

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202344Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA : 202344	Submission Date(s): 2/28/2011, 10/27/2011, and 1/12/2012
Brand Name	Binosto
Generic Name	Alendronate sodium
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Acting Team Leader	LaiMing Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	EffRx, Inc.
Relevant IND	103130
Submission Type	Original
Formulation and Strength	Effervescent tablet; 70 mg
Indication	Treatment of osteoporosis in postmenopausal women AND Treatment to increase bone mass in men with osteoporosis

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1 Executive Summary

The Clinical Pharmacology review of NDA 202344 (DARRTS, 2/9/2012) stated that NDA 202344 was acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert labeling. The final agreement was reached on 3/8/2012 and there are no pending issues from the Office of Clinical Pharmacology. The highlights of the prescribing information and Clinical Pharmacology relevant sections of the final agreed upon package insert labeling are included in Section 2 of this addendum.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the NDA 202344 acceptable.

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

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

/s/

HYUNJIN KIM
03/08/2012

LAI M LEE
03/08/2012

Memorandum

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

Date: March 5, 2012

From: Hitesh Shroff, Ph.D.

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
New Drug Quality Assessment Division II
ONDQA

To: CMC Review #1 of NDA 202-344

Subject: Final Recommendation

The CMC review #1 has noted the following two pending issues:

1. The Office of Compliance has issued an overall “Withhold” recommendation.
2. Label/labeling issues were not resolved.

And because of these deficiencies, in the CMC Review #1, this NDA was not recommended for approval from the ONDQA perspective.

On January 23, 2012, the Office of Compliance issued the “Acceptable” recommendation for the facilities involved in the NDA (see the **Attachment -1**).

On March 05, 2012, the final label and labeling were submitted and they are revised satisfactorily from the ONDQA perspective (see the **Attachment-2**).

Bionosto tablets did not have a code imprint required to market a new prescription drug product as required by 21 CFR 206.10. This issue was discussed within ONDQA management and it was decided (see the **Attachment-3**) that this NDA can be recommended for approval provided that the applicant commits to meet the following conditions:

1. The applicant will not market unmarked product
2. The applicant will submit CBE-30 supplement when they are ready for marketing the marked product.

The applicant has provided a commitment letter (see the **Attachment-4**) accepting all of the conditions on February 27, 2012.

Final Recommendation:

This NDA is **now** recommended for approval from the ONDQA perspective.

Attachments:

Attachment-1

EES report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT					
Application:	NDA 202344/000	Sponsor:	EFFRX PHARM SA		
Org. Code:	580		1 MAIN ST		
Priority:			CHATHAM, NJ 07928		
Stamp Date:	22-DEC-2010	Brand Name:	EX101 (alendronate sodium) 70 mg Efferve		
PDUFA Date:	15-MAR-2012	Estab. Name:			
Action Goal:		Generic Name:			
District Goal:	16-JUN-2011	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET, EFFERVEGENT, FOR SOLUTION; ALENDRONATE SODIUM, 70MG		
FDA Contacts:	R. MCKNIGHT	Project Manager	3017961765		
	H. SHROFF	Review Chemist	3017962116		
	D. CHRISTNER	Team Leader	3017961341		
Overall Recommendation:	ACCEPTABLE	on 23-JAN-2012	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 13-DEC-2011	by EES_PROCD		
	WITHHOLD	on 24-AUG-2011	by EES_PROCD		

Establishment:	CFN: (b) (4)	FEI: (b) (4)			
DMF No:	(b) (4)	AADA:			
Responsibilities:	DRUG SUBSTANCE MANUFACTURER				
	(b) (4)				
	DRUG SUBSTANCE RELEASE TESTER				
	DRUG SUBSTANCE STABILITY TESTER				
Profile:	(b) (4)	OAI Status:	NONE		
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	14-MAR-2011				
Decision:	ACCEPTABLE				
Reason:	BASED ON PROFILE				

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT					
Establishment:	CFN: (b) (4)	FEI: (b) (4)			
DMF No:	(b) (4)	AADA:			
Responsibilities:	FINISHED DOSAGE MANUFACTURER				
	FINISHED DOSAGE PACKAGER				
	FINISHED DOSAGE RELEASE TESTER				
	FINISHED DOSAGE STABILITY TESTER				
Profile:	TABLETS, PROMPT RELEASE	OAI Status:	NONE		
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	14-DEC-2011				
Decision:	ACCEPTABLE				
Reason:	DISTRICT RECOMMENDATION				

Attachment-2.

