# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**202344Orig1s000**

# SUMMARY REVIEW

Acting Deputy Division Director Summary Review

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|---|---|
| Date | March 12, 2012 |
| From | Audrey Gassman, MD |
| NDA # | 202344 |
| Applicant name | EffRx Pharmaceuticals SA |
| Date of receipt of original submission | February 15, 2011 |
| Date of receipt of major amendment | October 28, 2011 |
| PDUFA goal date (extended after submission of a major amendment) | March 15, 2012 |
| Proprietary name/established name | Binosto/alendronate sodium |
| Dosage Form/strength | Effervescent tablet/70 mg |
| Proposed Indications | 1. Treatment of osteoporosis in postmenopausal women; and<br>2. Treatment to increase bone mass in men with osteoporosis |
| Action | Approval |

| Material reviewed/consulted | Names of discipline reviewers |
|---|---|
| CDTL Review | Theresa Kehoe, MD |
| Medical Officer Review | Stephen Voss, MD |
| Statistical Review | Kate Dwyer, PhD<br>Mahboob Sobhan, PhD |
| Pharmacology/toxicology Review | Gemma Kuijpers, PhD<br>Lynnda Reid, PhD |
| Clinical Pharmacology Review | Hyunjin Kim, PharmD, MS<br>LaiMing Lee, PhD |
| ONDQA Review | Hitesh Shroff, PhD<br>Moo Jhong Rhee, PhD |
| DMEPA | Chi-Ming Tu, PharmD<br>Todd Bridges, RPh<br>Carol Holquist, RPh |
| ONDQA Biopharmaceutics | Tien-Mien Chen, PhD<br>Angelica Dorantes, PhD |
| DMPP | LaShawn Griffiths, RN, MSHS-PH, BSN<br>Melissa Hulett, RN, BSN, MSBA<br>Robin Duer MBA, BSN, RN |
| OPDP<br>DPP reviewer<br>DDTCP reviewer | <br>Jessica Cleck Derenick, PhD<br>Carrie Newcomer, PharmD |
| OSI | Xikui Chen, PhD<br>Sam Haidar, PhD, RPh |
| SEALD | Jeannie Delasko, RN, MS<br>Laurie Burke RPh, MPH |

CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
DMEPA=Division of Medication Error Prevention and Analysis
ONDQA – Office of new Drug Quality Assessment
DMPP=Division of Medical Policy Programs
OPDP= Office of Prescription Drug Promotion
DPP – Division of Professional Promotion
DDTCP – Division of Direct-to-Consumer Promotion
OSI=Office of Scientific Investigations
SEALD = Study Endpoints and Labeling Development Team

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## 1. Introduction

EffRx Pharmaceuticals SA submitted an NDA (202-344) containing a proposed new alendronate sodium formulation in a 70 mg effervescent tablet. The active ingredient in this alendronate sodium tablet is the most widely prescribed osteoporosis drug in the world. The proposed indications for this new alendronate effervescent tablet formulation include: 1) treatment of osteoporosis in postmenopausal women and 2) to increase bone mass in men with osteoporosis. The goal of alendronate sodium therapy is to reduce the risk of fractures in postmenopausal women and men with osteoporosis.

Alendronate sodium is a nitrogenated bisphosphonate (BP). BPs are analogues of pyrophosphate which become incorporated into calcium hydroxyapatite mineral within bone tissue. There they inhibit the bone resorptive activity of osteoclasts, which generally results in increased bone mineral density and strength, and reduced risk for bone fracture. Several BPs are used clinically to treat osteoporosis and other bone disorders characterized by excessive bone resorption, such as glucocorticoid-induced osteoporosis.

(b) (4)

Bisphosphonates, including alendronate sodium, become incorporated into bone matrix and remain there for years, therefore normal bone resorption and turnover may remain suppressed long after administration is stopped. Recently, there has been concern about the potential for adverse effects of BPs related to prolonged over-suppression of bone metabolism, especially osteonecrosis of the jaw (ONJ) and atypical femoral fractures (subtrochanteric and diaphyseal). Class labeling for all bisphosphonates used to treat osteoporosis now includes Warnings and Precautions pertaining to these conditions, as well as language indicating the uncertainty of long-term use of bisphosphonates. In

addition, a Medication Guide for Binosto will be required as part of Approval to address potential safety issues with bisphosphonate use that have been associated with prolonged over-suppression of bone metabolism such as ONJ and atypical fractures.

The main objective of this NDA was to demonstrate bioequivalence of the proposed alendronate sodium effervescent tablet product to a reference listed drug (Fosamax/ alendronate sodium) tablet 70 mg, hereafter referred to as Fosamax, and to demonstrate acceptable safety required by FDA.

