Osteoporosis] (hepatic alteration related to) gallbladder disorder [Gallbladder disorder] aggravation/worsened (gastritis, osteoporosis, gallbladder disorder) [Condition aggravated] Case Description: 29-Apr-2009: A report from Sanofi-Aventis Brazil (BR 20092345) was received by Procter &amp; Gamble Pharmaceuticals on 30-Apr-2009. The son of an 80 year old (born: 1928, 65 kg) female patient reported that his mother started taking Actonel (risedronate sodium; duration unspecified) 5 mg daily a long time ago for osteoporosis. The patient was hospitalized as a result of a fall in 2003 when she experienced 3 fractures of the tibia and other unspecified bone fractures requiring surgery. The event led to a fat embolism for which she remained in a coma for 16 days. As sequelae of the embolism the patient developed hemiparalysis of the left side causing dysphagia. On an unspecified date, Actonel 5 mg was not available and the patient started taking Actonel 35 mg once weekly. She experienced aggravation of gastritis with nausea and heartburn. It was noted that due to the dysphagia the patient's medications were macerated. Additionally, the patient had not taken Actonel while fasting and she did not remain standing for 1 hour after dosing. The reporter cited the excessive quantity of medications that the patient took as an alternative explanation for aggravation of gastritis. The patient started taking Actonel 5 mg daily on an unspecified date. Recently, the patient presented with increased SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamate pyruvate transaminase), and Gamma-GT (gamma-glutamyl transferase) 290. The reporter believed that this hepatic alteration was associated with an unspecified gallbladder disorder and to co-suspect medications Tramal (tramadol hydrochloride), paroxetine and Vytorin (ezetimibe/simvastatin). As corrective treatment, Tramal dose was gradually</p>	<p>Maladministration Non-fasting and did not remain upright</p>

ISR NUM	RECV DATE	Narratives	Error Type
		<p>decreased and gallbladder surgery was scheduled. According to the reporter, the bone fractures occurred due to severe osteoporosis and stated that the osteoporosis worsened during therapy with Actonel. Actonel 5 mg daily therapy was ongoing. The patient had not recovered. MEDICAL HISTORY/ALLERGIES: high cholesterol, gastritis, unspecified gallbladder disorder, hypothyroidism, sleep disorder, gastrointestinal disorder, anxiety, pain on articulations, migraine; previously took alendronate 20 years ago to treat severe osteoporosis; allergies: none reported</p> <p>CONCOMITANT MEDICATIONS: Rivotril (clonazepam), Oscal D (calcium carbonate/ergocalciferol), Maxsulid (nimesulide betadex), pantoprazole, Motilium (domperidone), dimeticone, Dasc (pancrelipase/bile salts/cellulose), Muvinalx (macrogol 3350/electrolytes), Puran T4 (levothyroxine), Benerva (thiamine hydrochloride), lorazepam, Reforgan (arginine aspartate), Vitamin C (ascorbic acid), Vitamin E (tocopherol), Somalgin Cardio (acetylsalicylic acid), Condroflex (glucosamine sulfate/chondroitin sulfate sodium), Flunarin (flunarizine hydrochloride)</p>	

**Appendix D: Risedronate Sodium versus Alendronate Sodium (n=1)**

ISR NUM	RECV DATE	Narratives	Error Type
4421810	8/9/04	<p>We have had a couple of mixups in our pharmacy recently involving Once weekly Fosamax 35 mg and Once weekly Actonel 35 mg. both products are packaged in yellow, 4 tablet card packs, are the same tablet strength, and are used for the same indication. We are not sure what the exact reasons are behind the mixups, but theorize that some pharmacy staff may be confusing the brand name Actonel-risedronate- with the generic name alendronate-Fosamax=. (b) (6)</p> <p>Medication Error</p>	<p>Wrong medication Fosamax 35 mg vs Actonel 35 mg Established name confusion</p>

**Appendix E:** Actonel Wrong Frequency Medication Errors (n=21)

ISR NUM	RECV DATE	Narratives	Error Type
4188587	6/2/03	<p>20Mar2003: A pharmacist reported that a female patient who started taking Actonel risedronate sodium duration unspecified 35 mg once weekly to treat osteoporosis, was hospitalized for chest pain and shortness of breath on (b) (6) and was given Actonel 35 2 days in a row (b) (6) and (b) (6). Actonel had not been discontinued. The outcome of the event was known</p>	Hospital staff administered wrong frequency
4253866	12/16/03	<p>hypotension[Hypotension NOS] patient fell[Fall] Patient was given a dose on Thursday, Sunday, Monday and Tuesday[Medication error] Case Description: (b) (6)            : A pharmacist reported that a female patient who took Actonel (risedronate sodium, duration unknown) 35 mg once weekly to treat osteoporosis experienced hypotension and a fall and was hospitalized. While in hospital she was given four Actonel 35 mg tablets between (b) (6).            I here was no adverse event report with this inadvertent administration. The patient's calcium levels were being monitored. Action taken with Actonel and outcome of the other events were unknown. MEDICAL HISTORY/ALLERGIES: allergies: none reported. CONCOMITANT MEDICATIONS: none reported. ADDITIONAL INFORMATION: 10-Dec-2003: Additional information from the pharmacist indicated that the patient was 88 years old (born 1915). the pharmacist confirmed that the patient's calcium levels stayed within range and that no adverse event was noted with the inadvertent administration. Actonel therapy was withdrawn temporarily then reintroduced. MEDICAL HISTORY/ALLERGIES: insulin dependent diabetes mellitus, hypotension; allergies: none known. CONCOMITANT MEDICATIONS: none reported.</p>	Hospital staff administered wrong frequency

ISR NUM	RECV DATE	Narratives	Error Type
6525908	12/22/09	<p>congestive heart failure (CHF) [Cardiac failure congestive] Actonel 150 mg taken weekly instead of monthly [Inappropriate schedule of drug administration] Case Description: 10-Nov-2009: A pharmacist reported that an 89 year old female patient who started taking Actonel (risedronate sodium) 150 mg once a month in Jul-2009 to treat osteoporosis, experienced congestive heart failure (CHF) and was hospitalized on (b) (6). While hospitalized, the patient was administered Actonel 150 mg weekly instead of once a month from (b) (6).</p> <p>The patient was admitted to the hospital from a nursing home. On (b) (6), the patient's baseline blood calcium level was 2.19 (units unspecified). On (b) (6), after Actonel administration error was noticed, the patient's blood calcium test was repeated. The test showed that calcium level was unchanged at 2.19. Actonel therapy was ongoing. The outcome of CHF was unknown. MEDICAL HISTORY/ALLERGIES: hypertension, dyslipidaemia, rheumatoid arthritis, Alzheimer's disease, depression, glaucoma, hip fracture, knee replacement; allergies: sulfa - rash CONCOMITANT MEDICATIONS: methotrexate, hydroxychloroquine, citalopram, ferrous sulfate, donepezil, heparin, rabeprazole, docusate sodium, calcium carbonate, folic acid, vitamin D (ergocalciferol), zopiclone, timolol, acetylsalicylic acid, Lasix (furosemide), metoprolol, simvastatin CORRECTION: 23-Nov-2009: While hospitalized, the patient was administered Actonel 150 mg weekly instead of once a month from (b) (6) as was reported previously) (b) (6).</p> <p>ADDITIONAL INFORMATION: 17-Dec-2009: Additional information provided by the pharmacist indicated that Actonel was discontinued as this patient was a palliative patient with cardiac amyloidosis and unnecessary medications were stopped to minimize discomfort due to short life expectancy.</p>	Hospital staff administered wrong frequency