(b) (4)





Labeling & Package Insert

1. Package Insert

a. “Highlights” Section

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BINOSTO™ safely and effectively. See full prescribing information for BINOSTO.

BINOSTO (alendronate sodium) effervescent tablets for oral solution

Initial US Approval: 1995

(b) “Full Prescribing Information” Section

#3. Dosage Form and Strength

-----**DOSAGE FORMS AND STRENGTHS**-----

Effervescent tablets, 70 mg (3)

#11. Description

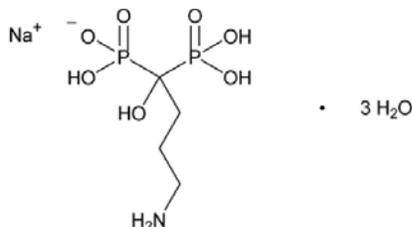
450 11 DESCRIPTION

451 BINOSTO (alendronate sodium) is a bisphosphonate that acts as a specific
452 inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic
453 analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

454

455 Alendronate sodium is chemically described as (4 amino-1-hydroxybutylidene)
456 bisphosphonic acid, monosodium salt, trihydrate. The molecular formula of
457 alendronate sodium is $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ and its molecular weight is 325.12.
458 The structural formula of alendronate sodium is

459



460

461

462 Alendronate sodium is a white or almost white crystalline powder that is soluble
463 in water, very slightly soluble in methanol, and practically insoluble in methylene
464 chloride.

465

466 BINOSTO for oral administration is an effervescent tablet formulation that must
467 be dissolved in water before use. Each individual tablet contains 91.37 mg of
468 alendronate sodium, which is equivalent to 70 mg of free alendronic acid. Each
469 tablet also contains the following inactive ingredients: monosodium citrate
470 anhydrous, citric acid anhydrous, sodium hydrogen carbonate, and sodium
471 carbonate anhydrous as buffering agents, strawberry flavor, acesulfame
472 potassium, and sucralose.

473

474 Once the effervescent tablet is dissolved in water, the alendronate sodium is
475 present in a citrate-buffered solution.

#16. How Supplied/Storage and Handling

897 16 HOW SUPPLIED/STORAGE AND HANDLING

898 BINOSTO effervescent tablets are round, flat faced, white to off-white tablets with
899 beveled edges. BINOSTO effervescent tablets, 70 mg are provided in blisters
900 made of aluminum foil composite, as follows:

901

902 NDC 10860-101-02 carton containing 4 units of use blisters

903

904 NDC 10860-101-03 carton containing 12 units of use blisters

905

906 Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F
907 to 86°F), [See USP Controlled Room Temperature.] Protect from moisture.

908 Store tablets in original blister package until use.

Attachment-3

Final Decision on the Marking Requirement (email describing the proposal from the management to the applicant):

Shroff, Hitesh

From: Rhee, Moo Jhong
Sent: Friday, February 24, 2012 11:42 AM
To: Christner, Donna
Cc: Shroff, Hitesh; Ocheltree, Terrance

Follow Up Flag: Follow up
Flag Status: Red

Hi Donna,

I just had a meeting with Terry and we made the following decision:

We can approve the NDA with the following stipulation:

1. The applicant makes a commitment that they will not launch any unmarked product. The current commitment they have made implicates that they can launch unmarked product and later they switch to the marked one.
2. They will also commit that when they are ready for the marked product, they will submit a CBE-30 supplement with information on the marked tablets such as schematic diagram of the new die for the puncher, revised labeling reflecting the new information, etc. We do not worry about stability data too much because of inherent rock solid stability of the API.

