

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202344Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 202344	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Binosto (conditionally acceptable) Established/Proper Name: alendronate sodium effervescent tablets Dosage Form: tablet Strengths: 70 mg		
Applicant: EffRx Pharmaceuticals SA		
Date of Receipt: February 15, 2011		
PDUFA Goal Date: March 15, 2012		Action Goal Date (if different):
Proposed Indication(s): 1) Treatment to increase bone mass in men with osteoporosis 2) Treatment of postmenopausal osteoporosis		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Fosamax tablets, 70 mg– referenced product (NDA 020560)	clinical efficacy and nonclinical safety data

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Study SCO 5361 explored the BE of an 70 mg effervescent tablet (b) (4) vs. a standard oral formulation. Study AE-1212-001-EM used a new formulation of the 70 mg effervescent tablet (b) (4) vs. marketed Fosamax (once weekly, 70 mg tablet) to establish BE

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Fosamax (alendronate sodium) tablets, 70 mg	NDA 020560	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO
If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO
If "YES", please list which drug(s) and answer question d) i. below.
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new dosage form

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): Fosamax, 70 mg tablets/5358941, 5358941*PED, 5681590, 5681590*PED, 6090410, 6090410*PED

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

Patent number(s): 5358941, 5681590, 6090410

- (a)
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO
If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO
If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): May 3, 4, and 11, 2011

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

MEREDITH ALPERT
03/12/2012

SEALD Director Sign-Off Memo and Labeling Review

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

PRODUCT TRADE NAME (NON-PROPRIETY NAME)	BINOSTO (alendronate sodium) effervescent tablets for oral solution
APPLICATION/SUPPLEMENT NUMBER	NDA 202344
TYPE OF APPLICATION	Original Submission
INDICATION	<ul style="list-style-type: none">• Treatment of osteoporosis in postmenopausal women• Treatment to increase bone mass in men with osteoporosis
APPLICANT	EffRx Pharmaceuticals SA
OFFICE/DIVISION	ODE III/DRUP
DIVISION PROJECT MANAGER	Meredith Alpert
RECEIPT DATE	February 15, 2011
PDUFA GOAL DATE	March 15, 2012
SEALD REVIEW DATE	March 8, 2012
SEALD LABELING REVIEWER	Jeanne M. Delasko
SEALD DIRECTOR	Laurie B. Burke

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**” [HL Limitation Statement is not bolded. Must bold.]

- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action. [There is a space between the product title and initial U.S. approval; the initial U.S. approval needs to be placed immediately beneath the product title. Delete space between.]

- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”. [Correct statement appears bolded, but also “italicized.” Delete italics.]

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI. [In FPI, Clinical Studies section, 14.1 is “Treatment of Osteoporosis in Postmenopausal Women” and 14.2 is “Treatment to Increase Bone Mass in Men with Osteoporosis.” The subsection headings in the TOC (14.1 and 14.2) are different and must match the subsection headings in the FPI. Please correct.]
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.

- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

JEANNE M DELASKO
03/08/2012

LAURIE B BURKE
03/08/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: February 29, 2012

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

From: Carrie Newcomer, PharmD, Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
Office of Prescription Drug Promotion (OPDP)

Subject: DDTCP labeling comments for BINOSTO (alendronate sodium)
effervescent tablets for oral solution
NDA: 202344

The Division of Direct-to-Consumer Promotion (DDTCP) in OPDP has reviewed the proposed Medication Guide for BINOSTO (alendronate sodium) effervescent tablets for oral solution (BINOSTO) as requested in the consult dated March 28, 2011.

Please note that the Division of Medical Policy Programs (DMPP) provided comments on the BINOSTO Medication Guide on February 28, 2012 and DDTCP's review is based on this version of the Medication Guide. Reference is also made to the February 28, 2012 e-mail discussion between DMPP and Theresa Kehoe in DRUP in which they agreed to [REDACTED] (b) (4) [REDACTED] from the Medication Guide.

DDTCP has no additional comments on the Medication Guide. If you have any questions, please contact Carrie Newcomer at carrie.newcomer@fda.hhs.gov or at 301-796-1233. We appreciate the opportunity to provide comments on the draft Medication Guide.

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/s/

CARRIE A NEWCOMER
02/29/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: February 28, 2012

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

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Medication Guide)

Drug Name (established name): BINOSTO (alendronate sodium)

Dosage Form and Route: Effervescent Tablets

Application Type/Number: NDA 202344

Applicant: EffRx, Inc.

OSE RCM #: 2011-1176

1 INTRODUCTION

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for BINOSTO (alendronate sodium) Effervescent Tablets.

The purpose of the Applicant's December 21, 2010 new drug application (NDA) 505(b)(2) submission was to seek approval for an effervescent dosage form of alendronate sodium for once-weekly treatment of osteoporosis in postmenopausal woman and to increase bone mass in men with osteoporosis. The reference listed drug for BINOSTO (alendronate sodium) is FOSAMAX (alendronate sodium).