ISR NUM	RECV DATE	Narratives	Error Type
5159321	11/20/06	<p>oedema in extremities[Oedema peripheral] arthritis[Arthritis] overdose[Overdose] took one Actonel 35 mg tablet a day for 3 days[Inappropriate schedule of drug administration] Case Description: 10-Nov-2006: A report from Sanofi-Aventis Pharma. (HKG-RIS-2006-035) was received by Procter &amp; Gamble Pharmaceuticals on (b) (6). A physician reported that a female patient about 70 plus years old taking Actonel (risedronate sodium) 35 mg once weekly to treat osteoporosis, took one Actonel 35 mg tablet daily the past three consecutive days and was hospitalized for observation. The events included overdose, edema in extremities and arthritis. Blood tests confirmed no hypocalcaemia. The a patient had not recovered. The reporting physician assessed causality as probable. MEDICAL HISTORY/ALLERGIES : deafness; allergies: none reported CONCOMITANT MEDICATIONS : none reported</p>	<p>Patient administered wrong frequency No reason reported</p>
3841331	11/30/01	<p>31Aug2001: A physician reported that a female patient who was prescribed Actonel Risedronate Sodium: dates and indication unspecified) 30 mg once weekly had taken Actonel 30 mg daily for 2 months and was experiencing headaches and a little nausea. The physician indicated that the patient was told to take Actonel once weekly but the patient took it daily. Actonel dosing compliance unknown. The physician reported that the patient was doing well and he planned to restart the patient on Actonel 5 mg daily after a short period of time off of ACtonel therapy.</p>	<p>Patient administered wrong frequency Reason not reported</p>
3924368	5/29/02	<p>05Feb2001: A pharmacist reported that a female patient who took Actonel risedronate sodium 30 mg once daily for over a year (dates and indication not specified) was hospitalized for something relating to her foot. She didn't think the reason for hospitalization was related to Actonel. The outcome of the event was unknown</p>	<p>Patient administered wrong frequency Reason not reported</p>

ISR NUM	RECV DATE	Narratives	Error Type
4040935	1/10/03	<p>fever of unknown origin [Pyrexia] Case Description: 02-Jan-2003: A pharmacist reported that a 49 year old female patient who started taking Actonel (risedronate sodium; duration unspecified) 35 mg daily to treat osteoporosis developed a fever of unknown origin and was hospitalized on (b) (6). MEDICAL HISTORY/ALLERGIES: unknown CONCOMITANT MEDICATIONS: atenolol, Cipro (ciprofloxacin hydrochloride), Vasotec (enalapril maleate), glipizide, heparin insulin, metformin, Aspirin (acetylsalicylic acid) DESCRIPTION OF EVENT: The hospital pharmacist reported that the patient claimed to be taking Actonel 35 mg once a day. The pharmacist was attempting to contact the dispensing pharmacy to determine if this was an error. Actonel had not been discontinued. The event was continuing. No further information was provided at the time of this event.</p>	<p>Patient administered wrong frequency Reason not reported</p>
4311116	3/2/04	<p>Mistakenly took Actonel one daily instead of weekly [Medication error] Case Description: 11-Feb-2004: A 58 year old female patient who was prescribed Actonel (risedronate sodium) 30 mg once weekly and mistakenly took it once daily from 21-Nov-2003 to 26-Nov-2003, and then switched to Actonel 35 mg once weekly from early Dec-2003 to late Jan-2004 to treat osteoporosis, reported that she experienced flashes of light in one eye and was diagnosed with posterior vitreous detachment on (b) (6) by an ophthalmologist. The cause of posterior vitreous detachment was unknown. The patient was not expected to recover from her condition. Actonel therapy had been discontinued. MEDICAL HISTORY/ALLERGIES: hyperparathyroidism, one parathyroid gland removed, tends to have wider than normal variation in blood calcium and higher than normal calcium levels; allergies: morphine CONCOMITANT MEDICATIONS: Armour Thyroid (thyroid), Altace (ramipril)</p>	<p>Patient administered wrong frequency Reason not reported</p>

ISR NUM	RECV DATE	Narratives	Error Type
4432620	8/23/04	<p>Case Description: (b) (6): A pharmacist reported that an elderly female patient who took Actonel (risedronate sodium, duration unspecified) 35mg twice weekly for an unspecified period in error to treat osteoporosis was hospitalised with fatigue and a rash. Upon admission the rash covered the patient's lower trunk and her doctor was investigating whether she may have shingles. Actonel was not noted on admission and was, therefore, not given. A subsequent blood test showed the patient to be hypercalcaemic. The outcome of the events are unknown. MEDICAL HISTORY / ALLERGIES: allergies: none reported CONCOMITANT MEDICATIONS: unspecified calcium supplement.</p>	<p>Patient administered wrong frequency Reason not reported</p>
4621138	3/28/05	<p>small non-Q myocardial infarction[Myocardial infarction] took risedronate 70mg daily[Medication error] Case Description: 17-Mar-2005: A healthcare professional reported via the Medicines and Healthcare products Regulatory Agency (b) (6) that a 63 year old female patient (53 kg) who took risedronate sodium 70 mg daily orally from 30-Jan-2005 to treat osteoporosis experienced a small non-Q myocardial infarction on (b) (6). The reporter to the MHRA considered the event medically significant. The reporter also stated that there were no other risk factors. Action taken with Risedronate and outcome of event were unknown. MEDICAL HISTORY / ALLERGIES: Blood test NOS and a ventriculogram were positive; allergies: none reported. CONCOMITANT MEDICATIONS: bimatoprost, Calcichew D3 (calcium carbonate, colecalciferol).</p>	<p>Patient administered wrong frequency Reason not reported</p>
6153595	4/9/09	<p>Case Description: 30-Mar-2009: A healthcare professional reported via the French regulatory authorities (b) (6) that a 58 year old female patient who took the wrong dose of Actonel (risedronate sodium), 75 mg per month, on (b) (6) and on (b) (6) for vertebral fracture, experienced allergic conjunctivitis and ocular discomfort on (b) (6). These events were assessed as medically significant. The patient was treated with Chibro Cadron (dexamethasone sodium phosphate/neomycin sulfate). The outcome of these events was recovered. Events occurred 48 hours after the second intake of risedronate. Actonel was discontinued on 01-MAR-2009. MEDICAL HISTORY/ALLERGIES: None reported. CONCOMITANT MEDICATIONS: None reported.</p>	<p>Patient administered wrong frequency Reason not reported</p>

