

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022560Orig1s000

**ADMINISTRATIVE and
CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 022560

SUPPL # 000

HFD # 580

Trade Name Atelvia

Generic Name risedronate sodium

Applicant Name Warner Chilcott Co., LLC

Approval Date, If Known October 8, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021823

Actonel Plus Calcium

NDA# 020835

Actonel

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

2007008 - Noninferiority

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

2007008 - Noninferiority

YES

NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

2007008 - Noninferiority

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

- c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

2007008 - Noninferiority

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

IND # 074086 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
! YES ! NO
! Explain: ! Explain:

Investigation #2 !
! YES ! NO
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Karl Stiller, R.Ph.
Title: Regulatory Health Project Manager
Date: September 8, 2010

Name of Office/Division Director signing form: George Benson, M.D.
Title: Deputy Director Division of Reproductive and Urologic Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

CELIA R PEACOCK
10/08/2010

GEORGE S BENSON
10/08/2010



NDA 022560/S-001 and S-002

SUPPLEMENT APPROVAL

Warner Chilcott (US), LLC
Attention: Matthew Lamb, PharmD
Senior Director, Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Dr. Lamb:

Please refer to your Supplemental New Drug Applications (sNDAs) S-001 (labeling) and S-002 (proposed risk evaluation and mitigation strategy [REMS]), dated November 11, 2010, received November 12, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Atelvia (risedronate sodium) 35 mg delayed-release tablets.

We acknowledge receipt of your amendments dated December 17 and 22, 2010 and January 10 and 14, 2011.

We also refer to our letter dated October 13, 2010, notifying you, under Section 505(o)(4) and 505-1 of the FDCA, of new safety information that we believe should be included in the labeling for bisphosphonates and that a REMS is necessary. This information pertains to the risk of atypical subtrochanteric and diaphyseal femoral fractures with the bisphosphonate drug class.

Supplemental new drug application S-001 provides for revisions to the labeling for Atelvia. The agreed upon changes to the language included in our October 13, 2010, letter are as follows (additions are noted by underline and deletions are noted by ~~striketrough~~).

1. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, the following text was added:
 - a. Recent Major Changes:
 - Indications and Usage (1.2) 01/2011
 - Warnings and Precautions (5.6) 01/2011
 - b. Indications and Usage:

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

c. Warnings and Precautions:

- Atypical femur fractures have been reported. Patients with new thigh or groin pain should be evaluated to rule out a femoral fracture. (5.5)

2. In the **INDICATIONS AND USAGE** section of the package insert, the following text was added:

1.2 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.

3. In the **WARNINGS AND PRECAUTIONS** section, the following text was added:

5.6 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)} 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 ^{(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.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days from the date of this letter, amend all pending supplemental applications for this NDA, including pending CBE supplements, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes with the revisions indicated above approved in this supplemental application.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels attached as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 022560/S-001 and S-002.**” Approval of this submission by FDA is not required before the labeling is used.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Supplemental new drug application S-002 provides for a proposed REMS.

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS, if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated October 13, 2010.

Since Atelvia was approved on October 8, 2010, we have become aware of the risk of atypical subtrochanteric and diaphyseal femoral fractures with the bisphosphonate drug class. We consider this information to be “new safety information” as defined in section 505-1(b) of FDCA.

Your proposed REMS, submitted on December 17, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, an evaluation of patients’ understanding of the serious risks of Atelvia.

We remind you that assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post-approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post-approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you will also need to submit a REMS, REMS supporting document, and any required appended documents for that authorized generic, to this NDA. In other words, you must submit a complete

proposed REMS that relates only to the authorized generic product. Review and approval of the REMS is required before you may market your product.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 022560 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 022560
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022560
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director for Safety
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling
REMS

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/s/

AUDREY L GASSMAN
01/25/2011



NDA 022560/S-001

LABELING DISCUSSION EXTENSION

Warner Chilcott (US), LLC
Attention: Matthew Lamb, PharmD
Senior Director, Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Dr. Lamb:

Please refer to your November 11, 2010, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Atelvia (risedronate sodium), 35 mg delayed-release tablets.