DMPP conferred with DMEPA on February 10, 2012 and a separate DMEPA review of the IFU was completed on February 7, 2012.

2 MATERIAL REVIEWED

- Draft BINOSTO (alendronate sodium) Effervescent Tablets Medication Guide (MG) received on December 21, 2010 and received by DMPP on February 16, 2012
- Draft BINOSTO (alendronate sodium) Effervescent Tablets Prescribing Information (PI) received December 21, 2010, revised by the Review Division throughout the current review cycle and received by DMPP on February 16, 2012
- Approved FOSAMAX (alendronate sodium) Tablets and Oral Solution comparator labeling dated January 25, 2011

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

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

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)

- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

21 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ROBIN E DUER
02/28/2012

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02/28/2012

LASHAWN M GRIFFITHS
02/28/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: February 23, 2012

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

From: Jessica Cleck Derenick, PhD
Regulatory Review Officer
Division of Professional Promotion (DPP)
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Comments on Binosto (alendronate sodium) effervescent tablets for oral use, NDA 202344

The Division of Professional Promotion in OPDP has reviewed the proposed product labeling (PI) for Binosto (alendronate sodium) effervescent tablets for oral use (Binosto) as requested in the consult dated March 28, 2011.

The following comments, using the proposed PI emailed to OPDP by Meredith Alpert on February 16, 2012, are provided below.

If you have any questions, please feel free to contact me (contact information: 301-796-0390; Jessica.Cleck-Derenick@fda.hhs.gov).

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

JESSICA N CLECK DERENICK
02/23/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: February 7, 2012

Reviewer(s): Chi-Ming (Alice) Tu, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh, Team Leader
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Binosto (Alendronate Sodium) Effervescent Tablets, 70 mg

Application Type/Number: IND 103130 and NDA 202344

Applicant: EffRx Pharmaceuticals SA

OSE RCM #: 2011-1186

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the Binosto (Alendronate Sodium) Effervescent Tablet container labels and carton labeling submitted on January 12, 2012, pouch labeling submitted on December 16, 2011, Prescribing Information submitted on October 20, 2011 and Medication Guide submitted December 21, 2010 for areas of vulnerability that can lead to medication errors in response to a request from the Division of Reproductive and Urology Products.

1.1 REGULATORY HISTORY

Binosto is a 505(b)(2) application and the reference listed drug (RLD) is Fosamax.

DMEPA previously reviewed and found the proposed Binosto container label and carton labeling submitted on October 10, 2011 inadequate because of the deficiencies in the (b) (4) carton design. The (b) (4) carton design required end users to flip the carton back and forth to read many instructions just to access the blister. The end user would then have to open the blister in order to obtain the Binosto effervescent tablet. Given that Binosto is a bisphosphonate product requiring many administration instructions, DMEPA found the (b) (4) carton design to be inadequate because the information on the Binosto label and labeling should focus and highlight the critical administration instructions to ensure safe use instead of focusing on the instructions for accessing the blister. Additionally, the label and labeling should not distract the end user with complex mechanisms just to obtain the blister from the carton. The Applicant agreed to re-design the carton labeling for Binosto, but would keep the blister container label for which the stability data was based on.

The Applicant submitted revised Binosto container label and carton labeling on January 12, 2012 and pouch labeling on December 16, 2011 for review.

1.2 PRODUCT INFORMATION

Binosto (Alendronate Sodium) Effervescent Tablets, 70 mg, is a bisphosphonate for the treatment of osteoporosis in postmenopausal women, and for the treatment to increase bone mass in men with osteoporosis. If approved, Binosto will be the first effervescent tablet dosage form for alendronate products. The recommended dose is one 70 mg effervescent tablet once weekly, upon arising for the day. The effervescent tablet should be dissolved in approximately half a glass of plain room temperature water (4 oz.), stirred for 10 seconds after the effervescence stops, and then drank. In clinical trials, Binosto effervescent tablet was dissolved for at least 5 minutes. Binosto must be taken at least 30 minutes before the first food, beverage, or medication of the day. After taking the drug, patients should not lie down for at least 30 minutes and until after food. Binosto will be supplied in cartons containing either 4 or 12 unit of use blister strips. It should be stored at temperatures between 20°C and 25°C in the original packaging until use.

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed container label and carton labeling for any vulnerability that can lead to medication errors. We also searched the FDA Adverse Event Reporting System (AERS) Database to determine if any medication errors due to labels and labeling have occurred with the currently marketed Fosamax (alendronate sodium) tablet and oral solution formulations.

