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APPLICATION NUMBER:

202344Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 23,2012
From	Theresa Kehoe, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	202344
Applicant	EffRx Pharmaceuticals SA
Date of Submission	February 15, 2011
PDUFA Goal Date	December 15, 2011 extended to March 15, 2012
Proprietary Name / Established (USAN) names	Binosto Alendronate sodium
Dosage forms / Strength	oral effervescent tablet 70 mg weekly
Proposed Indication(s)	1. Treatment of osteoporosis in postmenopausal women 2. Treatment to increase bone mass in men with osteoporosis
Recommended:	Approval

1. Introduction

EffRx Pharmaceuticals SA through their US Agent, Hurley Consulting Associates, Inc., has submitted this new drug application (NDA) seeking approval of Binosto (EX101), alendronate sodium 70 mg oral effervescent tablet once weekly for treatment of osteoporosis in postmenopausal women and treatment to increase bone mass in men with osteoporosis. The application was submitted December 21, 2010, and included a request for a small business waiver of the application fee. The waiver was granted on February 15, 2011, which became the effective date of the NDA submission. In this application, the Applicant is using the 505(b)(2) regulatory path, relying on the Agency's findings of safety and effectiveness of Fosamax (alendronate sodium). A single bioequivalence study (study AE-1212-001-EM) provides the scientific basis for bridging to Fosamax (alendronate sodium).

Binosto contains alendronate sodium, the active drug substance in Fosamax. Fosamax tablet 10 mg daily was approved for the treatment of osteoporosis in postmenopausal women September 29, 1995. Fosamax 70 mg tablet once weekly for the treatment of osteoporosis in postmenopausal women was approved October 20, 2000. For treatment to increase bone mass in men with osteoporosis, Fosamax 10 mg daily was approved September 29, 2000, and Fosamax 70 mg once weekly was approved 1/31/2001. Fosamax 70 mg oral buffered solution was approved 9/17/2003,

for treatment of osteoporosis in postmenopausal women and treatment to increase bone mass in men with osteoporosis.

Current therapies available for the treatment of osteoporosis in postmenopausal women include Fosamax (alendronate) 10 mg daily tablet, 70 mg tablet weekly, and 70 mg oral buffered solution weekly; Fosamax plus D (alendronate plus cholecalciferol) 70mg/2800 IU weekly or 70mg/5600 IU weekly; Actonel (risedronate) 5 mg daily, 35 mg weekly, 75 mg on two consecutive days monthly and 150 mg once monthly; Actonel and calcium (risedronate copackaged with calcium) 35 mg once weekly with calcium 1250 mg daily; Boniva (ibandronate) 2.5 mg daily oral, 150 mg once monthly oral or 3 mg intravenously every 3 months; Evista (raloxifene) 60 mg daily; Miacalcin (salmon calcitonin) nasal spray 200 IU daily; and Fortical (salmon calcitonin) nasal spray 200 IU daily. Forteo (teriparatide) 20 mcg daily by subcutaneous injection and Prolia (denosumab) 60 mg every 6 months by subcutaneous injection are indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture.

2. Background

The Applicant sought regulatory guidance from the Agency in July, 2008. They proposed development of an effervescent form of 70 mg alendronate sodium (EX101) and planned to demonstrate bioequivalence with the approved 70 mg Fosamax tablet. The Applicant was informed that a 505(b)(2) regulatory path was acceptable and strict bioequivalence of both the ratio amount and rate of alendronate excreted in urine would be necessary. If strict bioequivalence was not established, a one year non-inferiority study comparing EX101 and Fosamax, with change in lumbar sacral (LS) BMD as the primary endpoint would be necessary. (b) (4)

Three studies have been submitted in support of this application. Study SCO 5361 is an earlier bioequivalence study (b) (4) Bioequivalence with alendronate sodium 70 mg tablet was not achieved. The Applicant then reformulated their produc (b) (4) formulation. The definitive bioequivalence study is AS-1212-001-EM, which evaluated the bioequivalence of the (b) (4) formulation of effervescent alendronate sodium to Fosamax 70 mg. Study BC-118-07 was a pharmacodynamic study investigating gastric emptying and gastric pH with three different alendronate sodium formulations.