Please do contact the applicant ASAP.

Hitesh will write an addendum after labeling is finalized with documentation of all the discussions we have had on the issue..

Thanks.

Moo-Jhong

Attachment-4

The post-approval commitment from the applicant:



Freienbach, February 27, 2012

Scott Monroe, M.D., Director
Division of Reproductive and Urologic Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room, ATTN: DRUP
5901-B Ammendale Road
Beltsville, MD 20705-1266

**RE: NDA 202344 BINOSTO™ (alendronate sodium)
Commitments**

Dear Dr. Monroe:

As requested by the Division on February 27, 2012, EffRx Pharmaceuticals SA commits to the following:

1. Unmarked product will not be introduced into interstate commerce as per 21 CFR 206.10.
2. Prior to marketing, a CBE-30 supplement will be submitted that provides updated information on the marked tablets including:
 - Diagrams for the die
 - An updated manufacturing process
 - Revised labeling updating the HOW SUPPLIED and DOSAGE FORMS AND STRENGTHS sections and SPL
 - An updated specification sheet with revised APPEARANCE acceptance criteria
 - Full release testing for the new batch, including disintegration testing.
3. The first marketed batch will be placed on stability and updated stability data will be submitted in the next Annual Report.

FDA Commitment
Page 2

Sincerely,

A handwritten signature in blue ink, appearing to read 'M. Hayward', with a long horizontal flourish extending to the right.

Marshall A. Hayward, Ph.D.
Chief Scientific Officer

cc: Christer Rosén, EffRx Pharmaceuticals SA
Margaret E. Hurley, MD, FRAPS, Hurley Consulting Associates Ltd.

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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
03/07/2012

MOO JHONG RHEE
03/07/2012
Chief, Branch IV

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA : 202344	Submission Date(s): 2/28/2011, 10/27/2011, and 1/12/2012
Brand Name	Binosto
Generic Name	Alendronate sodium
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Acting Team Leader	LaiMing Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	EffRx, Inc.
Relevant IND	103130
Submission Type	Original
Formulation and Strength	Effervescent tablet; 70 mg
Indication	Treatment of osteoporosis in postmenopausal women AND Treatment to increase bone mass in men with osteoporosis

An Intra-Divisional Level Clinical Pharmacology Briefing was held on February 6, 2012 in a room 3134 of White Oak Bldg 51. Attendees included Drs' Dennis Bashaw, Hae-Young Ahn, Lee LaiMing and Hyunjin Kim.

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1 Executive Summary

Binosto is 70 mg effervescent alendronate tablets with a dosing regimen of one tablet weekly. The proposed indications are treatment of osteoporosis in postmenopausal women and treatment to increase bone mass in men with osteoporosis. Binosto contains the same amount of active ingredient (sodium alendronate trihydrate) as Fosamax 70 mg (NDA 020560, approval date September 29, 1995), which has the same indications the sponsor of Binosto is seeking for. The effervescent tablet is to be dissolved in 4 ounces of water in order to be taken.

In support of this new NDA, a pivotal bioequivalence (BE) study (AE-1212-001-EM) comparing the bioavailability of Binosto and Fosamax was submitted. Due to the nature of this NDA, of which the approvability relies on the pivotal BE, a request for inspection of the clinical and analytical sites of the pivotal BE study was made to the Office of Scientific Investigations (OSI, May 4, 2011).

In addition to the pivotal BE study, this NDA included two additional clinical studies, a BE/food effect study (SCO 5361) and gastric imaging and pH telemetry study (BC-118-07) which were conducted with a formulation different from the to-be-marketed formulation.