## 2. Background

A pre-NDA package with questions was submitted on October 3, 2008. The Applicant stated their intent to pursue a 505(b)(2) application for effervescent alendronate based upon demonstration of bioequivalence to an approved Fosamax formulation. In preliminary comments that were sent to the Applicant on November 4, 2008, the Division concurred that if bioequivalence criteria were met and there were no new safety issue identified, this regulatory pathway was acceptable. The preliminary comments were accepted by the Applicant, and the meeting with the Division was cancelled.

IND 103130 was opened on June 23, 2009, with submission of two clinical study reports that had been conducted in Europe and included:

- Study SCO 5361 - a bioequivalence and food effect study that compared the alendronate sodium effervescent formulation to an approved Fosamax tablet formulation.
- Study BC-118-07 – a pharmacodynamic gastric imaging and pH telemetry study.

1. Study BC-118-07 was a scintigraphic study to investigate the differences in gastric emptying and gastric pH in a conventional alendronate sodium tablet compared to two effervescent formulations of alendronate.

*Comment: In the preNDA meeting package in 2008, the Applicant described results of this pharmacodynamic study.* (b) (4) [redacted]

2. Bioequivalence Study SCO5361 failed to prove bioequivalence of the effervescent tablet to the Fosamax tablet (b) (4) [redacted] They indicated their intention to change (b) (4) formulation that would be used in a second bioequivalence study, AE-1212-001-EM.

Although this second bioequivalence study was also not intended to be conducted under the IND, the protocol for AE-1212-001-EM was included in the original IND submission, and several comments regarding the second bioequivalence study were sent to the Applicant on October 2, 2009. These recommendations were subsequently incorporated into the protocol. Study AE-1212-001-EM was conducted between 2009 and 2010 in Germany.

On September 1, 2010, a Pre-NDA meeting was held with the Applicant to discuss the results of Study AE-1212-001-EM. At that time, the Applicant confirmed that the formulation of the alendronate sodium effervescent tablet had not changes between the two bioequivalence studies (SCO5361 and AE-1212-001-EM) except for (b) (4)

On October 28, 2011, an amendment containing a new clinical and statistical report for the bioequivalence study (Study AE-1212-001-EM) was received. The reason for this amendment is outlined in Section 11 of this review. After review of the amendment, it was determined that this submission constituted a major amendment to the application and the user fee goal date was extended to March 15, 2012.

## 3. ONDQA

The Applicant's proposed alendronate sodium drug substance is manufactured in an effervescent tablet formulation. Each tablet contains approximately 70 mg of free alendronic acid and various compendial grade inactive ingredients such as monosodium citrate anhydrous, citric acid anhydrous, sodium hydrogen carbonate, sodium carbonate anhydrous, acesulfame potassium and sucralose. The final drug product contains approximately 653 mg of sodium per tablet and prepared by dissolving the tablet in 120 milliliters of room temperature water. Tablets are packaged in aluminum foil composite blister strips. Each container has blisters with 4 tablets or (b) (4).

The Biopharmaceutics review team initially reviewed the proposed disintegration methodology in a review dated September 19, 2011. At the time of the evaluation, the Biopharmaceutics team recommended that disintegration acceptance criterion be revised and implemented (See ONDQA Advice letter dated September 21, 2011). On September 29, 2011, the Applicant agreed to the Agency's recommendation. In an addendum to their September, 2011, review (dated October 23, 2011), the Biopharmaceutics team stated that, "ONDQA-Biopharmaceutics recommends approval of NDA 202-344 for Steovess (Alendronate Sodium) Effervescent Tablets."

The Chemistry Review (ONDQA) team made the following recommendation in their review dated October 13, 2011, "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."

On January 23, 2012, the overall recommendation from Office of Compliance for the NDA was posted as ACCEPTABLE, based on a satisfactory inspections of the drug product manufacturing sites (See ONDQA review dated March 7, 2012).

In an addendum to the October, 2011, ONDQA review, finalized on March 7, 2012, the ONDQA review team stated that, "This NDA is now recommended for approval from the ONDQA perspective."

*Comment: I concur with the recommendations of the ONDQA review team that there are no outstanding CMC issues.*

**4. Nonclinical Pharmacology/Toxicology**

The pharmacology/toxicology review team stated in their review dated February 9, 2012, that, "Based on bioequivalence of the listed drug (Fosamax, 70 mg tablet) and the 70 mg EX101 effervescent tablet, the Sponsor's referral to NDA 20-560 and NDA 21-575 for nonclinical support of NDA 202-344 is acceptable. Pharmacology/Toxicology recommends approval of the NDA."

*Comment: I concur with the recommendations of the pharmacology/toxicology review team. There are no outstanding pharmacology/toxicology issues.*

**5. Clinical Pharmacology**

The Clinical Pharmacology review team evaluated two of the three clinical studies submitted with this NDA as these studies contained relevant clinical pharmacology data. These two studies included: a pivotal bioequivalence study (AE-1212-001-EM) and a bioequivalence/food effect study (SCO 5361).