ISR NUM	RECV DATE	Narratives	Error Type
6055807	1/26/09	<p>Case Description: 16-Jan-2009: A healthcare professional reported via the Medicines and Healthcare Products Regulatory Agency (Ref: (b) (6)) that a 72 year old female patient who took Actonel (risedronate sodium, duration unknown) 35mg once daily orally to treat osteoarthritis, experienced a stroke on (b) (6) and was hospitalised for a few days. The patient was also taking co-suspects alendronic acid to treat osteoarthritis; Calcichew (calcium carbonate) one dose form daily orally to treat osteoarthritis; carbamazepine 200mg 3 times daily orally to treat epilepsy; codeine phosphate orally to treat migraine, Gaviscon (sodium alginate potassium bicarbonate); pantoprazole 20mg daily orally; paracetamol orally to treat migraine; Seretide (fluticasone propionate,salmeterol xinafoate) two dose form twice daily inhaled from 2005 to treat asthma; Thyroxine (levothyroxine) 100ug daily orally to treat decreased thyroid activity; Ventolin (salbutamol) inhaled to treat asthma; warfarin once daily sliding dose of 7-8mg orally to treat deep vein thrombosis and zolmitriptan orally to treat migraine. The patient underwent a computerized tomogram on (b) (6) which was normal. The physician considered that the events were not related to treatment with the suspect drugs Actonel and all other co-suspect products were not discontinued. The event was reported as resolved with sequelae. The patient was reported to have recovered from the stroke in early 2007 but had left side weakness and used a walking stick for support. Additional information later received from the patient stated that she had experienced cough and breathlessness on 07-Jan-2009. The outcome of the cough and breathlessness was unresolved.</p>	<p>Patient administered wrong frequency Reason not reported</p>
4776501	9/15/05	<p>Patient died [Unevaluable event] prescribed Actonel OAW 35mg tablets twice a week [Medication error] Case Description: (b) (6) A pharmacist reported that an elderly female patient (no further details) who was prescribed Actonel (risedronate sodium) 35 mg twice a week orally approximately 1 year ago died approximately four weeks later. Cause of death was unknown. The pharmacist called after reviewing patient notes and queried if it was a normal dosage. The pharmacist was unsure if the dosage was a prescribing error a mistake in the patient's notes. MEDICAL HISTORY/ ALLERGIES: None reported CONCOMITANT MEDICATION: None reported</p>	<p>Prescribing Error</p>

ISR NUM	RECV DATE	Narratives	Error Type
4331677	3/29/04	<p>Case Description: 07-Nov-2002: A 41 year old female patient (DOB unspecified) who started taking Actonel (risedronate sodium) in the fall of 2001 to treat osteoporosis reported that she took 30 mg daily and experienced aching bones and aching feet from Nov-2001. The patient stated that she was prescribed Actonel 30 mg daily for almost one year and that she did not realize this was a mistake until recently when she visited another doctor who prescribed 30 mg once a week. She stated that she was unsure of symptoms as she has always had aching bones and aching feet. The patient's family member called back later the same day and indicated that the patient took Actonel therapy for 8 months and experienced joint and back pains that she had never experienced prior to Actonel therapy. Actonel therapy was discontinued in Jun-2002 or Jul-2002. The events were resolved on 6-Nov-2002. The patient did not grant permission to follow-up with her physician as she indicated that she would speak to her physician first. MEDICAL HISTORY / ALLERGIES: no previous exposure to Actonel therapy, aching bones and aching feet, rheumatoid arthritis, premenstrual syndrome, hormonal imbalance; allergies: none known CONCOMITANT MEDICATIONS: Prozac (fluoxetine hydrochloride) 10 mg daily since the fall of 1999 for premenstrual syndrome, Cyclomen (danazol) 100 mg 2 times daily since Jan-2000 for premenstrual syndrome, methotrexate 7.5 mg once weekly on and off for six months, but maybe took for 2 months since May-2001 for rheumatoid arthritis, folic acid 5 mg 6 times weekly for rheumatoid arthritis, Celebrex (celecoxib) 400 - 600 mg daily since approximately 2001 for rheumatoid arthritis, all concomitant medications were ongoing. ADDITIONAL INFORMATION: 12-Nov-2002: Additional information provided by the patient indicated that she was prescribed Actonel 30 mg daily in 1999. However, in an earlier conversation, she had stated that she had started Actonel 30 mg daily in 2001. The patient stated that she was proceeding with legal action against the physician and had made a formal complaint with the Ontario College of Pharmacists regarding her administration of Actonel 30 mg daily for almost one year. ADDITIONAL INFORMATION: 21-Nov-2002: Additional information provided by the physician via telephone indicated that a 41 year old female patient (DOB unspecified) received 30 mg of Actonel daily for 8 months since Nov-2001 to treat osteopenia and experienced foot cramps since approximately Nov-2001. The patient experienced foot cramps since commencing Actonel therapy. The physician only provided details of the case that she felt</p>	Prescribing Error Prescribed daily versus monthly

ISR NUM	RECV DATE	Narratives	Error Type
		<p>were 'relevant' and declined to provide the patient's past medical history, as she stated this was not relevant. The physician stated that Actonel 30 mg was prescribed by another physician. The physician stated that when Actonel was first discontinued, the patient's serum calcium, phosphorus, 1,25 dihydroxy vitamin D and alkaline phosphatase levels were all checked and found to be normal. Additionally, the physician reported that the patient's BMD had improved. The physician noted that only a biopsy would show the impact of chronic overdose on bone turnover and formation/ quality and that a biopsy was unwarranted in this case. Actonel therapy was discontinued in Jun-2002. Foot cramps were ongoing. MEDICAL HISTORY/ ALLERGIES: minor surgery - date and type of surgery unknown, 'medically' menopausal; allergies none known CONCOMITANT MEDICATIONS: Celebrex (celecoxib) 100 mg twice daily 27-Dec-2002: Additional information provided by the physician confirmed that a female patient (DOB unspecified; 173 cm, 83 kg) who took 30 mg of Actonel daily for approximately 8 months from Nov-2001 to Jun-2002 experienced joint and back pain from Nov-2001 to 06-Nov-2002 and aching bones. The events were assessed as being mild in severity. The patient's 25(OH) Vitamin D level was 60 nmol/L (normal: 25-200 nmol/L) and ionized calcium was 1.25 mmol/L (normal: 1.15-1.37 mmol/L) on 21-Nov-2002. The physician also reported that the patient's NTx (N-Telopeptide Cross-Links) was 18 nmol BCE/mmol creatinine (normal: 5-65 nmol BCE/mmol creatinine) on 23-Nov-2002. ADDITIONAL INFORMATION: 23-Oct-2003: Additional information provided by the patient's partner indicated that the 42 year old female patient (born: 1961) started taking Actonel 30 mg once daily in Oct-2001 to treat osteoporosis and developed rheumatoid arthritis and joint aches and pains in Oct-2001. This information conflicted with previous statements when it was reported that the patient had a history of rheumatoid arthritis. The reporter stated that the patient was prescribed Actonel by her general practitioner/ gynecologist and took it every day for approximately 7-8 months. Within 1-2 weeks of starting her medication, the patient developed joint aches and pains. At this time, she went to see a rheumatologist who suggested that she might be developing rheumatoid arthritis. The patient had already been taking Celebrex (celecoxib) so this treatment was continued. The reporter did not recall if the patient informed the rheumatologist at that time that she was taking Actonel". her rheumatologist had given her a cortisone injection in her right shoulder prior to the</p>	