1.1 Recommendation

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.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The BE of Binosto and Fosamax (a marketed oral tablet formulation; dosing regimen: 70 mg once weekly) was studied in a single-site, open label, four period cross-over replicate trial after single dose administration of Binosto, a buffered effervescent soluble tablet, under fasting conditions, or Fosamax to assess the bioequivalence of Binosto versus Fosamax in healthy volunteers. The BE study supports that Binosto and Fosamax are bioequivalent under fasting conditions. The 90% confidence intervals (CIs) for the ratio of the Test and Reference least squares means (LSM) for the parameters A_{e0-48} and E_{max} were within the 80 to 125% bioequivalence limits. PK parameter values and bioequivalence evaluation is provided in Table 1.

Table 1 Summary of statistical reanalysis excluding data from 11 batches (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

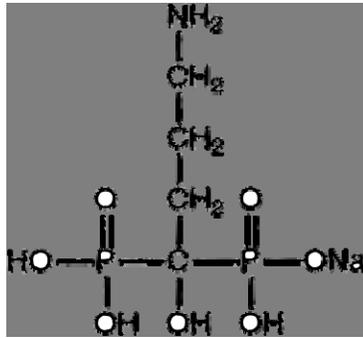
2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

<Physico-chemical properties>

- Structural formula:



- Molecular Weight: 325.12
- Molecular Formula: C₄H₁₂NNaO₇P₂·3H₂O
- Chemical Name: 4-amino-1-hydroxybutylidene bisphosphoric acid monosodium salt trihydrate

<Drug Formulation>

Component	Quantity per Tablet	Reference to Standards	Function
Sodium alendronate trihydrate (b) (4)	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)			

2.1.2 What is the proposed mechanism of action?

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [3H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [3H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

2.1.3 What are the proposed indications, dosage and route of administration?

The proposed indications are as following:

- Treatment of osteoporosis in postmenopausal women
- Treatment to increase bone mass in men with osteoporosis

(b) (4)

The proposed dosage and route of administration is once weekly by mouth with the following instruction:

- Binosto must be taken at least one-half hour before the first food, beverage, or medication of the day. Dissolve the effervescent tablet in 4 oz room temperature water only. Once the effervescence stops, the solution should be stirred for approximately 10 seconds and ingested. Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of Binosto. Waiting less than 30 minutes, or taking Binosto with food, beverages (other than plain water) or other medications will lessen the effect of Binosto by decreasing its absorption into the body.

2.2 General Clinical Pharmacology

The safety and efficacy of the current NDA is relying on Fosamax, NDA 020560. Therefore, no phase 3 clinical study was conducted with Binosto. Instead, a pivotal BE study, AE-1212-001-EM, was conducted to compare the BE between Binosto and Fosamax.

The pivotal BE study was designed as an open-label, 4-period cross-over with replicated treatment sequences in a single study site. The study population consisted of 70 healthy women and 45 healthy men between 45 and 75 years old. The subjects were randomized to 2 sequences of treatment. Each subject received 2 single oral administrations of Binosto (70 mg alendronate effervescent tablet) and 2 single oral administrations of Fosamax 70 mg, the Reference Listed Product. The subjects were randomly assigned to 2 sequences of treatment, Test-Reference-Test-Reference (T-R-T-R) or Reference-Test-Reference-Test (R-T-R-T). Between each administration of study drug, there was a washout of at least 14 days. For BE evaluation, urine data were obtained instead of plasma data due to the low concentrations of alendronate in the blood (bioavailability of less than 1%, from label of Fosamax, NDA 020560). Therefore, cumulative amount of alendronate excreted in urine during the entire period of sample collection (Ae_{0-48}) 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. For a statistical analysis, average BE approach was used. This average BE approach based on urinary data (Ae and C_{max}) was used in approving alendronate oral solution (NDA 021575, approval date: September 17, 2003).

There was another BE / food effect study, SCO 5361, submitted under this NDA. However, due to the formulation difference, the study SCO 5361 is not reviewed.

2.2.1 Are Binosto bioequivalent to Fosamax?

The PK parameter values and BE evaluation of 112 out of 115 subjects enrolled in the BE study are provided in Table 2. The 3 subjects excluded from the BE analysis finished 1 period out of 4 periods (T-R-T-R or R-T-R-T) of the study. 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.