2.1 LABELS AND LABELING

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted January 12, 2012
- Carton Labeling submitted January 12, 2012
- Pouch Labeling submitted December 16, 2011
- Prescribing Information submitted October 20, 2011
- Medication Guide submitted December 21, 2010

2.2 ADVERSE EVENT REPORTING SYSTEM (AERS)

DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving the RLD Fosamax. The AERS search conducted on August 11, 2011 used the following search terms: active ingredient “alendronate%”, trade name “fosamax”, and verbatim terms “alendro%” and “fosa%”. The reaction terms used were the MedDRA Preferred Terms (PT) “Drug Administration Error,” “Drug Prescribing Error,” “Inappropriate Schedule of Drug Administration,” “Incorrect Drug Administered,” “Incorrect Drug Administration Duration,” “Incorrect Drug Dosage Form Administered,” “Incorrect Route of Drug Administration,” “Medication Error,” and “Wrong Technique in Drug Usage Process.” The time frame of the search was limited to the last ten years from August 11, 2001 to August 11, 2011.

Foreign reports were excluded because foreign labels and labeling may differ from the ones marketed in the United States. The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that lacked detail, did not describe a medication error (e.g. accidental overdose, intentional misuse, or patient self-discontinuation due to drug intolerance), or did not describe an error applicable to this review (e.g. wrong drug error due to proprietary name confusion, wrong

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

strength error because Binosto is a single strength product, errors involving cutting or crushing the tablet because Binosto is an effervescent tablet, and omission or transcription error).

3 RESULTS AND DISCUSSION

The following sections summarize our AERS search and our analysis of the container label and carton labeling.

3.1 ADVERSE EVENTS REPORTING SYSTEM (AERS)

The AERS search retrieved 301 reports (See Appendix B for a list of ISR numbers). After combining duplicate reports into cases and excluding cases for reasons stated in Section 2.2 above, 20 cases were identified to be relevant to this review. Patient demographics of the 20 cases include 2 males, 17 females and 1 unknown gender. For those cases where age was reported, the average age was 67 years old (range 15 to 88), with unknown age in three cases. The initial received date for the 20 cases ranged from 2002 to 2009, with the largest number of cases (n=6) being reported in the year 2005.

3.1.1 Overdose (n=1)

One case of overdose error (ISR# 5453789) reported a patient who took ten 40 mg tablets once a day for 180 days in 2004 and experienced hearing loss. In 2007, the patient was diagnosed with the disabling Meniere's disease, which symptoms include hearing loss. The physician could not say if alendronate was related to the hearing loss or coincidental. Therefore, a definitive outcome was not reported.

3.1.2 Wrong drug (n=1)

One case of wrong drug error (ISR# 5940553) described that a prescription for Medrol dosepak was mistakenly dispensed as Alendronate packs from the pharmacy to the patient. The patient took all the pills in one day and experienced stomach upset but is doing fine by the time of reporting. The reporter also stated that the generic Medrol dosepak and Alendronate packs packaging configurations were similar in color and size.

3.1.3 Wrong Frequency of administration (n=3)

The first case associated with wrong frequency of administration error (ISR# 3895028) reported a patient who self administered Alendronate 20 mg twice daily instead of the prescribed frequency of once daily. Subsequently, the patient was hospitalized for "burning in her chest" but did recover after one or two weeks.

In the second case (ISR# 4072272), a stabilized patient was inadvertently given Alendronate 70 mg on two consecutive days instead of once weekly in the hospital. The patient experienced diarrhea, vomiting, and extreme hyponatremia (Na 108) requiring treatment with intravenous normal saline solution. Although these adverse events resolved within five days after treatment, the patient's physician considered this medication error as immediately life-threatening and had prolonged her hospitalization.

The third case (ISR# 5624755) reported the patient mistakenly took Alendronate 70 mg for three consecutive days and experienced nausea, sleepiness, diarrhea and hospitalization.

3.1.4 Wrong Technique in Administration (n=15)

One case (ISR# 4898970) reported that the patient did not take Alendronate on an empty stomach. The outcome of the event was not reported.

One case (ISR# 4168116) described that the patient was not instructed to sit up after taking Fosamax when hospitalized, and was subsequently diagnosed with an esophageal ulcer.

One case (ISR# 6601956) reported a 15 year old patient with a diagnosed unspecified progressive neurological disease sucking on the tablet instead of swallowing it whole but did not experience any adverse event.

Two cases of wrong technique in administration error described that patients chewed Alendronate tablets, and experienced erosive esophagitis, gastrointestinal bleeding and hospitalization in one case (ISR# 4167401) and erythema, irritation and laryngitis in the second case (ISR# 5145059).

Two cases reported that patients did not take Alendronate oral solution with water, resulting in esophagitis in both cases (ISR# 4376967 and 4524464). Additionally, four cases described that patients did not take Alendronate tablet with enough water, resulting in emergency room visit for chest pain in one case (ISR# 3936769), and hospitalization for gastrointestinal bleeding in the three cases (ISR# 4785749, 4861831 and 4818680).

Four cases reported that patients lay down within 30 minutes after taking Alendronate, resulting in gastric reflux in the first case (ISR# 4854058), esophageal ulceration in the second case (ISR# 4936857), inability to swallow in the third case (ISR# 5268614) and nausea in the fourth case (ISR# 5522125).