Bisphosphonates are incorporated into the hydroxyapatite crystals of bone and act by inhibition of osteoclasts. The result of osteoclast inhibition is decreased bone resorption and increased bone mass. Incorporation of the bisphosphonate into bone hydroxyapatite results in a long residency time in bone. In adults, oral bisphosphonates have been associated with a number of safety issues including upper gastrointestinal adverse events, osteonecrosis of the jaw, musculoskeletal adverse events related to pain, inflammatory eye events, and more recently, possible atypical fracture of the femur. This review will discuss these safety issues as they relate to the currently proposed product.

3. CMC/Device

Once product labeling is agreed upon, this NDA is recommended for approval from a CMC perspective. Please refer to Dr. Hitesh Shroff's product quality review, and Dr. Tien-Mien Chen's biopharmaceutics review for complete details.

Drug substance: The drug substance, alendronate sodium, is manufactured by (b) (4) The Applicant provided Letter of Authorization to reference DMF # (b) (4) for CMC information. The CMC information in DMF# (b) (4) was reviewed on 18-Feb-2009, and found to be adequate. There have been no significant changes in the manufacturing process and control of the drug substance. The proposed specifications including identification, assay, related substances, and particle sizes are adequate to assure the identity, strength, purity and quality of the drug substance.

(b) (4)

Drug Product: The manufacturing, packaging, release testing, and stability testing of the drug product, alendronate sodium effervescent tablets, are performed by (b) (4) 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. Each tablet contains inactive ingredients such as monosodium citrate anhydrous, citric acid anhydrous, sodium hydrogen carbonate, sodium carbonate anhydrous, acesulfame potassium, and sucralose that are all compendial grade.

The effervescent tablet manufacturing process (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. 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.

From a biopharmaceutics perspective, the proposed disintegration method in 20°C water was found acceptable. The acceptance criterion proposed by the Applicant required modification. (b) (4) The acceptance criteria at release and stability should generally be the same. Therefore, on September 21, 2011, the Applicant was informed to modify these criteria to: At release and stability (b) (4) On September 29, 2011, the Applicant communicated that the drug product specifications and acceptance criteria had been revised accordingly, effective September 27, 2011.

Packaging: Binosto (alendronate sodium) effervescent tablets 70 mg are moisture sensitive so the tablets are sealed in a blister (b) (4) . The Applicant provided specifications and a declaration of compliance certificate for the packaging materials in contact with the tablets. The Applicant has supplied enough information to establish that the container closure system is adequate to protect the drug product from light and moisture during the expiration dating period. Binosto tablets are packaged in aluminum foil composite blister strips. Each container has blisters with 4 tablets or (b) (4) tablets. The Applicant's original carton design was (b) (4) Therefore, the 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. The proposed packaging is now acceptable. However, further carton and container labeling revisions have been requested from both CMC and the Division of Medication Error Prevention and Analysis (DMEPA) and are further discussed in Section 12 of this review.

Facilities review/inspection: The applicant has requested a categorical exclusion for environmental assessment (EA) under 21 CFR 25.31(b). This was granted on March 17, 2011. The Establishment Evaluation System (EES) inspection request for (b) (4) was completed and found Acceptable based on profile on March 14, 2011. The EES establishment evaluation inspection for (b) (4) was recommended as Withhold on August 24,

2011. This was updated to Acceptable on December 14, 2011. An overall establishment evaluation recommendation of Acceptable was issued January 23, 2012.

Outstanding CMC issues: Final carton and container labeling as well as agreed-upon package insert labeling remain outstanding at the time of this review.

(b) (4)

4. Nonclinical Pharmacology/Toxicology

Please see Dr. Gemma Kuijper's review for complete details. There are no new nonclinical pharmacology and toxicology studies submitted. The Applicant is relying upon the nonclinical pharmacology and toxicology findings of safety and effectiveness from NDA 020560 (Fosamax, alendronate sodium tablet) and NDA 021575 (Fosamax, alendronate sodium oral buffered solution). No new excipients are found in the drug product. Impurities and alendronate-related degradation products fall within acceptable levels and do not require qualification.

5. Clinical Pharmacology/Biopharmaceutics

Once product labeling is agreed upon, this NDA is acceptable from a Clinical Pharmacology perspective. Please see Dr. Hyunjin Kim's review for complete details.