Table 2 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 [46%]	208 [48%]	0.88	0.83 – 0.94
E_{max} (ug/h)	63 [44%]	69 [48%]	0.90	0.85 – 0.97

Following the site inspection from the OSI, OSI recommended to remove 11 batches from the analysis (see section 2.6 for details). Therefore, BE reanalysis were conducted excluding the data from 11 batches and the results are provided in the Table 3. 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 confirmed the BE between Binosto and Fosamax.

Table 3 Summary of statistical reanalysis excluding data from 11 batches (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

Figures 1 and 2 show geometric mean (68% range) profiles of the urinary excretion rate, E_t , of alendronate from the administrations of Binosto or Fosamax. They show that the major part of alendronate excreted in urine occurs during the first 8 hours after dosing, with relatively small additional amounts excreted from 8 to 48 hours after dosing. Also, they demonstrate the interindividual variability of alendronate excretion in urine.

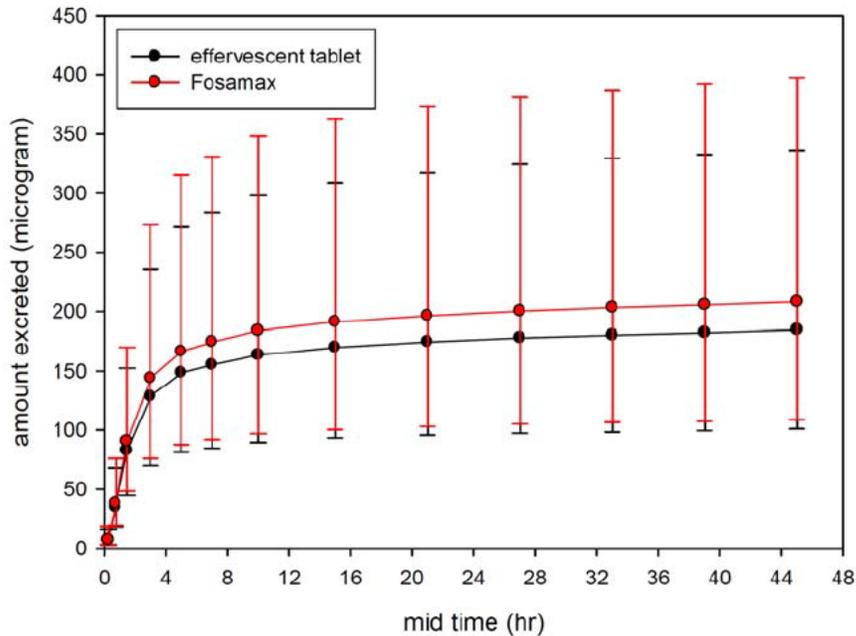


Figure 1 Geometric mean (68% range) cumulative urinary excretion of alendronate following repetitive doses of Binosto (Test) or Fosamax (Reference); n = 103