OSI conducted an inspection of the bioanalytic facility and issued a Form 483 expressing concern regarding the validity of some of the alendronate pharmacokinetic data from the pivotal bioequivalence study (AE-1212-001-EM). OSI recommended either re-assay of the batches of concern or exclusion of data from these batches and a reanalysis of the bioequivalence data. These options were discussed at a teleconference on October 12, 2011, between the Division and the Applicant; the plan agreed upon was that the Applicant would repeat the statistical analyses without the data from the batches in question. On October, 28, 2011, the Applicant submitted the requested reanalyses with their conclusion that the bioequivalence criteria were still met. The submission of the reanalysis and additional raw data to support the analysis were considered a major amendment and the PDUFA Goal Date for this NDA was extended from 12/15/11 to 3/15/12.

After evaluation of the revised pharmacokinetic data from Study AE-1212-001-EM, the Clinical Pharmacology review team concluded that, "The BE study supports that Binosto

and Fosamax are bioequivalent under fasting conditions." (See Clinical Pharmacology review dated February 9, 2012).

Before conducting pivotal BE study AE-1212-001-EM, the Applicant had conducted a BE/food effect study (Study SCO 5361). Study SCO 5361 compared an earlier formulation of the effervescent alendronate tablet to Fosamax under both fasted and fast conditions. This study did not show bioequivalence of the Binosto formulation to Fosamax (b) (4). The Applicant reformulated their product to (b) (4) and used the revised formulation in pivotal study AE-1212-001-EM. The Clinical Pharmacology reviewer noted that this study (SCO 5361) was submitted with the NDA, but "…due to the formulation difference, the study SCO 5361 is not reviewed."

The Clinical Pharmacology review team made the following recommendation in their review dated February 9, 2012: "The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 202344 acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert."

In an addendum dated March 8, 2012, the Clinical Pharmacology review team reviewed relevant sections of revised labeling from the Applicant submitted on March 8, 2012, and concluded that, The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the NDA 202344 acceptable."

*Comment: I concur with the recommendations of the clinical pharmacology review team. There are no outstanding clinical pharmacology issues.*

**6. Clinical Microbiology**

Microbiology consult was not requested by ONDQA and no issues related to Microbiology were identified during this review cycle. (See ONDQA review October 13, 2011).

**7. Efficacy/Statistics**

The principal study to support the efficacy of the Applicant's proposed alendronate sodium effervescent tablet that was submitted to the NDA was Study AE-1212-001-EM. Because the Applicant demonstrated comparable exposure of their alendronate sodium product to the approved comparator (Fosamax), efficacy for the Applicant's alendronate sodium product could be bridged to the efficacy data for Fosamax. The other two submitted studies (SCO 5361 containing data from the failed bioequivalence study and Study BC-118-07 with data on gastric emptying and pH) were considered to contain safety-related data and safety data from these studies is briefly outlined in section 8 of this review.

Bioequivalence Study AE-1212-001-EM:

The "pivotal study" reviewed to determine efficacy of this alendronate sodium effervescent tablet was bioequivalence Study AE-1212-001-EM. The primary objective of Study AE-1212-001-EM was to assess the bioequivalence of the test (alendronate sodium effervescent) and reference (Fosamax) tablets in the fasting state (first meal 4 hours after administration) as measured by the amount of alendronate excreted in the urine by the amount of alendronate excreted in the urine and the maximum excretion rate in the combined female and male group. The Applicant stated that for the US, bioequivalence would be demonstrated if the 90% CI of both the treatment ratio T/R for Ae0-48 and the treatment ratio of test/reference (T/R) for $E_{max}$ in the combined female and male group were within 80% to 125%.

Study AE-1212-001-EM was a single-site, open label, four period cross-over replicate study. A total of 115 healthy subjects (70 female and 45 male) were enrolled and dosed in the study; 107 of these enrolled subjects completed the study. The trial was performed and laboratory data was analyzed at (b) (4)

Subjects received both the test (Binosto) and reference (Fosamax) treatments twice in 2 sequences as single oral doses. The test product was the to-be-marketed alendronate sodium effervescent tablet dissolved in 120 mL of room temperature water. The reference product was a single dose of Fosamax (70 mg)) with 240 mL of room temperature water. Administration of each tablet was performed in the morning after at least a 12 hour fast, followed by a 4 hour fasting period. Between administration of each study drug, there was a washout period of at least 14 days but no longer than 28 days. Subjects were randomized to receive the 4 treatments either in the sequence Fosamax/Binosto/Fosamax/Binosto or the sequence Binosto/Fosamax/Binosto/Fosamax.