3.2 LABELS AND LABELING

3.2.1 Child-resistant Packaging

The Applicant's original (b) (4) carton design was child-resistant but involved complex mechanisms in order to remove the blister from the carton. Based on FDA feedback, the Applicant revised the carton but it did not meet the child-resistant packaging requirement outlined in 16 CFR 1700.14. Therefore, the Applicant proposed (b) (4) to meet the child-resistant packaging requirement. The currently proposed packaging of Binosto effervescent tablet is in the same originally proposed blister container, (b) (4), and four or twelve pouches are packaged in one carton box.

3.2.2 Prescribing Information

Because our AERS search found wrong technique of administration errors associated with upper gastrointestinal adverse reactions, we reviewed the Prescribing Information and Medication Guide for administration instructions. Our review found instructions on dissolving Binosto in approximately half a glass of plain room temperature water, take on

an empty stomach, and not to lie down within 30 minutes after taking the drug in both the Prescribing Information and the Medication Guide. However, our review only found the statement “Do not swallow, chew or suck on the [effervescent tablet]” in the Medication Guide but not in the Prescribing Information. This statement should also be included in the Prescribing Information because upper gastrointestinal adverse reactions related to bisphosphonates are serious and is already labeled as a Warning.

4 CONCLUSIONS AND RECOMMENDATIONS

The proposed label and labeling require further revision to provide clarity. We advise the following recommendations be implemented prior to approval of this NDA:

4.1 COMMENTS TO THE DIVISION

A. Prescribing Information

1. In the Dosage and Administration Sections of the Highlights of Prescribing Information and of the Full Prescribing Information,
 - a. Revise the statement (b) (4) to read “Wait at least 5 minutes for the effervescent tablet to dissolve, then stir for approximately 10 seconds and drink the entire contents.”
 - b. Add the statement “Do not swallow, chew or suck on the effervescent tablet.” Our AERS search found wrong technique of administration errors where patients were chewing on alendronate sodium tablets and experienced erosive esophagitis, gastrointestinal bleeding and hospitalization. Since upper gastrointestinal adverse reaction is a class Warning, the statement “Do not swallow, chew or suck on the effervescent tablet” should also be included in the Prescribing Information.

B. Medication Guide

1. In the “How should I take once weekly [Binosto]” section, revise the statement (b) (4) to read “Wait at least 5 minutes for the effervescent tablet to dissolve, then stir for approximately 10 seconds and drink the entire contents.”
2. Revise the statement “[Binosto] effervescent tablets need to be dissolved and then resulting solution drink” to consumer friendly language such as “Each Binosto effervescent tablet needs to be dissolved in approximately half a glass of plain room temperature water (4 oz). **Do not swallow, chew or suck on the effervescent tablet.**” (Only the second sentence is bolded for emphasis because the instruction for dissolving is also provided in other Medication Guide sections).

4.2 COMMENTS TO THE APPLICANT

A. General Comments

1. Present the proprietary name in title case as “Binosto” and the established name as “(Alendronate Sodium) Effervescent Tablets”.
2. Include a United States point of contact for questions and adverse event reporting.

B. Container Label (Blister)

1. Clarify if each blister contains 1 effervescent tablet or multiple effervescent tablets. As currently presented, each blister is labeled as “Effervescent Tablets.”
2. Ensure that “Lot #” instead of the batch number is printed on the back side of the blister along with the expiration date per 21 CFR 201.10(i).

C. Pouch Labeling

1. Replace the ✂ (scissors symbol) with the word “cut” so that the instruction is stated clearly and reduces the risk of misinterpreting the proposed symbol.
2. Clarify if each pouch contains 1 effervescent tablet or multiple effervescent tablets. As currently presented, each pouch is labeled as “Effervescent Tablets.”

D. Carton Labeling

1. Include the statement of dosage such as “Usual dose: see prescribing information” per 21 CFR 201.55.
2. Relocate the NDC number to the top third of the principal display panel of the label per 21 CFR 207.35(b)(3).
3. Clarify whether the Medication Guide is accompanied on the carton or enclosed inside the carton. As currently presented, the statement “Pharmacist: Dispense the accompanying Medication Guide...” on the principal display panel and the statement “Important Information: Please read the enclosed Medication Guide...” on the back panel convey different messages.
4. Revise the Medication Guide statement on the principal display panel to read “ATTENTION PHARMACIST: Each patient is required to receive the accompanying/enclosed Medication Guide” and increase its prominence per 21 CFR 208.24(d) (Clarify between accompany or enclosed, see Comment D3).