General clinical pharmacology: The Applicant is relying on study AE-1212-001-EM for demonstration of bioequivalence of Binosto (alendronate sodium) effervescent 70 mg once weekly tablet to Fosamax (alendronate sodium) 70 mg once weekly tablet. Because bone mineral density (BMD) increases achieved with Fosamax 70 mg once weekly were not inferior to the BMD increases achieved with Fosamax 10 mg daily, the demonstration of bioequivalence does provide the scientific basis for bridging to the fracture efficacy demonstrated with Fosamax 10 mg daily.

Study AE-1212-001-EM was a four period, open label cross-over study performed at a single treatment site. Each subject received two doses of each study drug, in an alternating manner. A total of 114 subjects (70 women and 45 men) between the age of 45 and 75 years (mean age 56.6 years) were enrolled. Study drug was administered after a 12 hour fast. The amount of water consumed during the dosing period of the study (740 mL over the 2 hours prior to and 30 minutes after study drug)

is different from the amount outlined in the labeled dosing instructions (fasting, then 240 mL). However, as outlined in Dr. Kim's review, the study drug is already fully dissolved on administration. Therefore, the increased water volume compared to the proposed dosing instructions is not expected to alter dissolution or bioavailability of the drug.

At the preIND meeting, the Applicant was informed that "*...both the ratio of mean amount and rate excreted in urine of your product and Fosamax should meet the BE criteria in order for your product to be approved...*". The primary PK variables for this study were the cumulative amount of alendronate excreted in urine during the entire period of sample collection (Ae_{0-48}) and the maximum excretion rate (E_{max}). As outlined in Table 1 below, the 90% confidence intervals were within the 80% – 125% bioequivalence limits. Therefore, bioequivalence between the two products was demonstrated.

Table 1: Study AE-1212-001-EM: Summary of statistical analysis (n=112)

Parameter	Geometric Mean [CV]		Ratio (Test : Ref)	90% Confidence Interval
	Binosto, Test	Fosamax, Reference		
Ae_{0-48} (ug)	184 [45%]	208 [47%]	0.88	0.83 – 0.94
E_{max} (ug/h)	63 [44%]	69 [47%]	0.90	0.85 – 0.97

Source: Clinical Pharmacology review, Table 2, page 6.

However, because this single study would be the basis for the regulatory action, the Office of Scientific Investigations (OSI) was consulted and site inspections of both the clinical site and the analytical site were performed by the Division of Bioequivalence and GLP Compliance (DBGC). The clinical site, CRS Clinical Research Services Mannhein GmbH, Mannheim Germany, was inspected July 18-22, 2011, and no Form FDA-483 was issued. The analytical site, (b) (4) . Chromatographic interference of study samples, calibrations standards and quality control samples were noted. On some batches, no reassay was performed. A FDA-Form 483 was issued. A written response from the firm was reviewed. After review of all information, the final recommendation was:

- The reported data generated from batches: 11108H27, 11108H28, 11108H30, 11108H34, 11108H90, 11108H92, 11108H93, 11108H102, 11108H121, and 11108H142 are questionable, and they should be either confirmed by re-assay or excluded from your consideration for bioequivalence study AE-1212-001-EM.
- The reported data from batch 11108H119 were not confirmed by re-assays, and should not be used for bioequivalence study AE-1212-001-EM.

Therefore, data from 11 batches were excluded from the bioequivalence analysis. The Applicant was informed of the need for reanalysis during a telephone conference on October 12, 2011. The Applicant conducted the necessary statistical reanalysis, which

was submitted to the application October 27, 2011. To allow adequate time for review of this data, considered a major amendment to the application, the review clock was extended.

As outlined in Table 2 below, after exclusion of the data from the 11 questionable batches, the 90% confidence intervals continued to be within the 80% – 125% bioequivalence limits. Therefore, bioequivalence between the two products continues to be demonstrated.

Table 2: Study AE-1212-001-EM: Summary of statistical analysis (n = 103)

Parameter	Geometric Mean [CV]		Ratio (Test : Ref)	90% Confidence Interval
	Binosto, Test	Fosamax, Reference		
Ae_{0-48} (ug)	186 [45%]	210 [47%]	0.88	0.83 – 0.94
E_{max} (ug/h)	63 [44%]	70 [47%]	0.90	0.85 – 0.97

Source: Clinical Pharmacology review, Table 1, page 3.

The to-be-marketed formulation and the clinical study formulations of Binosto are the same. The Applicant is relying upon data from Fosamax for the rest of the clinical pharmacology data, including the effect of food, pathway of elimination, special populations, and drug-drug interactions. Therefore, the Binosto product labeling will be identical to the current Fosamax product labeling.