Urine samples were collected prior to drug application, immediately before drug application, and post-dose in each treatment period. The primary efficacy evaluation included the following key pharmacokinetic parameters:

- $Ae_{0-48}$ (cumulative alendronate urinary excretion to 48 hrs post-dose, in µg)
- $E_{max}$ (maximal rate of alendronate urinary excretion, in µg/hr)

Adverse events, vital sign measurements, physical examination and laboratory evaluations were also collected and analyzed as safety parameters.

Demographics:

The demographics and baseline characteristics for the 115 subjects from Study AE-1212-001-EM is outlined in the table below.

**Table 1: Study AE-1212-001-EM: Demographics and baseline characteristics**

| Age (years) | Males | Females | M/F Combined |
|---|---|---|---|
| n | 45 | 70 | 115 |
| Mean ± SD | 54.5 ± 7.3 | 58.0 ± 8.0 | 56.6 ± 7.9 |
| Min - Max | 45 – 73 | 45 - 73 | 45 - 73 |
| Body height (cm) | | | |
| n | 45 | 70 | 115 |
| Mean ± SD | 177 ± 6.4 | 162 ± 6.0 | 168 ± 9.4 |
| Min - Max | 163 - 191 | 150 - 178 | 150 - 191 |
| Body weight (kg) | | | |
| n | 45 | 70 | 115 |
| Mean ± SD | 79.2 ± 9.6 | 64.3 ± 8.2 | 70.1 ± 11.4 |
| Min - Max | 60 - 99 | 45 - 87 | 45 - 99 |
| Body mass index ($kg/m^2$) | | | |
| n | 45 | 70 | 115 |
| Mean ± SD | 25.3 ± 2.1 | 24.5 ± 2.5 | 24.8 ± 2.3 |
| Min - Max | 21 - 28 | 19 - 28 | 19 - 28 |
| Source: Table 14.1.1, CSR | | | |

*Table 1 adapted from Table 14 from the Medical Officer's review dated February 7, 2012.

*Comment: No efficacy concerns were raised by the Medical Officer or CDTL concerning the demographic and baseline data above.*

Efficacy assessment (Study AE-1212-001-EM):

The key pharmacokinetic parameters that were evaluated for this bioequivalence analysis included $Ae_{0\text{-}48}$ and $E_{max}$. Bioequivalence would be determined if the 90% confidence intervals for the ratio of the test (T) and reference (R) least mean squares for the parameters $Ae_{0\text{-}48}$ and $E_{max}$ were within the 80 to 125% bioequivalence limits. As per standard methodology, the 90% geometric confidence interval of the ratio were calculated using the cumulative amount of alendronate excreted in urine during the entire period of sample collection ($Ae_{0\text{-}48}$) and maximum rate of alendronate excreted for each collection interval (obtained by dividing the fractional amounts excreted by the duration of the corresponding sampling intervals, $E_{max}$) were used as PK parameters.:

OSI conducted a GLP inspection of the bioanalytic site and issued a Form 483 expressing concern about the validity of some of the alendronate pharmacokinetic data from this study (See details of the OSI inspection in section 11 of this review). On October 28, 2011, the Agency received a revised study report and datasets for Study AE-1212-001-EM. The revised data were evaluated in the final determination of bioequivalence for this submission. The ratios of the $Ae_{0\text{-}48}$ and $E_{max}$ between Binosto and Fosamax and the 90% confidence interval for those ratios (the primary analyses used to support the bioequivalence comparisons) from the recalculated data received on October 28, 2011, are shown in the table below (Test/Reference) of least-squares means

**Table 2: Summary of statistical reanalysis excluding data from 11 batches (N=103)***

| Parameter | Geometric Mean | | Ratio (Test: Reference) | 90% Confidence Interval |
|---|---|---|---|---|
| $Ae_{0-48}$ (ug) | 186 [45%] | 210 [47%] | 0.88 | 0.83-0.94 |
| $E_{max}$ (ug/h) | 63 [44%] | 70 [47%] | 0.09 | 0.85-0.97 |

*Table 2 adapted from Table 3 in the Clinical Pharmacology review finalized February 9, 2012.

The 90% confidence intervals for the ratio of the Test (Binosto) and Reference (Fosamax) for the parameters $Ae_{0-48}$ and $E_{max}$ were within the 80-125% bioequivalence limits. Therefore, based on the reanalysis of the pharmacokinetic data presented above, bioequivalence of $Ae_{0-48}$ and $E_{max}$ between Binosto and Fosamax was established.

Clinical Pharmacology comments regarding the results of Study AE-1212-001-EM:

In the review dated February 9, 2012, the Clinical Pharmacology reviewer made the following conclusion regarding the bioequivalence study AE-1212-001-EM, "The BE study (AE-1212-001-EM) supports that Binosto and Fosamax are bioequivalent under fasting conditions. The 90% confidence intervals (CIs) for the ratio of the Test (Binosto) and Reference (Fosamax) least squares means (LSM) for the parameters $Ae_{0-48}$ and $E_{max}$ were within the 80 to 125% bioequivalence limits."