On October 13, 2010, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Atelvia to address the risk of atypical subtrochanteric and diaphyseal femoral fractures, with the use of the class of bisphosphonates, based on new safety information about this risk identified since the product was approved. You were directed to submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On November 12, 2010, we received your November 11, 2010 prior approval supplement containing your proposed safety related labeling changes. Section 505(o) requires FDA to promptly review the supplement and if we disagree with the proposed changes, to initiate discussions with you on the content of the changes. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

This letter is to inform you that we have determined that a 30-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for this supplement, ends on January 11, 2011.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director for Safety
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

AUDREY L GASSMAN
12/10/2010



NDA 022560

INFORMATION REQUEST

Warner Chilcott (US), LLC
Attention: Matthew Lamb, PharmD
Senior Director, Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Dr. Lamb:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Atelvia, (risedronate sodium) 35 mg delayed-release tablets.

We also refer to your November 12, 2010, submissions, containing your prior approval supplement proposing safety changes to the approved labeling, proposed Risk Evaluation and Mitigation Strategy (REMS), REMS Supporting Document, and proposed Medication Guide.

We are reviewing the referenced material and have the following comments and requests for information.

- a. The REMS for Actonel, Actonel with Calcium, and Atelvia have been separated because the products do not share a Medication Guide, however you can consider harmonizing the REMS Assessments for the three products.
- b. GOAL
Revise your goal as follows:
The goal of the REMS is to inform patients about the serious risks associated with the use of Atelvia including the possible risk of unusual thigh bone fractures.
- c. Your Medication Guide Distribution plan is acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CFR 208.24 is more appropriate for the REMS Supporting Document.
- d. Your proposed timetable for submission of assessments is acceptable.
- e. We will defer our comment until the full methodology is submitted, but offer the following guidance on your planned survey as you develop your proposal.

1. Submit for review the detailed plan you propose to use to evaluate patients' understanding about the safe use of Atelvia. You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." If the plan is to conduct the required assessment using a survey, make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of Atelvia.
2. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.

Explain how often you perform non-respondent follow-up or reminders.
If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

Explain how you select recruitment sites.

Submit for review any recruitment advertisements.

3. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
4. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
5. Ensure the sample is demographically representative of the population who use the drug (patients), regardless of the condition for which they use it.
6. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.
7. List the inclusion criteria. For example, eligible patient respondents must be:
 - Age 18 or older
 - Currently taking Atelvia or have taken the drug in the past 3 months
 - Not currently participating in a clinical trial involving Atelvia
 - Not a healthcare provider

Submit any screener instruments, and describe any quotas of sub-populations used.

8. Explain how you administer surveys and the intended frequency.
Offer respondents multiple options for completing the survey. Be sure to include an option for the lower literacy population. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.
Explain how you train surveyors.
9. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).
10. Submit for review the introductory text used to inform respondents about the purpose of the survey.

Tell potential respondents that their answers will not affect their ability to receive or take (patients) the drug, and that their answers and personal information will be kept confidential and anonymous.

11. Clarify in your methodology that respondents are eligible for one wave of the survey only.
12. The assessment evaluates the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug. The assessment does not evaluate consumer comprehension of the Medication Guide. According to regulation (21 CFR 208.24), patients receive the Medication Guide at the time the prescription is filled/dispensed. Do not offer respondents an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.
13. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
14. Ensure the patient knowledge survey includes questions that ask about the specific risks or safety information conveyed in the Medication Guide to determine if the patient understands the information and knows what to do if they experience an adverse event.

Derive the risk-specific questions from information located in the "What is the Most Important Information I should know about Atelvia?" section of the Medication Guide.

Ensure the risk-specific questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure that each question has an "I don't know" answer option.

Randomize the order of the multiple choice responses on each survey.

15. Order questions so the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Collect demographic questions last or as part of any screener questions.

Do not allow respondents the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

16. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
17. Prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example:
"Now we are going to ask you some questions about the Medication Guide you may have received with Atelvia. The Medication Guide is a paper handout that contains important information about the risks associated with use of Atelvia and how to use Atelvia safely." Medication Guides always include the title "Medication Guide" followed by the word Atelvia and its pronunciation. The Medication Guide usually

has sections titled “What is the most important information I should know about Atelvia,” “What is Atelvia,” and “Who should not take Atelvia.”

18. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

- Who gave you the Medication Guide for Atelvia? (Select all that apply)
 - a) My doctor or someone in my doctor’s office
 - b) My pharmacist or someone at the pharmacy
 - c) Someone else - please explain: _____
 - d) I did not get a Medication Guide for Atelvia
- Did you read the Medication Guide?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
- Did you understand what you read in the Medication Guide?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
- Did someone offer to explain to you the information in the Medication Guide?
 - a) Yes, my doctor or someone in my doctor’s office
 - b) Yes, my pharmacist or someone at the pharmacy
 - c) Yes, someone else – please explain: _____
 - d) No
- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

19. Analyze results on an item-by-item or variable-by-variable basis. You may present the data using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

You may stratify the data by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments utilized.