6. Clinical Microbiology

There are no clinical microbiology issues associated with this oral bisphosphonate product.

7. Clinical/Statistical- Efficacy

No new clinical efficacy data has been submitted in support of this NDA. 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.

8. Safety

8.1 General Safety Considerations

Please see Dr. Stephen Voss's review for complete details. The Applicant is relying on the Agency's finding of safety for the referenced drug, Fosamax. Binosto (alendronate sodium) effervescent 70 mg tablet and Fosamax (alendronate sodium) 70 mg tablet are in the pharmacologic class of bisphosphonates. Known safety signals with bisphosphonates include hypocalcemia, and upper gastrointestinal adverse events (with oral bisphosphonates). Safety signals that have become evident post marketing include osteonecrosis of the jaw, severe musculoskeletal bone pain, ocular inflammation, and atypical femur fractures.

Three studies are included in this safety review. Bioequivalence study SCO5361 (b) (4) bioequivalence study AE-1212-001-EM (b) (4) and gastrointestinal pharmacodynamic study, study BC-118-07, which used radiolabeled alendronate. The Applicant confirmed that the formulation of the drug product was the same in the two bioequivalence studies (b) (4). Therefore, these two studies form the basis for the integrated safety review. Dr. Voss has reviewed all dose regimens used in these trials. This review concentrates on the labeled dosing and does not include those events occurring when subjects were fed 15 minutes after dosing,

8.2 Safety Findings from Submitted Clinical Trials

Demographics: A total of 248 subjects (203 women, 45 men) were enrolled in the open-label bioequivalence trials. The mean age of the study population was 57 years and all subjects were Caucasian. For study BC-118-07, 12 subjects, all women, were enrolled in the study. The mean age was 24 years and the racial makeup was eight Caucasian, three Asian and one Other.

Exposure: In the bioequivalence studies, subjects were to receive one to two doses of Binosto, with approximately 95% of subjects receiving two doses of Binosto as well as one to two doses of Fosamax in a cross-over design. For study BC-118-07, 10 subjects completed the study and received one dose of Binosto, one dose of Fosamax, and one dose of a prepared effervescent Fosamax (b) (4)

Deaths: There were no deaths in any of the three Binosto studies.

Serious Adverse Events: Serious adverse events were reported by two subjects in the bioequivalence trials, both following the Fosamax 70 mg dose. Neither event (hypertension in a 70 year old woman with a history of hypertension; lower leg thrombosis in a 54 year old man) was considered related to study drug therapy

Adverse Events Leading to Study Withdrawal: In the bioequivalence studies, six subjects withdrew due to adverse events. As outlined, in Dr. Voss's review, four in the

Binosto/fed group withdrew due to an adverse event. In the labeled fasting groups, one subject with a serious adverse event of hypertension, discussed above, withdrew after receiving Fosamax. Additionally, a 57 year old woman withdrew after experiencing nausea and vomiting after receiving Fosamax. One subject in study BC-118-07 withdrew due to earache, sore throat and sore face, attributed to the placement of the required nasogastric tube.

Adverse Events: Overall, 119 (49%) of subjects reported an adverse event after receiving Binosto and 118 (49%) of subjects reported an adverse event after receiving Fosamax in the bioequivalence studies. The most common adverse event preferred terms were headache, fatigue, diarrhea, back pain, pain in extremity, and nasopharyngitis.

Adverse Events of Special Interest:

Gastrointestinal disorders: Oral, nitrogen-containing bisphosphonates are well known to cause upper gastroesophageal irritation. Tablet or particulate matter from the tablet resulting in prolonged contact with the upper gastrointestinal mucosa may contribute to the symptoms associated with bisphosphonates. Data with Binosto show that the tablet is disintegrated completely in water if left 5 minutes after the effervescence stops. The issue of adequate time for tablet disintegration is particularly important when evaluating upper gastrointestinal disorders. In the bioequivalence studies, subjects were instructed to wait 5 to 15 minutes after the effervescence stopped, then to stir the contents for 10 seconds prior to ingestion. In the bioequivalence studies, gastrointestinal adverse events were reported by 11.6% of subjects after receiving Binosto and 12% of subjects after receiving Fosamax. Looking specifically at subjects who received study drug under fasting conditions, diarrhea was reported more frequently following Fosamax (2% Binosto, 6% Fosamax) while nausea and dyspepsia were reported more frequently following Binosto (nausea: 5% Binosto, 3% Fosamax; dyspepsia 2.5% Binosto, 0.4% Fosamax).