ISR NUM	RECV DATE	Narratives	Error Type
		<p>start of Actonel for tendonitis and this was repeated 2 or 3 times after Actonel was started. Around Jan-2002 the patient noticed on occasions that her feet were turning blue and this was also reported to her rheumatologist. On one occasion after receiving cortisone injection the patient was in so much pain that she went to the hospital - she was examined but not admitted and she received no additional treatment at that time. During the time the patient took Actonel she experienced chest pain, atrophy of her whole body, no strength and muscle weakening. The patient had also developed several skin lesions. One of these skin lesions was recently biopsied and came back as "connective tissue disease related" in Oct-2003. The patient was still complaining of bone aches and pains, flu-like symptoms and described her feet as "feeling like she is walking on marbles". The patient stated that she "feels like things are rolling around". The patient has had both x-rays and ultrasound of her feet which were "OK", but a magnetic resonance imaging (MRI) in the summer of 2003 reported "torn and damaged ligaments, contusions of bone and narrowing of marrow" in her feet. The patient was able to sleep, lying down, for only short periods at a time because her pain increased when she would lay down. The patient was currently having physiotherapy 3 times a week. The patient had trouble walking up or down stairs. The patient stated that she did not have enough strength "to take the top off a pop bottle", especially now in the cooler, damp weather. During the warm days in the summer, the patient seemed to be "a little better". After the patient had stopped taking Actonel, on one of her visits to the rheumatologist around Jan-2003, the patient was seen to have swollen feet and her doctor wanted to take a sample of the fluid from her ankle - this fluid was "blood". The patient had been seeing a rheumatologist, her general practitioner and a dermatologist for treatment. Actonel therapy was discontinued in Jun-2002. The events were ongoing.</p> <p>MEDICAL HISTORY/ ALLERGIES: right shoulder tendonitis since 2000 - controlled with medication, premenstrual syndrome (PMS) since Dec-2002 - controlled with medication; allergies: none known</p>	

ISR NUM	RECV DATE	Narratives	Error Type
3854348	11/30/01	<p>17Jul2001: A physician reported 74 year old female patient who took Actonel 30 mg daily for approximately 30 days to treat postmenopausal osteoporosis experienced moderate left leg pain in shin area he felt was strip of calcium subcutaneously under the skin. The patient was mistakenly given Actonel 30 mg with the instructions to take one tablet daily. For the past 30 days the patient had taken Actonel 30 mg daily. The physician reported that the patient was unable to walk for a distance without pain.</p>	<p>Prescribing error Wrong instructions given to patient by healthcare provider</p>
3841233	11/30/01	<p>17Sept2001: A femal patient in her 60s who was prescribed Actonel 30 mg weekly to treat osteoporosis reported that she took 28 tablets of Actonel 30 mg once daily spread over six weeks beginning Oct 2000 and experienced upset stomach feeling bad and feeling gripey. Actonel dosing compliance was unknown. The patient's filler her prescription in error as Actonel 30 mg daily. Because of the events the patient did not take Actonel daily but spaced out 28 tablets over a 6-week period. After the 6-week period the patient discontinued Actonel and did not restart until approximately 6 weeks ago. She is now on Actonel 30 mg once weekly and denise adverse event</p>	<p>Transcription / Dispensing error</p>
6057008	1/27/09	<p>Patient presented to the Emergency Dept with symptoms of severe dizziness and vertigo that impaired function at rest and chest pain. Cardiac enzymes and ECG were normal and head CT was negative for acute findings. She was admitted to the hospital for further work-up. The hospital pharmacist noted the dose of Actonel of 30mg daily was high for patient with no diagnosis of Paget's disease. He called the patient's pharmacy who verified that they had filled the prescription for 30mg daily. He then called the patient's personal physician, who stated that the patient should be taking Actonel 35mg once a week, and adverse reaction to Actonel was suspected as the cause of the dizziness. She required isolation in the hospital due to history of MRSA. Actonel was held for the week, the patient was hemodynamically stable and the dizziness subsided. She was discharged after 2 days.</p>	<p>Transcription / Dispensing error</p>

ISR NUM	RECV DATE	Narratives	Error Type
3895924	4/4/02	<p>Case Description: (b) (6) In a report from Aventis Pharma, received by Procter and Gamble on (b) (6), a nurse practitioner reported that a patient had a possible side effect with Actonel (risedronate sodium; indication, dosage and duration unspecified). ADDITIONAL INFORMATION: 20-DEC-2001: Additional information provided by the nurse via a professional sales representative indicated that the patient was prescribed Actonel 30 mg once weekly, but had taken Actonel 30 mg daily for about 6 months since the pharmacy had labeled the prescription bottle "1 pill daily". ADDITIONAL INFORMATION: 02-Jan-2002: Additional information provided by the nurse indicated that the 75 year old female patient who took Actonel to treat osteoporosis, experienced numbness in hand, arm, tongue and "blank spots" when writing and reading; potential vascular etiology was being ruled out. DESCRIPTION OF EVENT" Actonel dosing compliance was unspecified. The numbness lasted for about 1 month. The patient was being worked up to rule out other causes. Plavix (clopidogrel busulfate) was started for potential vascular etiology (e.g. stroke). The patient's calcium level and vision were evaluated and found to be "ok". Actonel was discontinued. ADDITIONAL INFORMATION: 25-Mar-2002: Additional information provided by the nurse practitioner indicated that the patient (born:1926, 59.4kg), who took Actonel 30 mg daily from 16-Mar-2001 to 17-Dec-2001, experienced transient ischemic attack (TIA) symptoms on (b) (6) and was hospitalized from (b) (6). CONCOMITANT MEDICATIONS: Vioxx (rofecoxib) 25 mg as needed for pain from 16-Mar-2001, Synthroid (levothyroxine sodium) 0.075mg daily taken for years for hypothyroidism, Prilosec (omeprazole) 20 mg as needed for GERD from 12-Mar-2001, potassium for hypertension with diuretic use, Dyazide (hydrochlorothiazide/triamterene) taken for hypertension, Claritin (loratadine) 10 mg daily for allergic rhinitis, acetylsalicylic acid 81 mg daily for anticoagulation, Premarin (estrogens conjugated) 0.625 mg daily for being post-menopausal DESCRIPTION OF EVENT: The nurse reported that the events of potential vascular etiology, numbness in hand and arm, and numbness in tongue that were previously reported were due to the TIA. She indicated that the patient was started on antiplatelet therapy and made a complete recovery. The severity of the events was assessed as moderate. No further information was provided.</p>	Transcription error
4107857	5/7/03	Mrs. _____ Rx for Actonel was accidentally mistranscribed by a tech. It was supposed to read 1 q	Transcription Error