Statistical review:

In a review dated September 12, 2011, the statistical reviewer stated that, "There was no new clinical efficacy data submitted in support of this submission. Therefore, no statistical review was necessary."

*Comment: I concur that no evaluation of the clinical study data from the Division of Biometrics was required.*

Efficacy summary:

The main objective of the Applicant's NDA submission was to demonstrate bioequivalence of their proposed alendronate sodium effervescent tablet product to the reference listed drug (RLD) product Fosamax.

The Clinical Pharmacology review team concluded that, "The 90% CIs for the ratio of the Test and Reference LSM for the parameters $Ae_{0-48}$ and $E_{max}$ were within the 80 to 125% bioequivalence limits, hence showed the BE between Binosto and Fosamax."

In her review dated, February 24, 2012, the Cross-Discipline team leader further concluded that, "The applicant is relying on the Agency's findings of effectiveness for the referenced drug, Fosamax. Binosto (alendronate sodium) effervescent 70 mg tablet and Fosamax (alendronate sodium) 70 mg tablet are bioequivalent. Bone mineral density increases achieved with Fosamax 70 mg once weekly are non-inferior to the bone mineral density increases achieved with Fosamax 10 mg daily. Fosamax 10 mg daily was the dose used in the pivotal fracture efficacy trial. Therefore, by establishing the bioequivalence of Binosto (alendronate sodium) effervescent 70 mg tablet and Fosamax (alendronate sodium) 70 mg tablet, a bridge back to the fracture efficacy of Fosamax 10 mg daily has been made."

*Summary comment: Based on the submitted bioequivalence data that is bridged back to the efficacy data for Fosamax, it is reasonable to conclude that the proposed Applicant's product will be efficacious for the stated osteoporosis indications. Therefore, I concur with the recommendations of the clinical pharmacology review team and cross-discipline team leader that there are no outstanding efficacy concerns for this new alendronate sodium effervescent tablet product.*

## 8. Safety

The safety data for this application are derived from the three clinical studies that were submitted: 1) a comparative bioequivalence study (Study AE-1212-001-EM), 2) a failed bioequivalence study using previous formulations (Study SCO 5361) and 3) a study that evaluated gastric emptying and pH (Study BC-118-07). Only Study AE-1212-001-EM was conducted with the to-be-marketed alendronate sodium effervescent tablet formulations, the other two studies were conducted with previous (b) (4) formulations.

The safety database consists of a total of 260 subjects exposed to at least one dose of an alendronate sodium effervescent tablet formulation. Of these subjects:

- A total of 248 subjects were evaluated as the pooled safety population (ISS) obtained from the two bioequivalence studies (AE-1212-001-EM and SCO 5361).
- An additional 12 subjects were evaluated in the GI pharmacodynamic study (BC-118-07) and these subjects were reviewed separately.

Deaths, Serious Adverse Events and Discontinuations due to Adverse Events:

No deaths occurred in any of the three clinical studies (AE-1212-001-EM and SCO 5361 and BC-118-07) conducted for this NDA.

No serious adverse events occurred with use of the alendronate sodium effervescent tablet in any of the three clinical studies (AE-1212-001-EM and SCO 5361 and BC-118-07) conducted for this NDA. There were two SAEs reported that reported after receiving the comparator product (Fosamax), but neither were considered related to receiving a study drug by the Applicant.

A total of 7 subjects discontinued for adverse events in these three studies; 6 in the two bioequivalence studies and 1 in the pharmacodynamic GI study. Only one of these subjects was reported as related to the study drug (alendronate sodium effervescent tablets).

*Comment: The Medical Officer and CDTL reviewed the serious adverse events and discontinuations and concurred that there were no events of concern or imbalances between subjects receiving alendronate sodium effervescent tablet formulations and those subjects who received an approved comparator. I concur with their assessments.*

Adverse Events (AEs)

As requested by the Division at the pre-NDA meeting on September 1, 2010, most of the safety data from the two bioequivalence studies (AE-1212-001-EM and SCO 5361) were pooled and formed the basis of the safety profile (referred to as the Integrated Summary of Safety or ISS). The ISS included a total of 248 healthy subjects (203 women and 45 men). A total of 479 doses of alendronate sodium effervescent tablet were administered, with about ½ of the doses (258) with the initial (b) (4) formulation.

The most common AEs associated with both Binosto and Fosamax were consistent with the known safety profile of alendronate and included: headache, fatigue, diarrhea, nausea, back pain, pain in extremity, and nasopharyngitis. The table below displays an overview of common adverse events (>3% in any treatment group) in the ISS population.