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

APPENDICES

Appendix A: Label and Labeling

Container Label (Blister)



Carton Labeling (Pouch and Carton)

Pouch:



Carton:

(b) (4)





Appendix B: AERS ISR Numbers (n=301)

ISRNUM	CK												
3846076	1	4325155	9	4922451	9	5594042	0	7126065	4	7214412	4	7675066	6
3867833	1	4348706	7	4936857	5	5865307	X	6283966	7	7215959	7		
3895028	4	4366542	2	4961508	3	5893387	4	6507780	X	7220216	9		
3910358	5	4533543	0	5006076	5	5674754	0	6534996	9	7228437	6		
3936769	X	4366543	4	4913294	0	5655377	6	6537907	5	7276684	X		
3941362	9	4354773	7	5076872	7	5902526	8	6559158	0	7285942	4		
3978470	2	4391746	2	5010251	3	5917619	9	6582002	2	7296817	9		
3982037	X	4376967	7	5087690	8	5919165	5	6583088	1	7320904	X		
3995514	2	4377526	2	4946080	6	5940553	5	6583107	2	7328656	4		
4015844	8	4390751	X	4947385	5	5990601	1	6596755	0	7347800	6		
4023949	0	4385991	X	5096662	9	5990827	7	6601956	9	6580717	3		
4021996	6	4421810	0	5030622	9	5991200	8	6616116	5	7387839	8		
4025999	7	4591177	6	4978708	9	5992350	2	6639185	5	7389692	5		
4079642	1	4423128	9	4985257	0	5991839	X	6055807	4	7401391	X		
4037098	9	4470207	6	4990975	4	5651900	6	6661472	5	7424190	1		
4041068	4	4430942	2	5115823	3	5655367	3	6672006	3	7456021	8		
4058752	9	4477132	5	5143442	1	5992491	X	6693258	X	7479076	3		
4050238	0	4451707	1	5145059	1	5695348	7	6702250	8	6813891	1		
4059842	7	4499926	2	5145583	1	6011218	9	6149161	7	7479143	4		
4069747	3	4524464	8	5212244	X	6031768	9	6704360	8	7500679	1		
4072272	7	4494536	5	5268614	7	6051655	X	6722196	9	7501605	1		
4112167	3	4529514	0	5285420	8	6150798	X	6768804	8	7504713	4		
4091850	2	4531178	7	5394376	9	5731052	4	6894964	4	7510410	1		
4114966	0	4548299	5	5453789	7	6179650	0	6264451	5	7519496	1		
4134396	5	4618327	7	5478758	2	6212409	4	6251804	4	6971794	6		
4118996	4	4685638	9	5481336	2	6273292	4	6907196	8	7520443	7		
4192959	5	4703934	3	5340918	9	5866155	7	6908608	6	7529940	1		
4239440	2	4623444	1	5522125	X	6288654	9	6250696	7	7540388	6		
4167401	0	4715337	6	5386999	8	4182263	3	6260613	1	7553790	3		
4168116	5	4719001	9	5386666	0	6292135	6	6267090	5	7222248	3		
4168348	6	4704629	2	5526080	8	6309868	5	6909631	8	7571650	9		
4168435	2	4696463	7	5572633	0	6342008	5	6930609	2	7578485	1		
4168479	0	4726332	5	5582544	2	6357470	1	6943943	7	7580909	0		
4168725	3	4767423	2	5400978	3	6358153	4	6971155	X	7335824	4		
4168830	1	4785749	3	5407179	3	6436195	8	6977089	9	7593408	7		
4168925	2	4745502	3	6176432	0	6688566	2	6965765	3	7427546	6		
4169749	2	4818680	5	5616208	3	6438001	4	6354895	5	7392453	4		
4183066	6	4848893	8	5624755	3	6461809	6	6326041	5	7598451	X		
4191071	9	4854058	6	5684440	9	5859351	6	6618167	3	7402630	1		
4209602	9	4807936	8	5696004	1	5962408	2	7103180	2	7451915	1		
4209889	2	4815809	X	5722396	0	5873858	7	7131215	X	7395029	8		
4218961	2	4861354	5	5750960	1	6468141	5	7193050	6	7406790	8		
4254690	7	4909425	9	5752283	3	6498805	9	6731294	5	7407474	2		
4246106	1	4861381	8	5782031	2	6499080	1	7213385	8	7418431	4		
4276580	6	4836023	8	5802406	2	6501649	2	7213640	1	7432294	2		
4288710	0	4861416	2	5828768	8	6501672	8	7214122	3	7630722	0		
4294554	6	4861425	3	5828784	6	5941460	4	7214136	3	7636530	9		
4260740	4	4861831	7	5859836	2	5957073	4	7568617	3	7639293	6		
4312214	X	4874225	5	5839200	2	6502633	5	7205807	3	7659620	3		
4317664	3	4898970	0	5840366	9	5958303	5	7571673	X	7659638	0		

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/s/

CHI-MING TU
02/07/2012

TODD D BRIDGES
02/07/2012

CAROL A HOLQUIST
02/07/2012

MEMORANDUM

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

DATE: October 7, 2011

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

FROM: Xikui Chen, Ph.D.
Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Addendum to the Review of EIRs Covering NDA 202-344,
STEOVESS™ (Alendronate sodium) Effervescent Tablets,
70 mg, Sponsored by EffRx Pharmaceuticals

At the request of DRUP, Division of Bioequivalence and GLP Compliance audited clinical and analytical portions of study AE-1212-001-EM (CRS Study No.: 111/08-03.AE) in July 2011. DBGC's inspection summary memo was provided to DRUP on September 26, 2011.