ISR NUM	RECV DATE	Narratives	Error Type
		<p>week but instead was written 1 QD. Although the Pt. kept taking the med correctly as 1 Q Week. The error was made in transcribing. THIS ERROR OCCURRED DURING A TIME WHEN THE SCANNERS AT ___ IN ___ WERE NOT SCANNING CLEARLY. WE WERE HAVING PROBLEMS READING "DR. CALL LABELS" (DR CALL LABELS ARE RECEIPTS PRINTED WHEN A CUSTOMER NO LONGER HAS ANY REMAINING REFILLS ON THEIR RX., A DR CALL LABEL IS THEN GENERATED. THE DR. IS CALLED FOR ADDITIONAL REFILLS. IF &amp; WHEN THE DR. OK'S THE RX FOR REFILLS IT IS DOCUMENTED ON THE DR. CALL LABEL AND IS GENERATED INTO A NEW RX AND IS SCANNED INTO THE SYSTEM WHERE IT COULD BE READ AND VERIFIED @ THE QUALITY ASSURANCE STATION. SINCE WE WERE HAVING DIFFICULTY READING THESE DR. CALL LABELS AT QA. DUE TO LACK OF CLARITY WE DECIDED TO REWRITE THE RX INTO A HANDWRITTEN COPY WHICH COULD BE READ MUCH MORE CLEARLY @ Q.A. STATION. THIS IS WHERE THE ERROR WAS MADE, ALTHOUGH THIS IS NOT A TECH DUTY, _____ TOOK IT UPON HERSELF TO REWRITE THE RX AND TRANSCRIBED "TAKE 1 TAB WEEKLY, 1 Q W, INTO TAKE 1 TAB DAILY 1 QD." SHORTLY AFTER THE INCIDENT WE RECEIVED NEW SCANNERS WHICH ALLEVIATED THE NEED TO TRANSCRIBE DR. CALL LABELS. Did the error reach the patient? Yes</p>	
4208872	10/9/03	<p>New 24h retail A tech incorrectly transcribed from computer screen to hard copy one QD instead of one Q week, The Tech was not aware that she shouldn't transcribe d therefore made error Medication error</p>	Transcription Error
4762144	9/6/05	<p>Pt had new rx for Actonel 35 mg tablets which is dosed 1 tablet weekly. The doctor wrote the prescription correctly, but when it was dispensed the label stated 1 tablet daily. The error was not noted until the patient requested a refill 3 months later and the incorrect dosage was noted. The patient had been taking the med properly based on the interval between refills. DESCRIBE THE DIRECT RESULT OF THE ERROR ON THE PATIENT (e.g., death, type of harm, additional patient monitoring). INDICATE THE POSSIBLE ERROR CAUSE(S) AND CONTRIBUTING FACTOR (S) (e.g, abbreviation, similar names, distractions, etc.) medication error</p>	Wrong frequency Transcription error

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22560

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WARNER  
CHILCOTT CO LLC

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 (b) (4)

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CATHY A MILLER  
07/15/2010

ZACHARY A OLESZCZUK  
07/15/2010

DENISE P TOYER  
07/15/2010

CAROL A HOLQUIST  
07/21/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 15, 2010

To: Scott Monroe, M.D., Division Director  
**Division of Reproductive and Urologic Products (DRUP)**

Through: Claudia Karwoski, PharmD, Director  
**Division of Risk Management (DRISK)**  
LaShawn Griffiths, MSHS-PH, BSN, RN  
Patient Product Information Reviewer, Acting Team Leader  
**Division of Risk Management**

From: Melissa Hulett, MSBA, BSN, RN  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (PPI),

Drug Name(s): ATELVIA (risedronate sodium) delayed-release

Application Type/Number: NDA 22560

Applicant/sponsor: Warner Chilcott Pharmaceuticals, LLC.

OSE RCM #: 2009-2051

## 1 INTRODUCTION

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for ATELVIA (risedronate sodium) delayed-release tablets. Please let us know if DRUP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

On September 24, 2009 Procter and Gamble Pharmaceuticals Inc. submitted an original New Drug Application under 505(b)(1) of the Federal Food Drug & Cosmetic Act for NDA 22560 for ATELVIA (risedronate sodium) delayed-release tablets. ATELVIA (risedronate sodium) delayed-release tablets is a once-a-week risedronate 35 mg delayed-release formulation. (b) (4)  
(b) (4) treatment of postmenopausal osteoporosis (PMO) (b) (4). On February 26, 2010 the Sponsor was changed from Procter and Gamble to Warner Chilcott Pharmaceuticals, LLC.

## 2 MATERIAL REVIEWED

- Draft ATELVIA (risedronate sodium) delayed-release tablets Prescribing Information (PI) submitted September 24, 2009 and revised by the Review Division throughout the current review cycle and received by DRISK on July 1, 2010.
- Draft ATELVIA (risedronate sodium) delayed-release tablets Patient Package Insert (PPI) submitted on September 24, 2009 and received by DRISK on July 6, 2010.

## 3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the Medication Guide Regulations as specified in 21 CFR 208.20
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

We recommend ACTONEL (risedronate sodium), which has the same active ingredient as ATELVIA (risedronate sodium) delayed-release tablets, be updated to reflect the changes reflected in the Patient Package Insert (PPI) for ATELVIA (risedronate sodium) delayed-release tablets when a future supplement is received.

Please let us know if you have any questions.

APPEARS THIS WAY ON ORIGINAL

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22560

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MELISSA I HULETT  
07/15/2010

CLAUDIA B KARWOSKI  
07/15/2010  
concur

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: May 20, 2010

TO: Karl Stiller, Regulatory Project Manager  
Stephen Bienz, M.D., Medical Officer  
Division of Reproductive and Urologic Products

FROM: Roy Blay, Ph.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-560

APPLICANT: Procter & Gamble Pharmaceuticals, Inc.

DRUG: (b) (4) (risedronate sodium with EDTA delayed-release tablets)

NME: No

THERAPEUTIC  
CLASSIFICATION: Standard Review

INDICATION: Treatment of postmenopausal osteoporosis

CONSULTATION  
REQUEST DATE: November 4, 2009

DIVISION ACTION  
GOAL DATE: July 24, 2010

PDUFA DATE: July 24, 2010

## I. BACKGROUND:

The conduct of Protocol 2007008 entitled “A Non-inferiority Comparison of 35 mg Delayed-release Risedronate, Administered Once Weekly Either Before or After Breakfast, and 5 mg Immediate-release Risedronate, Administered Once-daily Before Breakfast, in the Treatment of Postmenopausal Osteoporosis as Assessed Over 2 Years; a Phase III, Multicenter, Double-blind, Double-dummy, Randomized, Active-controlled, Parallel-group Study” was inspected. The study was designed as a 2-year, Phase III, multi-center, multi-nation, double-blind, double-dummy, randomized, parallel group, active-controlled, non-inferiority study intended to assess the efficacy and safety of risedronate administered as a 35 mg delayed release weekly regimen (taken (b) (4) immediately following breakfast) as compared to a 5 mg immediate-release daily regimen (taken at least 30 minutes before breakfast).