**Table 3: Common Adverse Events (>3% in any treatment group): subject incidence in ISS Pooled Safety Population***

| System Organ Class<br>Preferred Term | Binosto 70 mg | | | Fosamax 70 mg |
|---|---|---|---|---|
| | All subjects (N = 245) n (%) | Fed (N = 130) n (%) | Fasted (N = 241) n (%) | Fasted (N = 241) n (%) |
| Gastrointestinal disorders | 43 (17.6) | 18 (13.8) | 30 (12.4) | 31 (12.9) |
| Diarrhea | 13 (5.3) | 9 (6.9) | **5 (2.1)** | **15 (6.2)** |
| Dyspepsia | 8 (3.3) | 2 (1.5) | **6 (2.5)** | **1 (0.4)** |
| Nausea | 14 (5.7) | 3 (2.3) | **13 (5.4)** | **8 (3.3)** |
| Vomiting | 9 (3.7) | 3 (2.3) | 6 (2.5) | 5 (2.1) |
| General Disorders and administration site conditions | 33 (1.5) | 20 (15.4) | 16 (6.6) | 18 (7.5) |
| Fatigue | 32 (13.1) | 19 (14.6) | 16 (6.6) | 18 (7.5) |
| Infections and infestations | 16 (6.5) | 6 (4.6) | 10 (4.1) | 6 (2.5) |
| Nasopharyngitis | 11 (4.5) | 3 (2.3) | 8 (3.3) | 4 (1.7) |
| Musculoskeletal and connective tissue disorders | 30 (12.2) | 15 (11.5) | 19 (7.9) | 27 (11.2) |
| Back pain | 11 (4.5) | 5 (3.8) | 7 (2.9) | 11 (4.6) |
| Pain in extremity | 11 (4.5) | 4 (3.1) | 8 (3.3) | 8 (3.3) |
| Nervous system disorders | 97 (39.6) | 31 (23.8) | 81 (33.6) | 74 (30.7) |
| Headache | 93 (38.0) | 31 (23.8) | 77 (32.0) | 72 (29.9) |

** Note that compared to the fasting groups in the 2 right columns, the "Binosto/all subjects" and "Binosto/fed" groups represent higher and lower alendronate exposure per subject, respectively
n (%) = number (percent) of exposed subjects with adverse events
Source: Summary of Clinical Safety, Table 7, M 2.7.4

*Table 3 adapted from Table 12 in the Medical Officer's review dated February 7, 2012.

*Comment: After review of the pooled adverse event data from the two bioequivalence studies, the Medical Officer and CDTL concluded that the safety profile for Binosto was similar to the Fosamax comparator.*

Vital Sign Findings

As Binosto contains a high level of sodium (, trends in mean blood pressure and adverse events related to blood pressure were evaluated by the Medical Officer. The Medical Officer concluded that, "Mean blood pressure declined modestly from baseline to around 24 hours, with no apparent difference between the two drug treatments." (See Medical Officer Review dated February 7, 2012)

*Comment: The Medical Officer and CDTL did not identify any new safety signals from the vital sign data for the proposed Binosto product from these results.*

Laboratory Findings

The Medical Officer evaluated laboratory parameters including hematology, chemistry, EKG and urinalysis that were measured at screening and final visit for each individual study. In addition, serum calcium and phosphorus levels were pooled from the two bioequivalence studies and evaluated because changes in these parameters had been

noted with other alendronate sodium products. (See Medical Officer Review dated February 7, 2012)

*Comment: In his February 7, 2012, review, the Medical Officer concluded that, "…. minor changes in serum calcium and phosphorus seen were consistent with the well-established safety profile of Fosamax." The Medical Officer did not identify any new safety signals from any other laboratory data submitted for the proposed Binosto product.*

Pharmacodynamic GI study – Study BC-118-07

Study BC-118-07 was a single site, open-label 3-way crossover study that evaluated a total of 12 healthy females. The study compared three formulations: 1) an alendronate sodium (b) (4) effervescent tablet, 2) an effervescent tablet with limited buffering capacity and 3) a conventional alendronate sodium tablet. The objectives of this study included:

- To evaluate dosing advantages of two different soluble effervescent alendronate dosage forms when compared to each other and to a conventional alendronate tablet.
- To determine differences between the upper gastrointestinal transit (as judged by gastric emptying) of the three different formulations with respect to post-dose fasting.
- To determine the effects of the three formulations on gastric pH after dosing.

After overnight fast, subjects received 3 treatment periods in random order, separated by at least 7 days:

- Treatment A – conventional Fosamax tablet 70 mg in 240 mL water
- Treatment B – Binosto effervescent tablet (b) (4) 70 mg in 100 mL water, then 20 mL water rinse of dosing glass
- Treatment C – comparator effervescent powder formulation (b) (4) in 100 mL water, then 20 mL rinse of dosing glass. This formulation was apparently similar in composition to Treatment B including sodium bicarbonate buffer (b) (4)

Each formulation was radiolabeled with technetium-99m diethylenetriamine pentaacetic acid complex to allow gastric emptying time to be determined using gamma scintigraphy. Simultaneous measurements of gastric pH were made using pH telemetry. The endpoints of this study were scintigraphic analysis of the gastric emptying of the formulations in vivo and pH telemetry of all subjects from 2 hours prior to dosing through 4 hours post dose.

