

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202344Orig1s000

CHEMISTRY REVIEW(S)

NDA 202344

**Binosto (alendronate sodium) effervescent tablets
70 mg**

EffRx Pharmaceuticals SA

Hitesh Shroff, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV**

**CMC Review of NDA 202344
For the Division of Reproductive and Urologic Drug
Products (HFD-580)**

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Chemistry Review Data Sheet

1. NDA 202344
2. REVIEW:#1
3. REVIEW DATE: 04-Oct-2011
4. REVIEWER: Hitesh Shroff, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|----------------------------------|----------------------|
| Original | 18-Feb-2011 |
| Amendment-Labeling | 12-May-2011 |
| Amendment-Quality Response to IR | 24-May-2011 |
| Amendment-Labeling | 07-July-2011 |
| Amendment-Quality/Stability | 29-July-2011 |
| Amendment-Labeling | 25-Aug-2011 |

1. NAME & ADDRESS OF APPLICANT

Name: EffRex Pharmaceuticals SA
Address: Biopole
Rue de la Corniche 4
CH-1066, Epalinges S
Lausanne, Switzerland
Representative: Susan M. Mondabaugh
VP Regulatory Affairs
One Main Street
Chatham, NJ 07928
Telephone: 973-635-9898

8. DRUG PRODUCT NAME/CODE/TYPE:

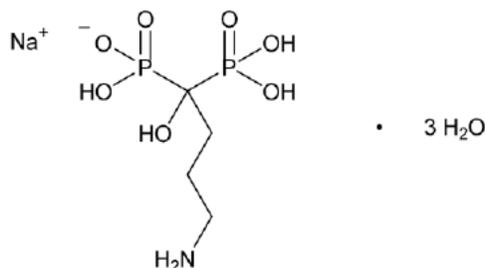
- a) Proprietary Name: Binosto
- b) Non-Proprietary Name (USAN): Alendronate sodium
- c) Code Name/# (ONDQA only): None
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

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

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: Bisphosphonate
11. DOSAGE FORM: Effervescent tablet
12. STRENGTH/POTENCY: equivalent to 70 mg alendronic acid
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: X Rx ___ OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___ SPOTS product – Form Completed
X Not a SPOTS product

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



alendronate sodium

Chemical Name: Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate
Sodium trihydrogen (4-amino-1-hydroxybutylidene)diphosphonate, trihydrate

Molecular Formula: $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$

Molecular Weight: 325.12

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYP E | HOLDER | ITEM REFERENCE D | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENT S |
|-------|-------|--------|------------------|-------------------|---------------------|-----------------------|-----------|
|-------|-------|--------|------------------|-------------------|---------------------|-----------------------|-----------|

Chemistry Review Data Sheet

| | | | | | | | |
|---------|----|---------|--------------------|---|----------|-------------|---|
| (b) (4) | II | (b) (4) | Alendronate sodium | 3 | Adequate | 18-Feb-2009 | No significant CMC related information provided since last review |
|---------|----|---------|--------------------|---|----------|-------------|---|

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

ONDQA:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATI ON | DATE | REVIEWER |
|-------------------------------------|--|-------------|----------------|
| Biometrics | N/A | | |
| EES | Withhold | 24-Aug-2011 | |
| Pharm/Tox | N/A | | |
| Biopharm | Approval | 21-Sep-2011 | Tien Mien Chen |
| LNC | N/A | | |
| Methods Validation | N/A per ONDQA policy | | |
| DMEPA | N/A | | |
| EA | Categorical exclusion granted (see review) | 17-Mar-2011 | Hitesh Shroff |
| Microbiology | N/A | | |

The Chemistry Review for NDA 202344

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

However, label/labeling issues are still pending (see “The list of Deficiencies” on page 60), and an overall “WITHHOLD” recommendation has been made from the Office of Compliance.

Therefore, from the CMC perspective, this NDA is *NOT* recommended for approval in its present form until the pending issues are resolved.

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

No recommendations at this time.