We have attached a copy of the REMS with the above recommendations shown as tracked changes.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director for Safety
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

AUDREY L GASSMAN
12/08/2010

REQUEST FOR CONSULTATION

TO (Office/Division): OSE/Patient Labeling
cc: Maria Wasilik

FROM (Name, Office/Division, and Phone Number of Requestor): Meredith Alpert, Division of Reproductive and Urologic Products, x61218

DATE
November 16, 2010

IND NO.
TSI #468

NDA NO.
20560,21575,
20835,21455,
21762,21817,
21823,21858,
22560

TYPE OF DOCUMENT

DATE OF DOCUMENT
11.15.10

NAME OF DRUG

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
Bisphosphonates

DESIRED COMPLETION DATE
November 29, 2010

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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COMMENTS / SPECIAL INSTRUCTIONS: The Division of Reproductive and Urologic Products (DRUP) has become aware of new safety information indicating a possible increased risk of atypical fractures and diaphyseal femoral fractures in patients using bisphosphonates. As a result, DRUP requested safety labeling updates and Med Guides for all drug products in the Bisphosphonate class. We would like Patient Labeling to review and provide comments for the recent labeling submissions of the following NDAs (Reclast, Boniva, Actonel, and Fosamax): 20560, 21575, 20835, 21455, 21762, 21817, 21823, 21858, and 22560. Please see the following EDR links for access to the documents. EDR links:

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\\CDSESUB1\EVSPROD\NDA020560\0069

\\CDSESUB1\EVSPROD\NDA021817\0072

Reference ID: 2864591
\\FDSWA150\NONECTD\N21455\S_011\2010-11-12

\\FDSWA150\NONECTD\N21858\S_009\2010-11-12

\\CDSESUB1\EVSPROD\NDA022560\0031

\\CDSESUB1\EVSPROD\NDA020835\0081

NDA 21823 (Actonel with Calcium) is a paper submission. A scanned copy will be emailed asap.

SIGNATURE OF REQUESTOR

Meredith Alpert, M.S., Acting Safety Project Manager

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

MEREDITH H ALPERT
11/16/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **OSE/DMEPA**
cc: **Maria Wasilik**

FROM (Name, Office/Division, and Phone Number of Requestor): **Meredith Alpert, Division of Reproductive and Urologic Products, x61218**

DATE
November 16, 2010

IND NO.
TSI #468

NDA NO.
20560,21575,
20835,21455,
21762,21817,
21823,21858,
22560

TYPE OF DOCUMENT

DATE OF DOCUMENT
11.15.10

NAME OF DRUG

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
Bisphosphonates

DESIRED COMPLETION DATE
November 29, 2010

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

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| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

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|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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COMMENTS / SPECIAL INSTRUCTIONS: The Division of Reproductive and Urologic Products (DRUP) has become aware of new safety information indicating a possible increased risk of atypical fractures and diaphyseal femoral fractures in patients using bisphosphonates. As a result, DRUP requested safety labeling updates and Med Guides for all drug products in the bisphosphonate class. We would like DMEPA to review and provide comments for the recent carton/container submissions of the following NDAs (Reclast, Boniva, Actonel, and Fosamax): 21762, 21575, 20835, 20560, 22560, 21817, 21455, 21823, and 21858. Please see the following EDR links for access to the documents. EDR links:

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 \\CDSESUB1\EVSPROD\NDA021575\0050
 \\CDSESUB1\EVSPROD\NDA020560\0069
 \\CDSESUB1\EVSPROD\NDA021817\0072
 Reference ID: 2864602
 \\FDSWA150\NONECTD\N21455\S_011\2010-11-12

\\FDSWA150\NONECTD\N21858\S_009\2010-11-12

\\CDSESUB1\EVSPROD\NDA022560\0031

\\CDSESUB1\EVSPROD\NDA020835\0081

NDA 21823 (Actonel with Calcium) is a paper submission. A scanned copy will be emailed asap.