A total of 10 subjects completed the study with one subject withdrawing because of an adverse event (attributed to placement of the nasogastric tube) and one subject withdrew consent. Results of Study BC-118-07 included:

- Imaging showed that gastric emptying times of radiolabel were slightly slower with Binosto, though great variability was noted for Binosto and the two Fosamax tablets that were used as reference products.
- Gastric pH rose above 3 immediately after the dose of the 2 effervescent formulations and remained elevated after administration. This was in contrast to conventional Fosamax, which yielded considerable quantities of acidic alendronate for a prolonged period.

After review of the results of Study BC-118-07, the Medical Officer concluded that, "There was a great deal of variability in these measurements, and their clinical significance is not entirely clear. However, this study does show that the effervescent tablet significantly buffers gastric acid during the 30-60 minutes after administration, compared to Fosamax tablet. Given the nonclinical evidence that pH plays an important role in BP-related esophagitis, this study provides some useful supportive safety information." (See Medical Officer review dated February 7, 2012.

*Comment: Alendronate sodium is poorly absorbed and has the potential to cause mucosal irritation effects in the upper GI tract, particularly in the esophagus. It is possible that the effervescent tablets may be preferred because of the perception of improved tolerability because of the effervescence. However, I concur with the Medical Officer and CDTL that although Study BC-118-07 provided some useful supportive safety information with respect to gastric emptying and pH changes,* (b) (4)

Safety summary:

The safety database for Binosto, although limited, support that there is no evidence to suggest that the safety profile of Binosto would be substantially different from other marketed alendronate sodium products. There is a significant history of use of other alendronate sodium products for these indications that can be considered supportive because Binosto was shown to be bioequivalent to a marketed alendronate sodium product. Therefore, the known safety profile of these alendronate sodium products can be incorporated in the Binosto labeling. Finally, potential safety concerns associated with long-term use of bisphosphonates, including alendronate sodium, will be addressed in physician labeling and also through a Medication Guide.

The only potential safety difference between Binosto and Fosamax that appeared to be of clinical concern was the difference in sodium content between products. The high sodium content in Binosto was evaluated and will be addressed in physician labeling and in the Medication Guide for Binosto.

The Medical Officer concluded the following in his review dated February 7, 2012, "In summary, there is no evidence indicating that safety of Binosto 70 mg effervescent tablet is expected to differ significantly from that of Fosamax 70 mg tablet."

The cross-discipline team leader (CDTL) concurred with the primary medical officer's recommendation in her CDTL review (dated February 24, 2012) and stated, "I agree with Dr. Voss that the safety data available indicate that there is no difference in the safety profile of Binosto (alendronate sodium) effervescent 70 mg tablet and Fosamax (alendronate sodium) 70 mg tablet. Overall, the number of subjects reporting adverse events was similar and there were no imbalances were noted in serious adverse events or adverse events leading to withdrawal."

*Comment: I concur with the recommendations of the primary Medical Officer and CDTL that there are no outstanding safety issues for this submission.*

**Advisory Committee Meeting**

The first bisphosphonate product, alendronate sodium, has been approved since 1995 for treatment of osteoporosis in postmenopausal women. Since then, other bisphosphonate products have been approved and used in clinical practice. The safety issues associated with bisphosphonate therapies are well known and can be adequately labeled. Therefore, no Advisory Committee was convened.

**9. Pediatrics**

The proposed indication is limited to postmenopausal women and men with osteoporosis. Although alendronate sodium is used off-label in some children with metabolic bone disease, studies of alendronate have failed to establish efficacy or safety in this age group. Based on this information, the Pediatric Review Committee (PeRC) has agreed to a full waiver for pediatric studies of Binosto, and none are currently planned.

**10. Other Relevant Regulatory Issues**

Division of Medical Policy Programs (DMPP):

DMPP reviewed the Medication Guide on February 28, 2012, and found it to be acceptable with several recommended changes. The recommendations were implemented.

Office of Prescription Drug Promotion (OPDP):

OPDP reviewed the Prescribing Information and the Medication Guide. OPDP completed their review of Prescribing Information on February 23, 2012, and the Medication Guide on February 29, 2012 . Their recommendations were implemented.

Office of Scientific Investigations (OSI):

OSI conducted a July, 2011, inspection of the clinical site for pivotal Study AE-1212-001-EM. The clinical portion of this pivotal study was conducted at CRS Clinical

Research Services in Mannheim, Germany. OSI's final classification of this clinical site was NAI.