II. Summary of Chemistry Assessments

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

(1) Drug Substance

The drug substance, alendronate sodium, is manufactured by (b) (4), which was reviewed on 18-Feb-2009 and found to be adequate. Since then there have been no significant changes in the manufacturing process and control of the drug substance. The applicant provided LOA to reference the DMF for CMC information. The proposed specification including identification, assay, related substances, and particle sizes is deemed adequate to assure the identity, strength, purity and quality of the drug substance. (b) (4)

Based on this study, the to-be marketed tablets are to be made using (b) (4).

(2) Drug Product

Binosto (alendronate sodium) effervescent tablets 70 mg are round, flat-faced, white to off-white effervescent tablets, 25 mm in diameter, with beveled edges containing 91.37 mg of alendronate sodium, which is equivalent to 70 mg of free alendronic acid. The

Executive Summary Section

tablets are packaged in aluminum foil composite blister strips. Each container has blisters with 4 tablets or (b) (4). Each tablet contains various compendial grade inactive ingredients such as monosodium citrate anhydrous, citric acid anhydrous, sodium hydrogen carbonate, sodium carbonate anhydrous, acesulfame potassium and sucralose.

The effervescent tablet manufacturing process requires (b) (4)

The release specification of the finished product include appearance, identification, pH of the solution, uniformity of dosage units (based on alendronic acid), assay (alendronic acid), disintegration, impurities, and microbial tests, and they are deemed adequate to assure the identity, strength, purity, and quality of the drug product..

Based on the stability data from three pilot scale batches of tablets at long term (36 months) and accelerated (6 months) conditions, the proposed 36 months expiration dating period when stored at room temperature is granted.

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

Binosto is prescribed as a treatment of osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis. The recommended Binosto dosage is one 70 mg effervescent tablet per week. Binosto effervescent tablets are supplied in an aluminum foil blister strip. Each carton contains 4 tablets or (b) (4).

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure the strength, purity and quality of drug product during the 36-month of expiration dating period.

However, labeling issues are still pending and an overall "WITHHOLD" recommendation has been made from the Office of Compliance for this application.

Therefore, from the CMC perspective, this NDA is *NOT* recommended for approval in its present form until all the pending issues are satisfactorily resolved.

Executive Summary Section

III. Administrative**A. Reviewer's Signature**

Hitesh Shroff/ October 06, 2011

B. Endorsement Block

Moo-Jhong Rhee, Branch Chief, Branch #4, Division 2

C. CC Block

Donna Christner
Theresa Kehoe

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

/s/

HITESH N SHROFF
10/13/2011

MOO JHONG RHEE
10/13/2011
Chief, Branch IV

Initial Quality Assessment
Branch IV
New Drug Quality Assessment Division II

OND Division: Division of Reproductive and Urologic Products
NDA: 202344
Applicant: EffRx Pharmaceuticals SA
Stamp Date: 15-Feb-2011
PDUFA Date: 15-Dec-2011
Trademark: Steovess
Established Name: Alendronate sodium
Dosage Form: Effervescent tablet
Route of Administration: Oral
Indication: Treatment of osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis

CMC Lead: Donna F. Christner, Ph.D.

| | YES | NO |
|-----------------------------------|-----|--------------------------|
| ONDQA Fileability: | X | <input type="checkbox"/> |
| Comments for 74-Day Letter | X | <input type="checkbox"/> |

Summary and Critical Issues:

A. Summary

The sponsor has provided the following information on the drug product:

Alendronate Effervescent Tablets are round, flat-faced, white to off-white effervescent tablets, 25 mm in diameter, with beveled edges containing 91.37 mg of alendronate sodium trihydrate, which is equivalent to 70 mg of free alendronic acid. The tablets are packaged in aluminum foil composite blister strips.

B. Critical issues for review

Because this is an effervescent tablet, the sponsor has included disintegration in lieu of dissolution testing. This should be reviewed by ONDQA BioPharm to determine if the specification is acceptable.