SIGNATURE OF REQUESTOR

Meredith Alpert, M.S., Acting Safety Project Manager

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

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PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

MEREDITH H ALPERT
11/16/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **OSE/DRISK**
cc: **Maria Wasilik**

FROM (Name, Office/Division, and Phone Number of Requestor): **Meredith Alpert, Division of Reproductive and Urologic Products, x61218**

DATE
November 16, 2010

IND NO.
TSI #468

NDA NO.
20560,21575,
20835,21455,
21762,21817,
21823,21858,
22560

TYPE OF DOCUMENT

DATE OF DOCUMENT
11.15.10

NAME OF DRUG

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
Bisphosphonates

DESIRED COMPLETION DATE
November 29, 2010

NAME OF FIRM:

REASON FOR REQUEST

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| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

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| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
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III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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COMMENTS / SPECIAL INSTRUCTIONS: The Division of Reproductive and Urologic Products (DRUP) has become aware of new safety information indicating a possible increased risk of atypical fractures and diaphyseal femoral fractures in patients using bisphosphonates. As a result, DRUP requested safety labeling updates and Med Guides for all drug products in the bisphosphonate class. We would like DRISK to review and provide comments for the recent REMS document submissions of the following NDAs (Reclast, Boniva, Actonel, and Fosamax): 20560, 21575, 20835, 21455, 21762, 21817, 21823, 21858, and 22560. Please see the following EDR links for access to the documents.
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 \\CDSESUB1\EVSPROD\NDA022560\0032

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\\FDSWA150\NONECTD\N21455\S_011\2010-11-12

\\FDSWA150\NONECTD\N21858\S_009\2010-11-12

NDA 21823 (Actonel with Calcium) is a paper submission. A scanned copy will be emailed asap.

SIGNATURE OF REQUESTOR

Meredith Alpert, M.S., Acting Safety Project Manager

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

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PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

MEREDITH H ALPERT
11/16/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Meredith Alpert, Division of Reproductive and Urologic
Products, x61218

REQUEST DATE
November 16, 2010

TSI NO.
#468

NDA/BLA NO.
20560,21575,
20835,21455,
21762,21817,
21823,21858,
22560

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

SLC/REMS submissions with carton/container labels

NAME OF DRUG

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
Bisphosphonates

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up meeting)
November 29, 2010

NAME OF FIRM:

PDUFA Date:

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR links to submissions:

[\\CDSESUB1\EVSPROD\NDA021762\0099](#)

[\\CDSESUB1\EVSPROD\NDA021575\0050](#)

[\\CDSESUB1\EVSPROD\NDA020835\0082](#) (Actonel REMS)

[\\CDSESUB1\EVSPROD\NDA020560\0069](#)

[\\CDSESUB1\EVSPROD\NDA022560\0032](#) (Atelvia REMS)

[\\CDSESUB1\EVSPROD\NDA021817\0072](#)

[\\FDSWA150\NONECTD\N21455\S_011\2010-11-12](#)

[\\FDSWA150\NONECTD\N21858\S_009\2010-11-12](#)

[\\CDSESUB1\EVSPROD\NDA022560\0031](#) (Atelvia labeling supplement and carton/container)

[\\CDSESUB1\EVSPROD\NDA020835\0081](#) (Actonel labeling supplement and carton/container)

NDA 21823 (Actonel with Calcium) is a paper submission. A scanned copy will be emailed asap.

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: The Division of Reproductive and Urologic Products (DRUP) has become aware of new safety information indicating a possible increased risk of atypical fractures and diaphyseal femoral fractures in patients using bisphosphonates. As a result, DRUP requested safety labeling updates and Med Guides for all drug products in the Bisphosphonate class. We would like DDMAC to review and provide comments for the recent REMS/SLC and carton/container label submissions of the following NDAs (Reclast, Boniva, Actonel, and Fosamax): 20560, 21575, 20835, 21455, 21762, 21817, 21823, 21858, and 22560. Please see the above EDR links for access to the documents. Actonel with Calcium is a paper submission, which will be sent ASAP.

SIGNATURE OF REQUESTER Meredith Alpert, M.S., Acting Safety Project Manager

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

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/s/

MEREDITH H ALPERT
11/16/2010



NDA 022560/Original-1

SAFETY LABELING CHANGE AND REMS NOTIFICATION

Warner Chilcott (US), LLC
Attention: Matthew Lamb, PharmD
Senior Director, Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Dr. Lamb:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Atelvia, (risedronate sodium) 35 mg delayed-release tablets.

Sections 505(o)(4) and 505-1 of the FDCA authorize FDA to require holders of approved drug and biological product applications to make safety related labeling changes, and to develop and comply with risk evaluation and mitigation strategies (REMS) based upon new safety information that becomes available after approval of the drug or biological product.