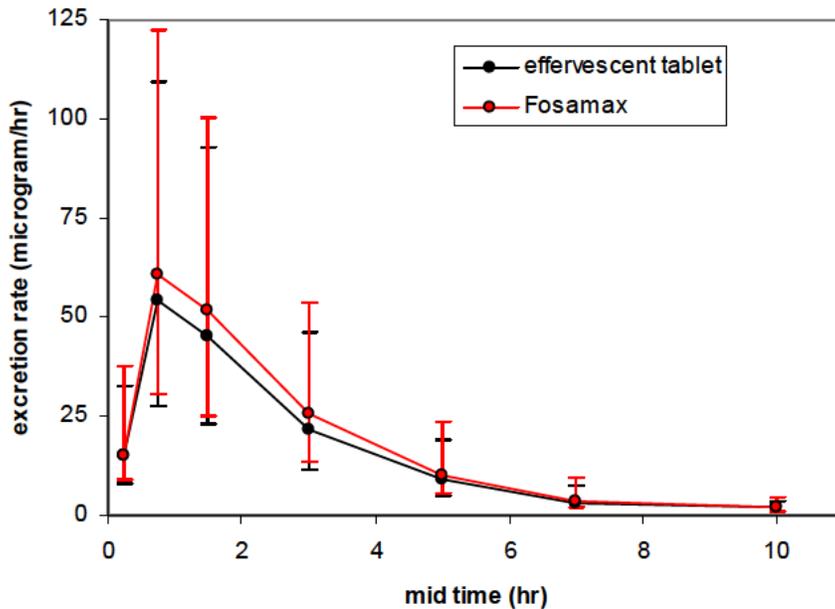


Figure 2 Geometric mean (68% range) of the urinary excretion rate of alendronate following repetitive doses of Binosto (Test) or as Fosamax (Reference), linear Y-scale; n = 103

2.2.2 Are the active moieties in the urine appropriately identified?

Urine fractions were collected starting from 2 hours before dosing until 48 hours after

dosing. The collection intervals were -2 - 0 hours (drug administration at 0 hours) and 0 - 0.5, 0.5 - 1, 1 - 2, 2 - 4, 4 - 6, 6 - 8, 8 - 12, 12 - 18, 18 - 24, 24 - 30, 30 - 36, 36 - 42, and 42 - 48 hours after dosing. At -2 hours, when the first urine collection period started the subjects were requested to void their bladder. This urine fraction was discarded. The first urine fraction to be analyzed was collected from -2 to 0 hours. The subjects were requested/advised to void their bladders at the end of each interval, i.e., at predose (0 hours) and at 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 30, 36, 42, and 48 hours after dosing.

To obtain enough urinary samples, subjects were asked to drink at least 100 mL of non-sparkling water approximately every 30 minutes from 2 hours prior to dosing to approximately 30 minutes after dosing for a total of approximately 740 mL (including water administered at dosing).

In Study AE-1212-001-EM, a total of 400 mL of water could have been consumed in 100 mL increments at approximately 30-minute intervals over the 2 hour interval before dosing with an alendronate tablet. Considering approximate mean half life of gastric emptying time of water (15 mins¹, ²), 33 mL of residual water would have been present in the stomach at the time of dosing. Considering the proposed label instructs patients to take the effervescent alendronate tablet in approximately 240 mL (4 ounces) of water, there could have been approximately 14% increase in volume of water when the study was conducted. Since the drug is already fully dissolved on administration, the increased water volume compared to the proposed dosing instructions is not expected to alter dissolution or bioavailability of the drug.

2.3 Intrinsic factors

2.3.1 Does age influence exposure and/or response of Binosto?

No studies have been conducted to evaluate the effect of age on the PK of Binosto. However, the following information is available from the reference product, Fosamax, NDA 020560:

Pediatric use: The efficacy and safety of FOSAMAX were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4-18 years, with severe osteogenesis imperfecta. One-hundred-and-nine patients were randomized to 5 mg FOSAMAX daily (weight <40 kg) or 10 mg FOSAMAX daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine bone mineral density (BMD) Z-score of the patients was -4.5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1.3 in the FOSAMAX-treated patients and 0.1 in the placebo-treated patients. Treatment with FOSAMAX did not reduce the risk of

¹ Coyle EF, Costill DL, Fink WJ, Hoopes DG. Gastric emptying rates for selected athletic drinks. The Research Quarterly 1978;42(2):119-24.

² Zeissman HA, Chander A, Clarke JO, Ramos A, Wahl RL. The added diagnostic value of liquid gastric emptying compared with solid emptying alone. J Nucl Med 2009;50:726-31.

fracture. Sixteen percent of the FOSAMAX patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In FOSAMAX-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the FOSAMAX and placebo groups in reduction of bone pain. FOSAMAX is not indicated for use in children.

Geriatric use: Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥ 65 years of age and 17% (n=550) were ≥ 75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies, 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

2.3.2 Does hepatic disease influence exposure and/or response of Binosto?

No studies have been conducted to evaluate the effect of hepatic disease on the PK of Binosto. However, the following information is available from the reference product, Fosamax, NDA 020560:

As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

2.3.3 Does renal disease influence exposure and/or response of Binosto?

No studies have been conducted to evaluate the effect of renal disease on the PK of Binosto. However, the following information is available from the reference product, Fosamax, NDA 020560:

Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function. No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min) due to lack of experience with alendronate in renal failure.