C. Comments for 74-Day Letter

Provide information on whether the blisters comply with 16 CFR 1700.14(a)(10) for child resistance. Refer to the US Consumer Product Safety Commission website (<http://www.cpsc.gov/businfo/dreg.html>) for more information.

Please clarify if a ^{(b) (4)} configuration will be available. If not, please correct the HOW SUPPLIED section of the Physician's Insert. In addition, please assign NDC numbers and update the PI and container closure systems.

D. Recommendation:

This NDA is fileable from a CMC perspective. Hitesh Shroff, Ph.D., has been assigned as the primary reviewer. Tien Mien(Albert) Chen, Ph.D. is the assigned Biopharmaceutics reviewer.

Donna F. Christner, Ph.D.

NDA Number: 202344 Type: 3

Established/Proper Name:
Steovess (alendronate
sodium)effervescent tablets

Applicant: EffRx
Pharmaceuticals

Letter Date: 21-Dec-2010 (not
accepted due to lack of fee)

Stamp Date: 15-Feb-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

| A. GENERAL | | | | |
|------------|--|-----|----|---------|
| | Parameter | Yes | No | Comment |
| 1. | Is the CMC section organized adequately? | X | | |
| 2. | Is the CMC section indexed and paginated (including all PDF files) adequately? | X | | |
| 3. | Are all the pages in the CMC section legible? | X | | |
| 4. | Has all information requested during the IND phase, and at the pre-NDA meetings been included? | X | | |

| B. FACILITIES* | | | | |
|----------------|---|-----|----|--------------|
| | Parameter | Yes | No | Comment |
| 5. | Is a single, comprehensive list of all involved facilities available in one location in the application? | X | | List on 356h |
| 6. | For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API. | X | | N/A |

| | | | | |
|----|--|---|--|--|
| 7. | <p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) | X | | Contact information was confirmed by sponsor. |
| 8. | <p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) | X | | Drug product manufacturing site did not appear to be in EES system and was added. Contact information was confirmed by sponsor. |

| | | | | |
|-----|--|---|--|--|
| 9. | <p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) | X | | All responsibilities performed by drug substance and drug product sites. No contract facilities are identified |
| 10. | Is a statement provided that all facilities are ready for GMP inspection at the time of submission? | X | | Signed statement on 356h |

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

| C. ENVIRONMENTAL ASSESMENT | | | | |
|----------------------------|--|-----|----|---|
| | Parameter | Yes | No | Comment |
| 11. | Has an environmental assessment report or categorical exclusion been provided? | X | | Waiver requested as per 21 CFR 25.31(a) |

| D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API) | | | | |
|--|---|------------|-----------|--|
| | Parameter | Yes | No | Comment |
| 12. | Does the section contain a description of the DS manufacturing process? | X | | Cross-reference provided for DMF (b) (4) |
| 13. | Does the section contain identification and controls of critical steps and intermediates of the DS? | X | | Cross-reference provided for DMF (b) (4) |
| 14. | Does the section contain information regarding the characterization of the DS? | X | | Cross-reference provided for DMF (b) (4) |
| 15. | Does the section contain controls for the DS? | X | | Cross-reference provided for DMF (b) (4) |
| 16. | Has stability data and analysis been provided for the drug substance? | X | | Cross-reference provided for DMF (b) (4) |
| 17. | Does the application contain Quality by Design (QbD) information regarding the DS? | | X | Not a filing issue |
| 18. | Does the application contain Process Analytical Technology (PAT) information regarding the DS? | | X | Not a filing issue |