Since Atelvia was approved on October 8, 2010, we have become aware of a possible increased risk of atypical subtrochanteric and diaphyseal femoral fractures in patients taking bisphosphonates, including Atelvia, for the treatment and/or prevention of osteoporosis. Recent publications, including the 2010 Report of a Task Force of the American Society for Bone and Mineral Research, suggest that the risk of atypical fractures and diaphyseal femoral fractures increases with increased duration of bisphosphonate exposure. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

SAFETY LABELING CHANGE

In accordance with section 505(o)(4) of the FDCA, we are notifying you that, based on the new safety information described above, we believe that the information regarding possible increased risk of atypical fractures and diaphyseal femoral fractures should be included in the labeling for bisphosphonates approved for the treatment and/or prevention of osteoporosis as follows:

1. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, under Recent Major Changes: add the following two bullets (underlined):

Recent Major Changes:

- Indications and Usage (insert date)
 - Warnings and Precautions (insert date)
2. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, under Indications and Usage: add the following (underlined):

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

3. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, under Warnings and Precautions: add the following bullet (underlined):

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

4. Add the following language to the **INDICATIONS AND USAGE** section of the package insert (underlined):

1.2 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.

5. Revise the **WARNINGS AND PRECAUTIONS** section of the package insert to add the following paragraphs (underlined) as described below:

5.6 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 impact 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. Subjects 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.

6. Medication Guide

In addition to the labeling changes described above, you should convert your patient package insert to a Medication Guide for Atelvia, as shown in the Medication Guide attached (See ENCLOSURES). Your Medication Guide must include information about the serious risk of atypical subtrochanteric and diaphyseal femoral fractures and will be considered part of the proposed REMS described below.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted. Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: “**SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT**” or “**SAFETY LABELING CHANGES UNDER 505(o)(4) - CHANGE NOT WARRANTED.**”

If you do not submit electronically, please send 5 copies of the submission.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Atelvia 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.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Atelvia poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Atelvia. FDA has determined that Atelvia is a product for which patient labeling could help prevent serious adverse effects and/or that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Atelvia.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Atelvia.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven years after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

In accordance with section 505-1, within 30 days of the date of this letter, you must submit a proposed REMS as a supplement to your NDA.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to Atelvia (see Appendix A). Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

For administrative purposes, designate the proposed REMS submission “**PROPOSED REMS for NDA 022560/S-###**” and all subsequent submissions related to the proposed REMS “**PROPOSED REMS-AMENDMENT for NDA 022560.**” If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director for Safety
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

REMS Appendix A
REMS Appendix B
Medication Guide

Initial REMS Approval: XX/XXXX
Most Recent Modification: XX/XXXX

APPENDIX A: MEDICATION GUIDE REMS TEMPLATE

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

To inform patients about the serious risks associated with the use of [drug name].

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each [drug name] prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, by 18 months, by 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX B:

**REMS SUPPORTING DOCUMENT TEMPLATE
MEDICATION GUIDE REMS**

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
 - a. Medication Guide
 - b. Describe in detail how you will comply with 21 CFR 208.24
 - c. Timetable for Submission of Assessments of the REMS (for products approved under and NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

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/s/

AUDREY L GASSMAN
10/13/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022560

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Warner Chilcott Pharmaceuticals, Inc.
Attention: Gary F. Galletta, Pharm.D.
U.S. Regulatory Affairs
8700 Mason-Montgomery Road
Mason, OH 45040-9760

Dear Dr. Galletta:

Please refer to your September 23, 2009, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for risedronate sodium delayed release tablets.

On June 28, 2010, we received your solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 24, 2010.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests no later than six weeks prior to the new PDUFA goal date.

If you have any questions, call Karl Stiller, R.Ph., Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22560

ORIG-1

WARNER
CHILCOTT CO LLC

 (b) (4)

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/s/

JENNIFER L MERCIER

07/14/2010



NDA 022560

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Warner Chilcott Pharmaceuticals Inc.
Mason Business Center
8700 Mason-Montgomery Rd.
Mason, Ohio 45040-9462

ATTENTION: Gary F. Galletta, PharmD
U.S. Regulatory Affairs

Dear Dr. Galletta:

Please refer to your New Drug Application (NDA) dated September 24, 2009, received September 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risedronate Sodium Delayed-release Tablets, 35 mg.

We also refer to your April 9 and April 26, 2010, correspondences, received April 12 and April 27, 2010, respectively requesting review of your proposed proprietary name, Atelvia. We have completed our review of the proposed proprietary name, Atelvia and have concluded that it is acceptable.

The proposed proprietary name, Atelvia, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 9, 2010 and April 26, 2010 submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567.