In the memo on September 26, 2011, DBGC recommended that the data from 9 analytical batches should either be confirmed by re-assay or excluded for bioequivalence study AE-1212-001-EM.

This addendum adds two more batches 11108H27 and 11108H28 for the data to be confirmed or excluded for the bioequivalence study, and provides subjects analyzed in the 11 batches.

Conclusions:

DBGC's recommendation concerning Study AE-1212-001-EM remains unchanged. The data listed in the following 11 batches should either be confirmed by re-assay or excluded from bioequivalence study AE-1212-001-EM: 11108H27 (subject 04), 11108H28 (subject 05 periods 2-4; subject 105, period

Page 2 - NDA 202-344, STEOVESS™ (Alendronate sodium)
Effervescent Tablets, 70 mg

1), 11108H30 (subject 06 periods 2-4; subject 106, period 1), 11108H34 (subject 10), 11108H90 (subject 63), 11108H92 (subject 65), 11108H93 (subject 66), 11108H102 (subject 30; subject 29_1_14, 29_2_14, 29_3_03, 29_3_04, 29_3_14, 29_4_14; subject 34_2_03; subject 37_2_05, 37_2_14, 37_4_13; subject 45_1_04, 45_1_05, 45_3_04; subject 47_1_04, 47_3_04), 11108H119 (subject 119), 11108H121 (subject 121), and 11108H142 (subject 140).

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

Xikui Chen, Ph.D.

cc:

CDER DSI PM TRACK

OC/Ball/Moreno

OC/OSI/DBGC/Salewski/Haidar/Chen/Skelly/Dejernet

ORA /NJ-DO/Jonee Mearns

OND/ODE3/DRUP/Karl Stiller/Meredith Alpert

OTS/OCP/DCPIII/Edward D. Bashaw/Hyunjin Kim,

Draft: XC 10/6/2011

Edit: MFS 10/6/2011

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/s/

XIKUI CHEN
10/07/2011

SAM H HAIDAR
10/07/2011

M E M O R A N D U M

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

DATE: September 26, 2011

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

FROM: Xikui Chen, Ph.D.
Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIRs Covering NDA 202-344, STEOVESS™
(Alendronate sodium) Effervescent Tablets, 70 mg,
Sponsored by EffRx Pharmaceuticals

At the request of DRUP, Division of Bioequivalence and GLP Compliance audited clinical and analytical portions of the following study:

Study Number: AE-1212-001-EM (CRS Study No.: 111/08-03.AE)

Study Title: Single-site, open label, four period cross-over replicate trial after single dose administration of a new alendronate 70 mg formulation, a buffered effervescent soluble tablet, under fasting conditions, to assess the bioequivalence versus a marketed oral tablet formulation (Fosamax® once weekly 70 mg) in healthy volunteers

Clinical Inspection:

The clinical portion of the study was conducted at CRS Clinical Research Services Mannheim GmbH, Grenadier Strasse 1, 68167 Mannheim, Germany. Following the inspection of CRS Mannheim GmbH (July 18 - 22, 2011), no Form FDA-483 was issued.

Analytical Inspection:

The analytical portion of the study was conducted at (b) (4)

(b) (4)
Following the inspection of (b) (4), Form FDA 483 was issued (**Attachment 1**). DBGC has received a written response from the firm to the Form FDA 483 observations (**Attachment 2**). Our evaluation of the Form FDA 483 observations and the response follows:

(b) (4)

Data from the first results for study samples in batch 11108H31 for Subjects 07 and 107 for and in batch 11108H35 for Subject 11 were not within the calibration ranges, and study samples were re-analyzed after dilutions. The results of samples after dilution were different with the first results (extrapolated). Two re-assays were performed and the re-assay results did not confirm the first results of Subjects 7, 11, and 107 in batch 11108H31 and 11108H35; see Table 4 in **attachment 3** for the investigation report. The first results in batches 11108H31 and 11108H35 were declared invalid, and the re-assay results were reported. The original results for Subject 119 were analyzed in batch 11108H119 and reported; however, the reported results were not confirmed by the 1st re-assay (17 out of 22 deviated >20%) and 2nd re-assay (17 out of 22 deviated >20%) provided in **attachment 4**. Based on the available data, initial results of batches 11108H31, 11108H35 and 11108H119 did not agree with later results from re-assays, even though the quality control samples in these batches met the run acceptance criteria. There were chromatographic interferences from peaks co-eluting near alendronate on chromatograms of study samples, calibration standards, and quality control samples in the batches 11108H31, 11108H35 and 11108H119. Chromatograms in batch numbers 11108H27, 11108H28, 11108H30, 11108H34, 11108H90, 11108H92, 11108H93, 11108H102, 11108H119, 11108H121, and 11108H142 were qualitatively similar to that in batches 11108H31, 11108H35, and 11108H119. Chromatograms for reference standard E3 in these

batches were provided in **attachment 5**, and chromatograms of the calibrator in other batches were in **attachment 6**. Since the first results in batches 11108H31 and 11108H35 were confirmed invalid and initial data of batch 1108H119 did not agree with the re-assays, the initial data generated from batches: 11108H30, 11108H34, 11108H90, 11108H92, 11108H93, 11108H102, 11108H121, and 11108H142 are questionable, and they should either be excluded from your evaluation or confirmed by re-analysis.