The primary objectives of this study were the following:

- To assess the non-inferiority of risedronate, administered as a 35 mg delayed release (DR) weekly regimen administered immediately following breakfast (DRFB regimen), compared to the 5 mg immediate release (IR) daily regimen administered at least 30 minutes before breakfast (IRB regimen), as determined by percent change from baseline in lumbar spine BMD at Week 52 (last observation carried forward [LOCF]).
- If, and only if, the DRFB regimen were non-inferior to the IRB regimen, to then assess the non-inferiority of the 35 mg DR weekly risedronate formulation, administered at least 30 minutes before breakfast (DRBB), compared to the 5 mg IR daily risedronate formulation, administered at least 30 minutes before breakfast (IRB), as assessed by percent change from baseline in lumbar spine bone mineral density (BMD) at Week 52 LOCF.

For this study, the primary efficacy endpoint was the DXA measurement of spine BMD at Week 52.

The clinical site of Dr. Racewicz was selected for inspection because only 23.6% of subjects reported adverse event compared to the trial average of 72.7%. Dr. Zanchetta’s and Dr. Recker’s sites were selected because of their high enrollments.

**II. RESULTS (by Site):**

<b>Name of CI, Location</b>	<b>Protocol #/ # of Subjects/</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Site #104680 Dr. Artur Racewicz, Niepubliczny Zakład Opieki Zdrowotnej, Centrum Medyczne, Ul. Pułaskiego 69, 15-337 Białystok - Poland	2007008/ 55 randomized/	12-16 Apr 2010	Pending. Interim classification NAI
Site # 104578 Dr. Jose Zanchetta, Libertad 836 3er Piso. Of 53 C1012 AAR, Ciudad Autónoma de Buenos Aires - Argentina	2007008/ 63 randomized/	5-9 Apr 2010	Pending. Interim classification NAI.
Site #104600 Robert Recker, MD Creighton University Osteoporosis Research Center, 601 North 30th Street, Room 4820, Omaha, NE 68131	2007008/ 34 randomized/	22-26 Mar 2010	Pending. Interim classification NAI.

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;  
EIR has not been received from the field and complete review of EIR is pending.

## 1. Dr. Artur Racewicz

Niepubliczny Zakład Opieki Zdrowotnej, Centrum Medyczne

Ul. Pułaskiego 69, 15-337

Białystok - Poland

**a. What was inspected:** At this site, 82 subjects were screened, 55 were randomized, and 47 completed the study. The records of those subjects who were screen failures and those who were randomized to the study were audited with respect to informed consent. The primary endpoint data (DXA reports) for all enrolled subjects were compared to data listings. The source records for an additional 21 subjects were reviewed in a comprehensive manner, including adverse event reporting.

**b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies, regulatory violations, or evidence of under-reporting of adverse events.

**c. Assessment of data integrity:** Data appear acceptable in support of the respective application.

2. Dr. Jose Zanchetta  
Libertad 836 3er Piso. Of 53 C1012 AAR  
Ciudad Autónoma de Buenos Aires - Argentina

- a. **What was inspected:** At this site, 182 subjects were screened, 95 were randomized, 30 completed the study, 29 were discontinued or withdrew from the study, and 36 subjects remained ongoing in the study. Informed consent was reviewed for all screen failures and 47 of the enrolled subjects. The primary endpoint data (DXA scans) were reviewed for 70 subjects. Source records for 33 subjects were audited in a comprehensive manner.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

3. Robert Recker, MD  
Creighton University Osteoporosis Research Center,  
601 North 30th Street, Room 4820, Omaha, NE 68131

- a. **What was inspected:** At this site, 93 subjects were screened, 34 were enrolled, 28 completed the study, and six subjects were withdrawn from the study. The records of all 34 enrolled subjects were audited with respect to informed consent, subject eligibility, laboratory results, concomitant medications, adverse event reporting, test article administration, and primary endpoint data.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Racewicz, Zanchetta, and Recker were inspected in support of this NDA. Based on preliminary information, no significant regulatory violations were observed at these three sites. The study appears to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication.

Note: Receipt and review of the EIRs for the inspections of the clinical investigator sites of Drs. Racewicz, Zanchetta, and Recker are pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be any observations of clinical and regulatory significance discovered after reviewing the EIRs.

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

Application  
Type/Number

Submission  
Type/Number

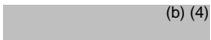
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CHILCOTT CO LLC

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/s/  
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ROY A BLAY  
05/21/2010

TEJASHRI S PUROHIT-SHETH  
05/21/2010

# RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22-560 BLA#	NDA Supplement #:Original BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: risedronate sodium Dosage Form: delayed-release tablet Strengths: 35 mg		
Applicant: Procter & Gamble Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: September 24, 2009 Date of Receipt: September 24, 2009 Date clock started after UN:		
PDUFA Goal Date: July 24, 2010	Action Goal Date (if different): July 23, 2010	
Filing Date: November 23, 2009	Date of Filing Meeting: November 3, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): Treatment (b) (4) of postmenopausal osteoporosis, (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a>            and refer to Appendix A for further information.</i></b>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	
Collaborative Review Division (if OTC product):		

List referenced IND Number(s): 31,029 74,086 58,394				
<b>Goal Dates/Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			Changes to the dosage form, applicant name, and address sent to document room – 12-Nov-09. Dosage form changed. Others are correct as per their directives.
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>		X		
<b>If yes</b> , explain in comment column.			X	
<b>If affected by AIP</b> , has OC/DMPQ been notified of the submission? <b>If yes</b> , date notified:			X	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application:  <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
  <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees:  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	

Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?  <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></b>  <b>If yes, please list below:</b>	X			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
NDA 20-835	ACTONEL	M-61	1-23-2012	
NDA 20-835	ACTONEL	PED	1-23-2013	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></b>		X		(b) (4)
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  <b>If yes, # years requested:</b> 3  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?			X	

<i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				
<b>Format and Content</b>				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance <sup>1</sup> ? <b>If not</b> , explain (e.g., waiver granted).	<b>X</b>			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<b>X</b>			
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no</b> , explain.	<b>X</b>			
<b>Controlled substance/Product with abuse potential:</b> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>			<b>X</b>	
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes</b> , BLA #			<b>X</b>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature?  <i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information</b> (NDAs/NDA efficacy supplements only)	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