2.4 Extrinsic factors

2.4.1 Does taking medications with Binosto influence exposure of Binosto?

No drug-drug interaction studies have been conducted to evaluate the effect of taking medications on the PK of Binosto. However, the following information is available from the reference product, Fosamax, NDA 020560:

- *Calcium Supplements/Antacids*

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other oral medications.

- *Aspirin*

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products.

- *Nonsteroidal Anti-inflammatory Drugs (NSAIDs)*

FOSAMAX may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10 mg/day compared to those taking placebo.

However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX.

2.5 General Biopharmaceutics

Binosto is 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.

Before the pivotal BE study, AE-1212-001-EM, was conducted, the sponsor conducted a BE / food effect study, SCO 5361 comparing the bioavailability of earlier formulation (b) (4) of effervescent alendronate tablet under both fasting and fast conditions AND the bioequivalence of Binosto and Fosamax under fasting condition. BE criteria did not meet (b) (4)

Therefore, the sponsor reformulated (b) (4) the effervescent alendronate tablet (b) (4) and used in the pivotal BE study, AE-1212-001-EM.

2.5.1 Are the Clinical trial and to-be-marketed formulations the same?

The Binosto formulation studied in the BE study, AE-1212-001-EM, is the same as the to-be-marketed formulation.

2.6 Analytical Section

Urine alendronate concentrations were determined by HPLC-MS/MS method. The method validation report, MALe/FKM/101 satisfied the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, May 2001).

	alendronate
Type of Biological Fluid	Human urine
Range of Standard Curve	2.42 – 1211 ug/L
Linearity (r^2)	0.99457 – 0.99561
QC Sample Precision	2.31 – 5.39 %
QC Sample Accuracy	-11.05 – 7.55 %
Stability	96 hrs at 4 °C; 24 hrs at room temperature; 3 cycles of freezing/thawing

All human urine samples of study AE-1212-001-EM were analyzed for the content of alendronate according to the validated method validation report, MALe/FKM/101.

OSI report of study AE-1212-001-EM:

The Division of Clinical Pharmacology III requested for OSI to conduct audits of the both clinical and bioanalytical sites of study AE-1212-001-EM on May 4, 2011 due to the nature of this NDA for which approvability is solely relying on the pivotal BE study, AE-1212-001-EM. Following the inspection of clinical site, no form FDA-483 was issued. However, following the inspection of the analytical site OSI found that there were interferences from peaks co-eluting near alendronate on chromatograms from 11 batches. The OSI inspector's final recommendation was to remove data from 11 batches (11108H27, 11108H28, 11108H30, 11108H34, 11108H90, 11108H92, 11108H93, 11108H102, 11108H119, 11108H121, 11108H142) in interpreting data from the study AE-1212-001-EM.

This reviewer concurred and followed the OSI inspector's recommendation. Thus, BE reanalysis was conducted excluding the following datasets from those 11 batches. See results of BE reanalysis in Table 3.

Table 4 The 11 batches identified in the OSI report and associated datasets

Batch #	Subject #	Datasets
11108H27	004	Periods 1-4
11108H28	005	Periods 2-4
11108H28	105	Period 1
11108H30	006	Periods 2-4
11108H30	106	Period 1
11108H34	010	Periods 1-4

11108H90	063	Periods 1-4
11108H92	065	Periods 1-4
11108H93	066	Periods 1-4
11108H102	030	Periods 1-4
11108H119	119	Periods 1-4
11108H121	121	Periods 1-4
11108H142	140	Periods 1-4

3 Detailed Labeling Recommendations

Detailed labeling recommendations will be added later.