In their response on August 3, 2011, [REDACTED] ^{(b) (4)} stated that all runs cited in the Form FDA 483 observation were validated with respect to acceptance criteria of the calibration standards and quality control samples, and no-reassay was justified.

Conclusions:

Following the above inspections, DBGC recommends the following:

- The reported data generated from batches: 11108H30, 11108H34, 11108H90, 11108H92, 11108H93, 11108H102, 11108H121, and 11108H142 are questionable, and they should either be confirmed by re-assay or excluded from your consideration for bioequivalence study AE-1212-001-EM.
- The reported data from batch 1108H119 were not confirmed by re-assays, and should not be used for bioequivalence study AE-1212-001-EM.

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

Xikui Chen, Ph.D.

Final Classifications:

Clinical

**NAI - CRS Clinical Research Services Mannheim GmbH, Grenadier
Strasse 1, 68167 Mannheim, Germany
FEI: 3006660278**

Analytical

VAI

(b) (4)

cc:

CDER DSI PM TRACK

OC/Ball/Moreno

OC/OSI/DBGC/Salewski/Haidar/Chen/Skelly/Dejernett

ORA /NJ-DO/Jonee Mearns

OND/ODE3/DRUP/Karl Stiller

OTS/OCP/DCPIII/Edward D. Bashaw

Draft: XC 9/23/2011

Edit: MFS 9/23/2011

OSI: 6210; O:\BE\EIRCOVER\202344eff.ale.doc

FACTS 1284898

69 pages have been Withheld in Full as b4 immediately following this page

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

/s/

XIKUI CHEN
09/26/2011

SAM H HAIDAR
09/27/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 202344 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: alendronate sodium Dosage Form: effervescent tablet Strengths: 70 mg		
Applicant: EffRx Pharmaceuticals SA Agent for Applicant (if applicable): Hurley Consulting Associates Ltd.		
Date of Application: December 21, 2010 Date of Receipt: December 22, 2010 Date clock started after UN: February 15, 2011		
PDUFA Goal Date: December 15, 2011	Action Goal Date (if different):	
Filing Date: April 16, 2011	Date of Filing Meeting: March 30, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed indication(s)/Proposed change(s): Treatment of postmenopausal osteoporosis in women and treatment to increase bone mass in men with osteoporosis		
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Type of NDA Supplement:		
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 103130				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?		X		Submitted, but not signed – SBW granted

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			Corrected form submitted 3-31-2011
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?		X		
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			Corrected 3454 submitted 3-31-2011
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			Corrected form submitted 3-31-2011

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			Request for PeRC meeting sent 3-28-2011
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			Full pediatric waiver requested
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>			X	
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>	X			consult sent 3-28-2011
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			PI, MedGuide, and C&C to DDMAC
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			REMS and MedGuide to DRISK
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			C&C and PI to DMEPA and ONDQA
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): September 1, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 30, 2011

NDA: 202344

PROPRIETARY NAME: alendronate sodium

ESTABLISHED/PROPER NAME: Steovess (proposed)

DOSAGE FORM/STRENGTH: effervescent tablet

APPLICANT: EffRx Pharmaceuticals SA

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of postmenopausal osteoporosis in women and treatment to increase bone mass in men with osteoporosis

BACKGROUND: On June 23, 2009, IND 103130 was submitted to FDA. The IND contained the following information:

- 1) CMC information on EX101 effervescent alendronate tablet
- 2) A statement that no new nonclinical studies were performed to support this IND because they will reference nonclinical information in the Fosamax labeling for submission of an NDA pursuant to 505(b)(2)
- 3) Reports on 2 clinical studies from Europe:
 - a) SCO5361, a bioequivalence and food effect study comparing the 70 mg effervescent tablet to the 70 mg Fosamax tablet
 - b) BC-118-07, a gastric imaging and pH telemetry study
- 4) A new Phase 1 bioequivalence protocol AE-1212-001-EM, to be conducted in Germany thus not strictly an IND study, but "provided for FDA comment." This will be conducted because the above study SCO5361 failed to prove bioequivalence.
- 5) Investigator brochure

EffRx Pharmaceuticals SA submitted a 505(b)(2) NDA application to the FDA on December 21, 2010. A UN letter was issued on December 27, 2010, because the appropriate user fee was not submitted with the application. A small business waiver for the application fee was granted on February 15, 2011. The PDUFA Goal Date for the application is December 15, 2011.