| E. DRUG PRODUCT (DP) | | | | |
|-----------------------------|---|------------|-----------|---|
| | Parameter | Yes | No | Comment |
| 19. | Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging? | X | | |
| 20. | Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable? | X | | |
| 21. | Is there a batch production record and a proposed master batch record? | X | | English translation of German executed batch records provided in Module 3.2.R. with statement confirming the correctness and completeness of the translation. |
| 22. | Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product? | X | | |
| 23. | Have any biowaivers been requested? | | X | Not a filing issue. NDA based on bioequivalence to approved product |
| 24. | Does the section contain description of to-be-marketed container/closure system and presentations)? | X | | Information provided on components of blister packaging including references to indirect food additives portions of 21 CFR. The sponsor has not stated if the blister packs comply with 16 CFR 1700.14(a)(10) for child resistance. |
| 25. | Does the section contain controls of the final drug product? | X | | |
| 26. | Has stability data and analysis been provided to support the requested expiration date? | X | | Sponsor requests 36 month expiration dating period based on 12 months of primary stability data on 3 batches and 24 months of stability data on supportive batches |
| 27. | Does the application contain Quality by Design (QbD) information regarding the DP? | | X | Not a filing issue |
| 28. | Does the application contain Process Analytical Technology (PAT) information regarding the DP? | | X | Not a filing issue |

| F. METHODS VALIDATION (MV) | | | | |
|----------------------------|--|-----|----|---|
| | Parameter | Yes | No | Comment |
| 29. | Is there a methods validation package? | X | | Provided in Certificate of Suitability in Module 3.2.R. (b) (4) drug substance provided in 3.2.S.4.2. |

| G. MICROBIOLOGY | | | | |
|-----------------|--|-----|----|--|
| | Parameter | Yes | No | Comment |
| 30. | If appropriate, is a separate microbiological section included assuring sterility of the drug product? | | X | Microbiology specifications set in accordance with Ph.Eur. |

| H. MASTER FILES (DMF/MAF) | | | | |
|---------------------------|---|-----|----|---------|
| | Parameter | Yes | No | Comment |
| 31. | Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete? | X | | |

| DMF # | TYPE | HOLDER | ITEM REFERENCED | LOA DATE | COMMENTS |
|---------|------|---------|--------------------|-------------|---|
| (b) (4) | II | (b) (4) | Sodium alendronate | 13-Oct-2010 | ADEQUATE on 15-Jan-2009 for ANDA 75-871 by Liang Lii Huang. Annual Reports since last review. |
| | | | | | See ONDC Policies on Bottles and Blisters* |
| | | | | | |

*Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001
 Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002

| I. LABELING | | | | |
|-------------|---|-----|----|--|
| | Parameter | Yes | No | Comment |
| 32. | Has the draft package insert been provided? | X | | HOW SUPPLIED section indicates a (b) (4) configurations, while SPL table indicates a 12 tablet configuration. Both sections also include 4 tablet configurations. NDC numbers not assigned. Sponsor should clarify |
| 33. | Have the immediate container and carton labels been provided? | X | | Cartons provided for 4 and 12 tablet configurations. Space for NDC number not provided. See comment above. |

| J. FILING CONCLUSION | | | | |
|----------------------|--|-----|----|------------|
| | Parameter | Yes | No | Comment |
| 34. | IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? | X | | |
| 35. | If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant. | | X | N/A |
| 36. | Are there any potential review issues to be forwarded to the Applicant for the 74-day letter? | X | | See page 1 |

{See appended electronic signature page}

Donna F. Christner, Ph.D.
 CMC Lead
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

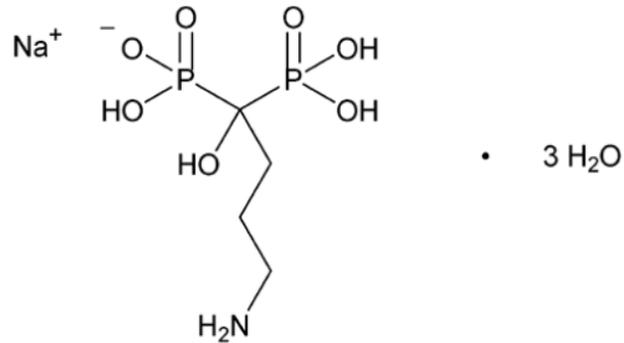
Moo-Jhong Rhee, Ph.D.
 Chief, Branch IV
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