OSI also conducted a July, 2011, inspection of the analytic site for pivotal Study AE-1212-001-EM. The analytic portion of this pivotal study was (b) (4) identified deficiencies regarding the adequacy of the bioequivalence findings. OSI's final classification of this analytic site was VAI and a Form 483 was issued. Following the inspections, OSI recommended the following actions:

- 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.

Based the concerns that were raised in this FDA-483 Form, the Division held a teleconference with the Applicant on October 12, 2011 to convey the deficiencies and recommendations to the Applicant listed in the 483 form. At that October, 2011, meeting, the Division proposed a plan for reanalysis of the bioequivalence data and requested resubmission of all raw data sets. The proposal and requests were accepted by the Applicant.

On October 28, 2011, the revised study report for Study AE-1212-001-EM was received. This October, 2011, submission contained a revised pharmacokinetic and statistical analysis with accompanying raw datasets. The submission containing revised data was considered a major amendment, and the user fee goal date was extended to March 15, 2012. The Clinical and Clinical Pharmacology evaluations of the revised pharmacokinetic data from that October 28, 2011, submission are presented in Section 7 of this review.

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team reviewed the carton and container labels, labeling. In their review dated February 7, 2012, the DMEPA review team made recommendations to the FPI and carton/container labeling. DMEPA's recommendations were implemented.

DMEPA also re-assessed the proposed tradename "Binosto" on February 9, 2012, and found it acceptable.

Financial Disclosures**:**

The clinical review team did not identify any issues related to financial disclosures for these studies (See clinical review dated February 7, 2012).

Study Endpoints and Labeling Development Team (SEALD)**:**

The SEALD review team concluded in a review finalized on March 8, 2012, that the final labeling is acceptable.

**11. Labeling**

Labeling negotiations are complete. Labeling for Binosto is now consistent with previously approved bisphosphonate products. Labeling was also evaluated by the following groups:

- Office of Medical Policy Programs (DMPP) reviewed the label and the Medication Guide and their recommendations were considered during labeling negotiations with the Applicant.
- Office of Prescription Drug Promotion (OPDP) reviewed the label and Medication Guide and their recommendations were considered during labeling negotiations with the Applicant.

Labeling was also acceptable to the Study Endpoints and Label Development (SEALD) Team.

**12. Decision/Action/Risk Benefit Assessment**

Decision:

I agree with the cross-discipline team leader, primary medical officer, and the clinical pharmacology, pharmacology/toxicology, CMC, and statistical reviewers that this alendronate sodium effervescent tablet application can receive an Approval action.

Risk Benefit Assessment:

The primary endpoint for the pivotal phase 1 bioequivalence study (Study AE-112-01-EM) was determined by the Clinical Pharmacology and Clinical teams to be acceptable. The pharmacokinetic data that was submitted along with the other two supportive studies are acceptable "bridging data" to support the approval of this proposed alendronate sodium effervescent tablet product from an efficacy standpoint. After review of the pharmacokinetic data, the CDTL, primary medical officer, and the clinical pharmacology and statistical reviewers believe that these data support Approval and I agree.

From an efficacy perspective, the data submitted in this NDA was sufficient to demonstrate that the product will provide similar alendronate exposure to an approved product when used as directed. It also is reasonable to conclude, based on data showing equivalence to an approved alendronate product from the submitted study and no identified safety signals in the supportive studies on food effect and gastric effects, that the proposed product will have comparative safety to other approved bisphosphonate products. In addition, based on comparable exposure of the Applicant's product to a

reference list alendronate sodium product (Fosamax), the extensive safety experience with the approved product (Fosamax) is relevant and provides robust support for safety.

In summary, based on the data presented in this NDA submission as well as previous data and experience with other approved bisphosphonate products, I believe that the proposed alendronate sodium effervescent tablet product will be effective and safe for the indications of 1) treatment of osteoporosis in postmenopausal women and 2) treatment to increase bone mass in men with osteoporosis. Finally, this product does contain relatively high sodium content (approximately 653 mg per tablet) compared to other marketed bisphosphonate products, but this potential safety issue was adequately addressed in labeling.

Labeling, including the package insert, the Medication Guide and container/carton labeling has been completed. The proposed Medication Guide, which pertains to the risks of use of bisphosphonate products for both treatment of osteoporosis indications have been determined to be acceptable by all review teams.

The benefit/risk evaluation favors approval of the Applicant's alendronate sodium effervescent tablet.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

- Although the Applicant proposed a REMS for this product, it was determined that it was not necessary as there were no new safety issues that were identified for this product. The requirement of REMS for bisphosphonate products was eliminated in August 2011.
- The other review teams determined that no other postmarketing studies were necessary for approval of Binosto.

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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.**

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/s/

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AUDREY L GASSMAN
03/12/2012