REVIEW TEAM:

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

Clinical Pharmacology	Reviewer:	Hyunjin Kim	Y
	TL:	Myong-Jin Kim	N
Biostatistics	Reviewer:	Kate Dwyer	Y
	TL:	Mahboob Sobhan	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Gemma Kuijpers	Y
	TL:	Lynnda Reid	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hitesh Shroff	Y

	TL:	Donna Christner	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Chi-Ming Tu	Y
	TL:	Carlos Mena-Grillasca	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:	Marcea Britt Williams	N

Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	Y
	TL:	Tejashri Purohit-Sheth	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other Reviewers Biopharmaceuticals (ONDQA)	Reviewer:	Tien-Mien Chen	Y
	TL:	Angelica Dorantes	N
Other attendees	Samantha Burgess, RPM, DRUP		Y
	Maria Wasilik, RPM, OSE		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? 	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES
--	---

<p>If yes, list issues:</p>	<input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: none</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL Comments: 2 comments to send re: risk benefit discussion and applicability of data to U.S. population</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: Not first in its class
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: 1 comment to send re: dosing instructions used in study AE-1212-001-EM</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>• Clinical pharmacology study site(s) inspections(s) needed?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: 2 comments to send re: blister packaging</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <p>• Categorical exclusion for environmental assessment (EA) requested?</p> <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES

Comments:	<input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments: inspection dates not yet set	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review</u> Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: George Benson 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u>

	<input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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
04/28/2011

MARGARET M KOBER
04/28/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 202344

Name of Drug: alendronate sodium effervescent tablets, 70mg

Applicant: EffRx Pharmaceuticals SA

Labeling Reviewed

Submission Date: December 21, 2010

Receipt Date: December 22, 2010

Background and Summary Description

EffRx Pharmaceuticals SA submitted a new drug application (NDA) on December 21, 2010. Because the Applicant did not pay a user fee and the small business waiver that they requested in early December 2010 was still under review, the Division issued an Unacceptable for Filing letter on December 27, 2010.

A small business waiver was granted on February 15, 2011, which started the PDUFA clock.

Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an "X."

Highlights (HL)

General comments

OK N N/A

HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.

*** Need to reset margins to meet requirements**

HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.

* HL slightly over ½ page length

- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

Highlights Limitation Statement (required statement)
Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
Initial U.S. Approval (required information)
Boxed Warning (if applicable)
Recent Major Changes (for a supplement)
Indications and Usage (required information)
Dosage and Administration (required information)
Dosage Forms and Strengths (required information)
Contraindications (required heading – if no contraindications are known, it must state “None”)
Warnings and Precautions (required information)
Adverse Reactions (required AR contact reporting statement)
Drug Interactions (optional heading)
Use in Specific Populations (optional heading)
Patient Counseling Information Statement (required statement)
Revision Date (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

*Need to change “Initial US Approval XXXXX” to “Initial U.S. Approval 1995”

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

- * “Hypersensitivity to any component of this product” listed

- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”

- * Statement should be changed from “FDA-approved patient labeling” to “Medication Guide”

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

- Contents: Table of Contents (TOC)**

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented

and not bolded.



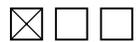
When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

8.1 Pregnancy

8.3 Nursing Mothers (not 8.2)

8.4 Pediatric Use (not 8.3)

8.5 Geriatric Use (not 8.4)



If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**



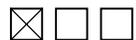
A horizontal line must separate the TOC and FPI.

* Need to add line



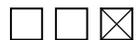
The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.

* Need to add heading

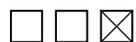


The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

Boxed Warning



Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.



Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**



For Pregnancy Category X drugs, list pregnancy as a contraindication.

Adverse Reactions

Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:
“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

* Need to add subsection and statement and information re: trials

For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:
“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

* Need to reword the statement

- **Use in Specific Populations**

Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

This section is required and cannot be omitted.

Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

“See FDA-approved patient labeling (Medication Guide)”

“See FDA-approved patient labeling (Medication Guide and Instructions for Use)”

“See FDA-approved patient labeling (Patient Information)”

“See FDA-approved patient labeling (Instructions for Use)”

“See FDA-approved patient labeling (Patient Information and Instructions for Use)”

* Need to add statement

In addition, the following labeling issues were identified. Additions to current labeling are shown by underlined text and deletions are shown by ~~strike through~~ text.

1. HIGHLIGHTS, ADVERSE REACTIONS:

The most common adverse reactions for alendronate sodium (incidence >3%) are (b) (4)

2. FULL PRESCRIBING INFORMATION: CONTENTS*:

17 PATIENT COUNSELING INFORMATION

(b) (4)

3. 12.2 Pharmacodynamics, Osteoporosis in Postmenopausal Women subsection:

Unbold **Osteoporosis in Postmenopausal Women**

4. 17 PATIENT COUNSELING INFORMATION

(b) (4)

Recommendations

All labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by May 13, 2011. The resubmitted labeling will be used for further labeling discussions.

Karl Stiller, R.Ph.

Regulatory Project Manager

Date

Margaret Kober, R.Ph., M.P.A.

Chief, Project Management Staff

Date

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
04/14/2011

MARGARET M KOBER
04/15/2011