DRUG SUBSTANCE

Full information on the drug substance, alendronate sodium, is provided in the cross-referenced DMF (b) (4) which was reviewed in January 2009. There have been Annual Reports since that time. The sponsor has provided the following information in the NDA:

Figure 1 Structural Formula of Sodium Alendronate Trihydrate



The following site has responsibilities for the manufacture of the drug substance:



Comment: The EES was submitted on 14-Mar-2011. The Office of Compliance made an ACCEPTABLE recommendation for this site based on profile. An overall recommendation has not been made for this application at this time.

SPECIFICATION

The drug substance quality is controlled by the following specification:

Table 1 Specification for Sodium Alendronate Drug Substance

| Test | Specification | Analytical Procedure |
|---------|---------------|----------------------|
| (b) (4) | | |

Comment: Information is adequate to allow review.

DRUG PRODUCT

The sponsor has provided the following information on the drug product:

Alendronate Effervescent Tablets are round, flat-faced, white to off-white effervescent tablets, 25 mm in diameter, with beveled edges containing 91.37 mg of alendronate sodium trihydrate, which is equivalent to 70 mg of free alendronic acid. The tablets are packaged in aluminum foil composite blister strips.

Table 1 Quantitative Composition per Tablet of Alendronate Effervescent Tablets 70 mg

| Component | Quantity per Tablet | Reference to Standards | Function |
|--|---------------------|------------------------|-------------------|
| Sodium alendronate trihydrate (micronized) | 91.37 mg | USP / Ph. Eur. | Active ingredient |
| Monosodium citrate anhydrous | (b) (4) | (b) (4) | (b) (4) |
| Citric acid anhydrous | | | |
| Sodium hydrogen carbonate | | | |
| Sodium carbonate anhydrous | | | |
| Strawberry flavor | | | |
| (b) (4) | | | |
| Acesulfame potassium | | | |
| Sucralose | | | |
| (b) (4) | | | |

| Component | Quantity per Tablet | Reference to Standards | Function |
|---------------------|---------------------|------------------------|----------|
| Total tablet weight | 4,050.00 mg | | |
| (b) (4) | | | |

Comment: Information is adequate to allow review.

The clinical supplies used in [Study AE-1212-001-EM](#) are the same as the to-be-marketed formulation. The only difference between the formulations used in the 2 bioequivalence studies (Studies AE-1212-001-EM and SCO 5361) is that (b) (4)

Comment: Study SCO 5361 was performed from Nov 2007 to April 2008 and explored the BE of the 70 mg effervescent tablet (batch # 2046710-^{(b) (4)}) vs. a standard oral formulation. Study AE-1212-001-EM was performed from September 2009 to January 2010 and used a new formulation of the 70 mg effervescent tablet (batch # 00003278/2046-09503 manufactured March 2009-^{(b) (4)}) vs. marketed Fosamax (once weekly, 70 mg tablet).

Manufacturer

The following site is responsible for manufacturing of the drug product:



Comment: The EES was submitted on 14-Mar-2011. The site is scheduled for inspection.

The sponsor has provided the following flow chart for the manufacture of the drug product. A narrative is provided as well.

Figure 1 Flow Chart of the Drug Product Manufacturing Process



Ingredients

Process

In-Process Controls



Comment: *Information is adequate to allow review.*

Specifications

The sponsor has provided the following specifications for control of the drug product.

Table 5 Release and Shelf-life Specifications for Alendronate Effervescent Tablets 70 mg

| Test Parameters | Release Specification | Stability Specification | Analytical Procedures |
|-----------------|-----------------------|-------------------------|-----------------------|
| (b) (4) | | | |

| Test Parameters | Release Specification | Stability Specification | Analytical Procedures |
|-----------------|-----------------------|-------------------------|-----------------------|
| (b) (4) | | | |

| Test Parameters | Release Specification | Stability Specification | Analytical Procedures |
|-----------------|-----------------------|-------------------------|-----------------------|
| (b) (4) | | | |

Comment: Because this is an effervescent tablet, the sponsor has included disintegration in lieu of dissolution testing. This should be reviewed by ONDQA BioPharm to determine if the specification is acceptable.