NDA 022560

Page 2

For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Karl Stiller at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

Application
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Submission
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Submitter Name

Product Name

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CHILCOTT CO LLC

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/s/

CAROL A HOLQUIST
06/23/2010



NDA 022560

INFORMATION REQUEST

Warner Chilcott Pharmaceuticals, Inc.
Attention: Gary Galletta, PharmD
U.S. Regulatory Affairs
Mason Business Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

Dear Dr. Galletta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for risedronate sodium delayed-release tablets.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comment and information request. We request a written response by May 28, 2010, in order to continue our evaluation of your NDA.

The following dissolution specifications are recommended based on the mean dissolution values from clinical drug product release, clinical drug product pivotal stability, and commercial scale drug product release batches:

- *Acid Stage: No individual tablet exceeds (b) (4) dissolved at (b) (4) hours.*
- *Buffer Stage: Not less than (b) (4) (Q) of the label amount of risedronate sodium is dissolved at (b) (4) minutes.*

Revise your specification table accordingly.

If you have any questions regarding this letter, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22560

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CHILCOTT CO LLC

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/s/

MOO JHONG RHEE
05/11/2010
Chief, Branch III



NDA 022560

INFORMATION REQUEST

Warner Chilcott Pharmaceuticals, Inc.
Attention: Gary Galletta, PharmD
U.S. Regulatory Affairs
Mason Business Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

Dear Dr. Galletta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for risedronate sodium delayed-release tablets.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The higher absorption and extent of exposure of the risedronate delayed-release (DR) formulation may adversely affect the long-term safety profile of this formulation when compared to the immediate-release (IR) formulation. Discuss and clarify why you believe that the extent of risedronate exposure will not have an impact on long-term safety.
2. Preclinical data suggest that EDTA may enhance absorption of risedronate, at least partially, through mechanisms other than the chelation (b) (4). This may potentiate risedronate toxicity, including toxicity in the gastrointestinal tract. We also note in the 120 day safety update that adverse event data in your Phase 3 trial, 2007008, show significantly more subjects with adverse events with the DR formulation (231 of 307 (75.2%) for 5 mg IRBB, 241 of 307 (78.5%) for 35 mg DRFB, 257 of 308 (83.4%) for DRBB, and for DR groups combined 498 of 615 (81.0%), $p=0.0483$). Discuss the role EDTA may have in the increased adverse events with the DR formulation.

If you have any questions, please call Karl Stiller, Regulatory Health Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22560

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/s/

MARGARET M KOBER

04/27/2010

Chief, Project Management Staff



NDA 022560

INFORMATION REQUEST

Warner Chilcott Pharmaceuticals, Inc.
Attention: Gary Galleta, Pharm.D.—U.S. Regulatory Affairs
Mason Business Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

Dear Dr. Galleta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for risedronate sodium delayed-release tablets.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Our analysis of serum intact parathyroid hormone (iPTH) levels in the Phase 3 trial for NDA22-560, Trial 2007008, indicates more subjects with high (≥ 66 pg/ml) and very high (≥ 98 pg/ml) iPTH values following treatment with the risedronate DR formulation, especially when taken at least 30 minutes before breakfast (DRBB). This increase appears to be sustained to the 26 and 52 week time points (see table). These findings raise potential safety concerns with regard to mineral metabolism and bone quality. Prior trials of various immediate release risedronate strengths in postmenopausal osteoporosis appear not to have shown similar PTH elevation.

Trial 2007008 Serum PTH

	5 mg IR Daily	35 mg DRFB	35 mg DRBB
N	307	307	308
High PTH at screening ¹ or baseline	43	38	36
High PTH at 2 weeks	58	68	70
High PTH at 26 weeks	29	30	47
High PTH at 52 weeks	35	30	42
High PTH at any protocol time	94	101	115
High PTH at 26 or 52 weeks with normal at baseline and screening ¹	26	33	48
Very high PTH at screening ¹ or baseline	9	4	9
Very high PTH at 2 weeks	14	13	23
Very high PTH at 26 weeks	6	3	13
Very high PTH at 52 weeks	5	7	11

	5 mg IR Daily	35 mg DRFB	35 mg DRBB
Very high PTH at any protocol time	20	19	37
Very high PTH at 26 or 52 weeks with normal at baseline and screening ¹	2	5	8
DRFB = delayed release formulation immediately following breakfast weekly DRBB = delayed release formulation at least 30 minutes before breakfast weekly High PTH \geq 66 pg/ml Very high PTH \geq 98 pg/ml 1 Screening PTH only done in Argentine subjects			

1. Address the etiology of PTH elevation with the DR formulation. Specifically, is the increased systemic risedronate absorption with this formulation responsible and/or does the ethylenediaminetetraacetate (EDTA) have a role?
2. For subjects with elevated PTH at 52 weeks, supply any follow up PTH values now available.
3. For subjects with elevated and markedly elevated PTH levels, discuss the effect on serum calcium, phosphate, and magnesium levels. Differentiate between subjects who entered the trial with elevated PTH and those who developed elevated PTH with dosing.
4. We believe bone histomorphometry results from Trial 2007008 will likely be necessary to address our concerns regarding bone quality. Clarify when the bone histomorphometry results for Trial 2007008 will be available.