Musculoskeletal Pain: An increased incidence of muscular and bone pain has been reported with bisphosphonate use. There was no significant difference in musculoskeletal adverse events between the treatment groups.

Vital Signs: As outlined in Dr. Voss's review, Binosto contains 653 mg (28.4 mEq) of sodium per tablet, equivalent to ~1600 mg dietary NaCl. For this reason, careful review of blood pressure was performed. There was no significant change in blood pressure noted following a single dose of Binosto in the submitted trials.

Laboratory Data: As outlined in Dr. Voss's review, no clinically significant changes in laboratory parameters were noted in the bioequivalence trials.

Calcium: Bisphosphonate use, most notably intravenous bisphosphonates, has been associated with hypocalcemia. The nadir in serum calcium historically occurs 7 – 10 days post dose. Asymptomatic decreases in serum calcium were noted in the bioequivalence trials at 24 and 48 hours post dose with both Binosto and Fosamax.

8.3 Safety Update

In their safety update, the Applicant states that there are no new safety data to report. There are no ongoing studies with Binosto and Binosto is not marketed in any country. at the preNDA meeting, the Division did agree that it was not necessary for the Applicant to conduct an extensive literature review for alendronate sodium.

8.4 Summary of Safety

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.

The applicant is relying on the Agency's findings of safety for Fosamax. I agree that product labeling should clearly outline the dosing instructions to ensure the gastrointestinal safety of patients using Binosto. I also agree that the osteoporosis population who require therapy and may use this product are older patients in whom hypertension, heart failure, are renal disease may be common. Therefore, it will be important to label the concerns regarding the sodium content of Binosto.

9. Advisory Committee Meeting

An Advisory Committee meeting was not conducted for this New Drug Application.

10. Pediatrics

The Applicant's request for a full waiver of pediatric studies was reviewed by PeRC on October 5, 2011, and PeRC agreed to the full waiver. A full waiver for pediatric studies was recommended because studies would be impossible or highly impracticable and because the indications for this drug product (postmenopausal osteoporosis) do not occur in the pediatric population.

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP): There are no AIP issues with this product or Applicant.

Exclusivity or patent issues: In this New Drug Application, the Applicant is relying on nonclinical, clinical, and clinical pharmacology data from Fosamax. The Applicant has submitted Paragraph IV certification and documentation that notice of patent certification for Patents 5358941, 5681590, 6090410, and 6194004, has been sent as required by 21 CFR 314.52(a). EffRx Pharmaceuticals SA has been granted a patent license from Merck for US Patent 5853759 and US Patent application 11/390114. In a letter dated October 14, 2011, the Applicant certified that EffRx has not been sued for patent infringement during the 45-day period following the notification of patent holders. At this time, there is no unexpired exclusivity for Fosamax.

Financial disclosure: Dr. Voss has reviewed the financial disclosure statements for all investigators and sub-investigators. No financial relationships of concern are noted.

OSI audits: As previously discussed in the Clinical Pharmacology Section (Section 5) of this review, the Office of Scientific Investigations, Division of Bioequivalence and GLP Compliance conducted inspections of the clinical site and the analytical site for study AE-1212-001-EM. The clinical site did not have a Form FDA-483 issued. A Form FDA-483 was issued for the analytical site. Based on the results of the inspection, statistical reanalysis of the results for bioequivalence study AE-1212-001-EM was required. This reanalysis was performed by the Applicant and submitted for review. As discussed in Section 5 of this review, bioequivalence of Binosto 70 mg and Fosamax 70 mg continued to be demonstrated.

12. Labeling

Proprietary name: The Applicant initially proposed the proprietary name Steovess. After review, the Division of Medication Error Prevention and Analysis (DMEPA) found (b) (4) Subsequently, the Applicant submitted the proposed proprietary name Binosto. After further analysis, both the clinical team and DMEPA agree that the proprietary name Binosto is acceptable. The Applicant was informed on September 9, 2011. Re-analysis of the proprietary name Binosto was performed within 90 days of approval and the name remains acceptable.