Container Closure System

The sponsor has provided the following information on the container closure system:

Alendronate Effervescent Tablets 70 mg are sealed in blisters between 2 aluminum foil composite strips consisting of (b) (4)
(b) (4)

Table 9 Description of Packaging Material for Alendronate Effervescent Tablets 70 mg

| Material Type | Specification | Supplier(s) | Standard |
|---------------|---------------|-------------|----------|
| (b) (4) | | | |

Comment: The sponsor has not provided information on whether the blisters are child resistant. The blister packs would need to comply with 16 CFR 1700.14(a)(10) for child resistance. The sponsor should refer to the US Consumer Product Safety Commission website (<http://www.cpsc.gov/businfo/dreg.html>) for more information.

Stability

The sponsor is requesting a 3-year expiry based on the following stability package:

Table 1 Primary Stability Study Tablet Batch Description

| Description | Batch A | Batch B | Batch C |
|-----------------------------|---------------------------|---------------------------|---------------------------|
| Lot no. / Control No. | Batch 2046-9501 | Batch 2046-9502 | Batch 2046-9503 |
| Packaging material | Aluminum composite strips | Aluminum composite strips | Aluminum composite strips |
| Date of manufacture | March 2009 | March 2009 | March 2009 |
| Site of manufacturing | (b) (4) | | |
| Batch size | (b) (4) | | |
| Batch no. of drug substance | (b) (4) | | |
| Supplier of drug substance | (b) (4) | | |
| Present storage time | 12 months | 12 months | 12 months |

Table 2 Supporting Stability Study Tablet Batch Description

| Description | Batch A | Batch B | Batch C |
|----------------------------|---------------------------|---------------------------|---------------------------|
| Lot no. / Control No. | Batch 2046-7101 | Batch 2046-7103 | Batch 2046-7104 |
| Packaging material | Aluminum composite strips | Aluminum composite strips | Aluminum composite strips |
| Date of manufacture | August 2007 | November 2007 | November 2007 |
| Site of manufacturing | (b) (4) | | |
| Batch size | (b) (4) | | |
| Supplier of drug substance | (b) (4) | | |
| Present storage time | 24 months | 24 months | 24 months |

The proposed shelf-life is based on results obtained from the 3 primary stability batches manufactured using (b) (4) (b) (4) and stored for 12 months at 25°C / 60% RH and 30°C / 75% RH and for 6 months at 40°C / 75% RH and the 3 supporting stability batches manufactured using (b) (4) (b) (4) and stored for 24 months at 25°C / 60% RH and 30°C / 70% RH and for 6 months at 40°C / 75% RH. All test results for these batches were found to be well within the stability specification limits.

The results of stability testing presented in [Module 3.2.P.8.3 Stability Data](#), support an expected shelf-life period of 3 years for Alendronate Effervescent Tablets 70 mg when packaged in aluminum foil (b) (4) composite strips.

Comment: The provided data should provide adequate information to set an expiry. However, it may not support a 36 month expiry.

Labeling

The sponsor has a Physician's Insert which includes SPL labeling. The HOW SUPPLIED section indicates a (b) (4) configurations, while SPL table indicates a 12 tablet configuration. Both sections also include 4 tablet configuration. NDC numbers are not assigned. Sponsor should clarify if a (b) (4) configuration will be available.

They have also provided carton and container labels for 4 and 12 table configurations. Space for NDC number not provided.

Comment: Please clarify if a (b) (4) configuration will be available. If not, please correct the HOW SUPPLIED section of the Physician's Insert. In addition, please assign NDC numbers and update the PI and container closure systems.

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

/s/

DONNA F CHRISTNER
04/04/2011

MOO JHONG RHEE
04/04/2011
Chief, Branch IV