If you have any questions, please call Karl Stiller, Regulatory Health Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22560

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WARNER
CHILCOTT CO LLC

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/s/

SCOTT E MONROE
03/31/2010



NDA 022560

**ACKNOWLEDGE CORPORATE
NAME/ADDRESS CHANGE**

Warner Chilcott Company, LLC c/o Warner Chilcott Pharmaceuticals, Inc.
Attention: Gary Galletta, PharmD
U.S. Regulatory Affairs
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Galletta:

We acknowledge receipt of your correspondence, dated February 8, 2010, and received February 9, 2010, notifying the Food and Drug Administration that the corporate name and address has been changed from

Procter & Gamble Pharmaceuticals, Inc.
Mason Business Center
8700 Mason-Montgomery Road
Mason, OH 45040-9760

to

Warner Chilcott Pharmaceuticals, LLC
Union Street, Road 195 Km. 1.1
Fajardo, PR 00738

for the following new drug application:

NDA 022560 for risedronate sodium, delayed-release tablets.

We have revised our records to reflect this change.

We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

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Type/Number

Submitter Name

Product Name

NDA-22560

GI-1

PROCTER AND
GAMBLE
PHARMACEUTICA
LS INC

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/s/

MARGARET M KOBER

02/26/2010

Chief, Project Management Staff



NDA 022560

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Procter and Gamble Pharmaceuticals, Inc
Mason Business Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

ATTENTION: Gary F. Galletta, Pharm.D
U.S. Regulatory Affairs

Dear Dr. Galletta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risedronate Sodium Delayed-release Tablets, 35 mg.

We also refer to receipt of your November 12, 2009, correspondence, received November 12, 2009, requesting a review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is unacceptable for the following reasons.

(b) (4)

(b) (4)

2. Use of Alternate Name

We note that your submission included the alternate proprietary name (b) (4) Since this alternate proprietary name (b) (4) (b) (4)

Therefore, we find this name unacceptable. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, [HTTP://www.fda.gov/cder/guidance/7935dft.pdf](http://www.fda.gov/cder/guidance/7935dft.pdf) and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Karl Stiller at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application
Type/Number

Submission
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Submitter Name

Product Name

NDA-22560

ORIG-1

PROCTER AND
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PHARMACEUTICA
LS INC

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/s/

CAROL A HOLQUIST
02/19/2010



NDA 22-560

INFORMATION REQUEST

Procter & Gamble Pharmaceuticals, Inc.
Attention: Gary F. Galletta, PharmD
US Regulatory Affairs
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Galletta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for risedronate sodium delayed-release tablets, 35 mg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Submit data supporting the robustness of your proposed dissolution method for risedronate sodium delayed-release tablets. This data should also include tabulated values of individual and mean % dissolved under the conditions tested.

If you have any questions, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22560

ORIG-1

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/s/

MOO JHONG RHEE
02/02/2010
Chief, Branch III



NDA 022560

FILING COMMUNICATION

Procter & Gamble Pharmaceuticals, Inc.
Attention: Gary F. Galletta, PharmD
US Regulatory Affairs
Mason Business Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Galletta:

Please refer to your new drug application (NDA) dated and received on September 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for risedronate sodium delayed-release tablets, 35 mg.

We also refer to your submissions dated September 25, 2009, November 2, 2009, and November 12, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 24, 2010.

During our filing review of your application, we identified the following potential review issues and have the following comments and information requests:

CLINICAL

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 pre-NDA meeting minutes, this safety issue, which requires adequate bone histomorphometry data at the anticipated drug exposure levels, remains a concern.
 - 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.
 - b. Provide justification for why the bone histomorphometry data provided in the submission is 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.

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 analysis of the calcium and vitamin D status in the various populations enrolled.