Physician labeling: The Applicant has based the full prescribing information on the currently approved Fosamax label. Agreement on physician labeling is pending at this time. The major changes to product labeling proposed by the review team include:

1. Updated Dosage and Administration language. In order to help prevent esophagitis related to mucosal contact with undissolved alendronate for Binosto, the labeling should specify that preparation of each dose would reproduce the

procedure used in study AE-1212-001-EM, i.e. allowing at least 5 minutes for dissolution of the effervescent tablet in 4 oz. of room temperature plain water, and stirring for 10 seconds prior to ingestion. Therefore, the following language was proposed:

2.3 Dosing Instructions

(b) (4)

2. A new Warning and Precaution outlining the concerns regarding the sodium content. Because of its acid buffering and effervescent properties, Binosto contains 653 mg (28.4 mEq) of sodium per tablet, equivalent to ~1600 mg dietary NaCl. There was no evidence of a significant effect on blood pressure in the healthy subjects in the submitted studies. However, Fosamax is used predominantly by elderly women, a population with very high prevalence of hypertension and risk for congestive heart failure (CHF) and stroke; there is some published evidence that lapses in dietary sodium restriction may contribute to hospital admissions for CHF. Although this is unlikely to be a significant safety issue for this product, information about the sodium content of Binosto should be included in physician and patient labeling. The following language is proposed:

5.7 Patients on Sodium Restriction

BINOSTO contains approximately 650 mg of sodium in each effervescent tablet. Use caution in patients who must restrict their sodium intake *[see Patient Counseling Information (17.3)]*.

Carton and immediate container labels: The Carton and Container labeling have been found generally acceptable by the CMC reviewer, and the Division of Medication Error, Prevention and Analysis. At this time, labeling review from the Office of Prescription Drug Promotion is pending.

The Applicant's original (b) (4) carton design was (b) (4) The currently proposed packaging of Binosto effervescent tablet is in the originally proposed blister container, (b) (4) with four or twelve pouches packaged in one carton box. This packaging configuration is acceptable.

Final acceptable carton and container labeling is pending at the time of this review. The follow comments were conveyed to the Applicant on February 16, 2012:

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).

Pouch Labeling:

1. Replace the (b) (4) 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."

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 (b) (4) on the principal display

panel and the statement (b) (4) 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 CDR 208.24(d) (Clarify between accompany or enclosed, see Comment D3).

Patient labeling: The Applicant has submitted a Medication Guide, which is predominantly based on the Fosamax Medication Guide. Review by the Office of Medical Policy’s Patient Labeling Team and the Office of Prescription Drug Promotion is pending at the time of this review.

13. Recommendations/Risk Benefit Assessment

13.1 Treatment of Postmenopausal Osteoporosis

Recommended Regulatory Action:

I recommend APPROVAL of Binosto (alendronate sodium) effervescent tablet 70 mg once weekly for the treatment of postmenopausal osteoporosis and treatment to increase bone mass in men with osteoporosis.

Risk Benefit Assessment:
Binosto (alendronate sodium) effervescent tablet 70 mg is bioequivalent to Fosamax (alendronate sodium) 70 mg tablet. The bioequivalence of these two products adequately supports a bridge to the fracture reduction efficacy achieved with Fosamax 10 mg daily.

The safety profile of Binosto is also similar to that of Fosamax, based on the small amount of short-term data available. I agree with Dr. Voss that due to the similarity of Binosto and Fosamax, differences in the safety or efficacy profile are unlikely. With appropriate dosing procedures, there is no evidence to indicate that risk of important upper gastrointestinal adverse reactions would be increased (or decreased) with Binosto in comparison to Fosamax.

I agree with Dr. Voss that the benefits outweigh the potential risks of using Binosto for the treatment of osteoporosis in postmenopausal women and for treatment to increase bone mass in men with osteoporosis. Marketing was recently discontinued for Fosamax oral buffered solution. Binosto would provide a treatment option that allows oral bisphosphonate therapy in patients who cannot tolerate or swallow the currently available tablet formulations.

Recommendation for Postmarketing Risk Evaluation and Management Strategies:

At this time, a Postmarketing Risk Evaluation and Management Strategy is not recommended.

(b) (4)

(b) (4)

Recommended Comments to Applicant

No further comments need to be sent to the Applicant.

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/s/

THERESA E KEHOE
02/24/2012

AUDREY L GASSMAN
02/24/2012