Is patent information submitted on form FDA 3542a?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?  <i>Forms must be signed by the APPLICANT, not an Agent.</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X			
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature? ( <i>Certification is not required for supplements if submitted in the original application</i> )  <i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)</i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
<b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b>		X		
<b>If studies or full waiver not included, is a request for full</b>	X			

waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>				
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)  <i>If no, request in 74-day letter</i>	X			
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			OSE/DMEPA consult sent 9-30-2009
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			consult sent 9-30-2009
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	X			consult sent 9-30-2009
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		X		link to labeling sent in consult

<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>		X		
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> June 28, 2007  <i>If yes, distribute minutes before filing meeting</i>	X			EOP2 minutes available via DARRTS/EDR and NDA (checked into DARRTS under IND 074086 8-31-2007)
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> April 21, 2009  <i>If yes, distribute minutes before filing meeting</i>	X			Pre-NDA minutes available via DARRTS/EDR and NDA (checked into DARRTS under IND 074086 5-20-2009)
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** November 3, 2009

**NDA #:** 22-560

**PROPRIETARY NAME:** (b) (4)

**ESTABLISHED/PROPER NAME:** risedronate sodium delayed-release

**DOSAGE FORM/STRENGTH:** tablets 35 mg

**APPLICANT:** Procter & Gamble Pharmaceuticals, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

(1) Treatment (b) (4) of postmenopausal osteoporosis (b) (4)

**BACKGROUND:** Actonel is a bisphosphonate currently approved for the prevention and treatment of postmenopausal osteoporosis, treatment to increase bone mass in men with osteoporosis, treatment and prevention of glucocorticoid-induced osteoporosis, and treatment of Paget's disease under NDA 20-835.

P&G (b) (4) developed a once-a-week risedronate delayed release (RIS-DR) formulation that may allow for administration without regard to the timing of food or drink.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Karl Stiller	Y
	CPMS/TL:	Margaret Kober	Y
Cross-Discipline Team Leader (CDTL)	Theresa Kehoe		Y
Clinical	Reviewer:	Steve Bienz	Y
	TL:	Theresa Kehoe	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Doanh Tran	Y
	TL:	Myong-Jin Kim	N
Biostatistics	Reviewer:	Xin Fang	N
	TL:	Mahboob Sobhan	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Gemma Kuijpers	Y
	TL:	Lynnda Reid	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Caroline Strasinger	Y
	TL:	Donna Christner	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other: Biopharm Reviewer	Reviewer:	Sandra Suarez	N
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**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p> <p>1. Insufficient information is available to assure adequate bone safety for the level of risedronate exposure achieved with the proposed product (35 mg DR formulation). As outlined in the preNDA meeting minutes, this safety issue, which requires adequate bone histomorphometry data at the anticipated drug exposure levels, remains a concern for the Division.</p> <p>a. Provide the tables referenced in sections 4.3.5.1 and 4.3.5.2 of Clinical Report 1998033 regarding bone histopathology and histomorphometry (Appendix 3.16 Tables 1 and 2 and Appendix 5.18 Table 1) and any other tables, figures, or listings related to bone histopathology or histomorphometry from Clinical Report 1998033 not included in your NDA submission.</p> <p>b. Provide justification for why the bone histomorphometry data provided in the submission should be adequate to demonstrate the bone safety of the proposed product. This discussion should include an in depth analysis of the risedronate exposures achieved or anticipated for each histomorphometry study submitted. Pharmacokinetic data should be submitted in support of your discussion.</p> <p>2. Submit a rationale for assuming the applicability of foreign data in the NDA submission to the U.S. population or provide the location of this rationale in the submission. This discussion should include an in-depth</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

analysis of the calcium and vitamin D status in various populations enrolled.	
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: this drug/biologic is not the first in its class
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>CLINICAL MICROBIOLOGY</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL PHARMACOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>Comments:</b></p> <p>Phase 3 study 2007008 administered 2 different risedronate delayed release tablet formulations (material number [REDACTED] (b) (4)) that had different risedronate cores. Please provide the following information:</p> <ul style="list-style-type: none"> <li>A listing of all patients in the phase 3 study 2007008 that were administered the [REDACTED] (b) (4) formulation and the start and stop time relative to the first dose that each patient used this formulation.</li> <li>Any information that was used to bridge between formulations [REDACTED] (b) (4).</li> <li>Proposal and rationale for how data from patients that were administered formulation</li> </ul>	

<p>(b) (4) should be treated.</p>	
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> (b) (4)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b>          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.</p> <p>For Residual Solvents, you state that the tablets have been assessed as per USP/NF &lt;467&gt; Residual Solvents and levels were found to be below the permitted daily exposure. Provide data in support of this conclusion.</p> <p>Update the specification and acceptance criteria for APPEARANCE to identify the imprint used on the tablet.</p> <p>Update the container labels with the NDC numbers. Ensure that it corresponds with the NDC number listed on the Physician's Insert</p> <p>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).</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p>The labeling includes a <span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span> as a manufacturing site, while the application lists only the Norwich Pharmaceutical site. Explain the discrepancy and either remove the <span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span> site from the labeling or add the site to the NDA as a manufacturing site available for inspection.</p> <p>As per 21 CFR 314.50(d)(1)(ii)(c), provide a copy of the proposed Master Batch Record</p>	
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p style="margin-left: 40px;"><b>If no</b>, was a complete EA submitted?</p> <p style="margin-left: 40px;"><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<p><b>CMC Labeling Review (BLAs/BLA supplements only)</b></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Scott Monroe</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached) (optional):</b></p> <p>Comments:</p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<p><input checked="" type="checkbox"/></p>	<p>Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p><input type="checkbox"/></p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>
<p><input type="checkbox"/></p>	<p>BLA/BLA supplements: If filed, send 60-day filing letter</p>
<p><input type="checkbox"/></p>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>

<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Application  
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Submission  
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Submitter Name

Product Name

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NDA-22560

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PROCTER AND  
GAMBLE  
PHARMACEUTICA  
LS INC

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/s/  
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KARL J STILLER  
11/25/2009

MARGARET M KOBER  
11/28/2009

# DSI CONSULT

## Request for Biopharmaceutical Inspections

**DATE:** November 23, 2009

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**THROUGH:** Hae-Young Ahn, Ph.D.  
Acting Director, Division of Clinical Pharmacology III  
Office of Clinical Pharmacology

**FROM:** Karl Stiller, Regulatory Project Manager, Division of Reproductive and Urologic Products, HFD-580

**SUBJECT: Request for Biopharmaceutical Inspections**  
NDA 022560  
(b) (4) (risedronate sodium) delayed-release tablets, 35 mg  
Procter & Gamble Pharmaceuticals, Inc.

**Study/Site Identification:**

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
2008119	<p><b>Site 104970: Comprehensive Phase One Miramar</b></p> <p><b>Principal investigator:</b> Dr. Maria Gutierrez</p> <p><b>Sub-investigators:</b> (b) (4)</p> <p><b>Address and contact information:</b> 3400 Enterprise Way Miramar, FL 33025 Phone: 954-266-1000</p>	<p><b>Bioanalysis site:</b> (b) (4)</p> <p>(b) (4)</p>

**International Inspections:**

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain): Pivotal BE study

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **April 1, 2010**. We intend to issue an action letter on this application by **July 23, 2010**.