CLINICAL PHARMACOLOGY

1. Phase 3 study 2007008 administered 2 different risedronate delayed-release tablet formulations (material numbers (b) (4) and (b) (4)) that had different risedronate (b) (4). Provide the following information:
 - a. A listing of all patients in phase 3 study 2007008 who were administered the (b) (4) formulation, and the starting date and total treatment duration for each patient who used this formulation. For example, if a patient was administered formulation (b) (4) at the start of the phase 3 trial and switched to formulation (b) (4) after 130 days of treatment, the patient's starting date would be Day 1 and the total treatment duration would be 130 days.
 - b. Any information that was used to bridge between formulations (b) (4) and (b) (4).
 - c. Proposal and rationale for how data from patients that were administered formulation (b) (4) should be analyzed.

CHEMISTRY, MANUFACTURING, AND CONTROLS

1. We acknowledge that agreement was made in a meeting held on May 20, 2009, that all information on the drug substance could be included in the current NDA by cross-reference to NDA 020835. 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 022560.
2. For Residual Solvents, you state that the tablets have been assessed as per USP/NF <467> Residual Solvents and levels were found to be below the permitted daily exposure. Provide data in support of this conclusion.
3. Update the specification and acceptance criteria for APPEARANCE to identify the imprint used on the tablet.
4. Update the container labels with the NDC numbers. Ensure that they correspond with the NDC numbers listed in the package insert.
5. Ensure that the established name on the container/carton labels is at least ½ the size of the proprietary name as per 21 CFR 201.10(g)(1).
6. The labeling includes a (b) (4) as a manufacturing site, while the application lists only the Norwich Pharmaceutical site. Explain the discrepancy and either remove the (b) (4) site from the labeling or add the site to the NDA as a manufacturing site available for inspection.

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

GENERAL COMMENTS

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22560

ORIG-1

PROCTER AND
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PHARMACEUTICA
LS INC

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/s/

SCOTT E MONROE
12/04/2009



NDA 22-560

NDA ACKNOWLEDGMENT

Procter & Gamble Pharmaceuticals, Inc.
Attention: Gary F. Galletta, PharmD
US Regulatory Affairs
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Galletta:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: risedronate sodium delayed-release tablets, 35 mg

Date of Application: September 24, 2009

Date of Receipt: September 24, 2009

Our Reference Number: NDA 22-560

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 23, 2009, in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22560

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RISEDRONATE SODIUM
DELAYED-RELEASE

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/s/

MARGARET M KOBER

10/08/2009

Chief, Project Management Staff

REQUEST FOR CONSULTATION

TO (*Office/Division*): Division of Drug Marketing, Advertising and Communications (DDMAC) HFD-42, BLD WO 51 Room 3251
Attn: Janice Maniwang
cc: Jialynn Wang

FROM (*Name, Office/Division, and Phone Number of Requestor*): Karl Stiller
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5371
Phone 301-796-1993 karl.stiller@fda.hhs.gov

DATE
9/29/09

IND NO.

NDA NO.
22-560

TYPE OF DOCUMENT

DATE OF DOCUMENT
9/23/09

NAME OF DRUG
RISEDRONATE SODIUM
DELAYED-RELEASE

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
2/23/10

NAME OF FIRM: PROCTER & GAMBLE PHARMACEUTICALS

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|--|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): |
| <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (<i>List below</i>) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

This is an electronic submission, please see EDR.
*** Please review the PPI, PI, carton, and container labeling.
Thank you, Karl Stiller 301-796-1993

SIGNATURE OF REQUESTOR
Karl Stiller 301-796-1993

METHOD OF DELIVERY (Check one)
 DARRTS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22560

ORIG-1

PROCTER
GAMBLE
PHARMACEUTICA
LS

RISEDRONATE SODIUM
DELAYED-RELEASE

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

/s/

KARL J STILLER
09/30/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): CDER OSE CONSULTS		FROM: Karl Stiller Regulatory Project Manager FDA/Center for Drug Evaluation and Research Division of Reproductive and Urologic Products WO22 - Room 5371 Phone 301-796-1993 karl.stiller@fda.hhs.gov		
DATE 9/29/09	IND NO.	NDA 22-560	TYPE OF DOCUMENT	DATE OF DOCUMENT 9/23/09
NAME OF DRUG RISEDRONATE SODIUM DELAYED-RELEASE		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 2/23/10
NAME OF FIRM: PROCTER & GAMBLE PHARMACEUTICALS				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This is an electronic submission, please see EDR. *** Please review the PPI, PI, carton, and container labeling. Thank you, Karl Stiller 301-796-1993				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application
Type/Number

Submission
Type/Number

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09/30/2009