Should you require any additional information, please contact Karl Stiller, Regulatory Project Manager, 301-796-1993.

Concurrence:

Myong-Jin Kim, Pharm.D. – Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCPIII), Office of Clinical Pharmacology (OCP)

Doanh Tran, Ph.D. – Clinical Pharmacology Reviewer, DCPIII, OCP

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/s/  
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KARL J STILLER  
11/23/2009

HAE YOUNG AHN  
11/23/2009

# DSI CONSULT: Request for Clinical Inspections

**Date:** November 4, 2009

**To:** Leslie Ball, M.D., Branch Chief, GCP2  
Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
*Name of DSI Primary Reviewer (if known): Not known*  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Stephen Bienz MD, Division of Reproductive and Urologic Products /  
HFD-580  
Theresa Kehoe MD, / Division of Reproductive and Urologic Products /  
HFD-580

**From:** Karl Stiller, Regulatory Health Project Manager/ Division of Reproductive  
and Urologic Products / HFD-580

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA-22-560

Sponsor/Sponsor contact information (to include phone/email):

Procter & Gamble Pharmaceuticals, Inc./

Gary F. Galletta, PharmD

U.S. Regulatory Affairs

Procter & Gamble Pharmaceuticals

Mason Business Center

8700 Mason-Montgomery Road

Mason, OH 45040-9760

Phone: 513-622-4952

Fax: 513-622-5363

E-mail: Galletta.gf@pg.com

Drug: (b) (4) (risedronate sodium with EDTA delayed-release tablets)

NME: No

Standard or Priority: Standard

Study Population < 18 years of age: No

Pediatric exclusivity: Waiver pending

PDUFA:

Action Goal Date: July 24, 2010

Inspection Summary Goal Date: April 24, 2010

**II. Background Information**

With NDA 22-560 Procter & Gamble Pharmaceuticals seeks approval to market an enteric-coated delayed release risedronate sodium (DR) with indications for treating (b) (4) postmenopausal osteoporosis (b) (4). Immediate release risedronate (IR) is already approved at multiple doses and multiple dosing intervals under NDAs 20-835 and 21-823 (b) (4). This formulation contains EDTA (b) (4). The Applicant seeks labeling to allow this formulation to be taken in the morning with (b) (4) food. Effectiveness when taken with food would be unique among oral bisphosphonates, as usually food markedly attenuates the already poor absorption of bisphosphonates and therefore this class of drugs is taken after an overnight fast at least 30 to 60 minutes before breakfast.

Osteoporosis is a condition of mineral loss and increased fragility in bone which becomes increasingly prevalent with increased age and predisposes to fracture with minimal or no trauma and the resultant morbidity and mortality. While most common in postmenopausal females, it occurs in males as well. Bisphosphonates such as risedronate have been shown to increase bone mineral content (bone mass) and reduce fracture risk.

The single phase 3 trial in this application is trial 2007008, *A Non-inferiority Comparison of 35 mg Delayed-release Risedronate, Administered Once-weekly Either Before or After Breakfast, and 5 mg Immediate-release Risedronate, Administered Once-daily Before Breakfast, in the Treatment of Postmenopausal Osteoporosis as Assessed Over 2 Years; a Phase III, Multicenter, Double-blind, Double-dummy, Randomized, Active-controlled, Parallel-group Study*. This trial is being done in Argentina, Belgium, Canada, Estonia, France, Hungary, Poland, and the United States. Lumbar spine BMD is the primary endpoint. This NDA application is filed based on one year data from this trial. Two major early concerns with the application both have to do with the systemic risedronate absorption with the DR formulation being considerably higher than that from the IR formulation. Overall safety will need to be closely reviewed. Potential long-term bone negative effects from the high exposure are also worrisome. Bone biopsy will not be done until the end of this trial at 2 years, and bone biopsy data from prior trials with high dose risedronate appear limited. Inspections are requested at several sites from this trial.

**III. Protocol/Site Identification**

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
104680 (Dr. Artur Racewicz, Niepubliczny Zakład Opieki Zdrowotnej, Centrum Medyczne, Ul. Pułaskiego 69, 15-337 Białystok - Poland)	2007008	82 screened, 55 randomized	Postmenopausal Osteoporosis

<b>Site # (Name, Address, Phone number, email, fax#)</b>	<b>Protocol #</b>	<b>Number of Subjects</b>	<b>Indication</b>
104578 (Dr. Jose Zanchetta, Libertad 836 3er Piso. Of 53 C1012 AAR, Ciudad Autónoma de Buenos Aires - Argentina)	2007008	182 screened, 95 randomized	Postmenopausal Osteoporosis
104600 (Robert Recker, MD, Creighton University Osteoporosis Research Center, 601 North 30th Street, Room 4820, Omaha, NE 68131)	2007008	93 screened, 34 randomized	Postmenopausal Osteoporosis
Alternates:			
104577 (Dr. Carlos Mautalen, Azcuénaga 1860 8vo Piso C1128AF, Ciudad Autónoma de Buenos Aires - Argentina)	2007008	98 screened, 63 randomized	Postmenopausal Osteoporosis
104679 (Prof. Jan Krzysztof Łącki, Instytut Reumatologii im. prof. dr hab. Med. Eleonory Reicher; Klinika i Poliklinika Układowych Chorób Tkanki Łącznej, Ul. Spartańska 1, 02-637 Warszawa - Poland)	2007008	76 screened, 29 randomized	Postmenopausal Osteoporosis
104590 (Michael Bolognese, MD, Bolognese Research Services, 10215 Fernwood Road, Suite 40, Bethesda, MD 20817)	2007008	93 screened, 35 randomized	Postmenopausal Osteoporosis

#### **IV. Site Selection/Rationale**

Site 104680: 23.6% of subjects reported adverse event compared to trial average of 72.7%

Site 104578: High enrolling site

Site 104600: High enrolling US site

Site 104577: 25.4% of subjects discontinued compared to trial average of 16.8%

Site 104679: 37.9% of subjects reported adverse event compared to trial average of 72.7%

Site 104590: High enrolling US site. However, this site has been previously inspected for multiple other osteoporosis studies.

#### **Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data – only 15% of enrolled subjects were in the US.
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) High enrollment, lower than expected adverse events, high discontinuation – see site rationale above.

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**V. Tables of Specific Data to be Verified (if applicable): NA**

Should you require any additional information, please contact Karl Stiller at Ph: 301-796-1993 or Stephen Bienz at Ph: 301-796-3921.

Concurrence: (as needed)

\_\_\_\_\_ Medical Team Leader  
\_\_\_\_\_ Medical Reviewer  
\_\_\_\_\_ Director, Division Director (for foreign inspection requests only)

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/s/  
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STEPHEN R BIENZ  
12/09/2009

THERESA E KEHOE  
12/09/2009

SCOTT E MONROE  
12/09/2009