4 Appendix

4.1 Individual Clinical Study Review

Study AE-1212-001-EM: Single-site, open label, four period cross-over replicate trial after single dose administration of a new alendronate 70 mg formulation, a buffered effervescent soluble tablet, under fasting conditions, to assess the bioequivalence versus a marketed oral tablet formulation (Fosamax once weekly 70 mg) in healthy volunteers

-Primary Objective:

The primary objective was to assess the bioequivalence of the Test and Reference alendronate tablets in the fasting state (at least 12 hours of fasting before administration of study drugs and at least 4 hours of fasting after administration of study drugs), as measured by the amount of alendronate excreted in urine and the maximum excretion rate.

-Overall Study Design

The study was designed as an open-label, 4-period cross-over with replicated treatment sequences in a single study site. The study population consisted of 70 healthy women and 45 healthy men between 45 and 75 years old. The subjects were randomized to 2 sequences of treatment. Each subject received 2 single oral administrations of Binosto (70 mg alendronate effervescent tablet) and 2 single oral administrations of Fosamax 70 mg, the Reference Listed Product. The subjects were randomly assigned to 2 sequences of treatment, Test-Reference-Test-Reference (T-R-T-R) or Reference-Test-Reference-Test (R-T-R-T). Between each administration of study drug, there was a washout of at least 14 days. The study consisted of a screening period from 28 until 2 days before the first administration of study drug, a treatment phase with 4 treatment periods, and an end-of-study period with a final examination performed within 7 days after the end of the last treatment. The replicate design was chosen as urinary PK parameters show a higher variability than plasma PK parameters. The replicate study design allows comparisons of within-subject variances for the test and reference products, and may provide information

about the intrinsic factors underlying formulation performance, and reduced the number of subjects participating in the bioequivalence study.

-Inclusion Criteria

Subjects who met the following criteria were eligible to participate in the study:

1. The subject was informed both verbally and in writing about the objectives of the clinical study, the methods, the anticipated benefits and potential risks, and the discomfort to which he or she could be exposed, and gave written consent to participate in the study prior to the study start and any study-related procedures.
2. Healthy female or male subjects aged between 45 and 75 years (inclusive), assessed as healthy based on a screening examination including medical history, physical examination, blood pressure, pulse rate, and clinical laboratory results.
3. Non-smokers, ex-smokers, or light smokers (≤ 10 cigarettes a day).
4. Body weight according to a body mass index between 18 and 28 kg/m² inclusive.
5. The subject was cooperative and available for the entire study.

-Exclusion Criteria

Any of the following criteria excluded potential subjects from the study:

1. Evidence in the subject's medical history or in the medical examination of any clinically significant hepatic, renal, gastrointestinal, cardiovascular, pulmonary, hematological, or other significant acute or chronic abnormalities that could influence either the safety of the subject or the absorption, distribution, metabolism, or excretion of the active agent under investigation.
2. History or presence of any of the following:
 - Alcoholism or drug abuse within the past year;
 - Upper gastrointestinal disease (such as dysphagia, esophageal diseases, duodenitis, or gastritis, or severe diseases, such as upper gastrointestinal bleeding, ulcers, or surgery of the upper gastrointestinal tract).
3. Abnormalities of the esophagus and other factors, such as stricture or achalasia, which delayed esophageal emptying.
4. Inability to stand or sit upright for at least 30 minutes.
5. Subjects who were on an abnormal diet (for whatever reason) during the 28 days prior to the scheduled admission to the first study period, as stated by the subject at screening.
6. Hypersensitivity to drugs (especially alendronate and ingredients of the formulation).
7. Atopic eczema or allergic bronchial asthma.
8. Laboratory test results outside the reference values as specified by the study site, which could be an evidence of disease. A positive result for human immunodeficiency virus (HIV) antibodies, hepatitis C virus (HCV) antibody, or hepatitis B surface antigen (HBsAg) testing.
9. Evidence of hypocalcemia (serum calcium below 2.0 mMol/L at screening).
10. Any chronic use of bisphosphonates or any use of bisphosphonates within the last 3 months prior to the scheduled admission to the first study period, as stated by the subject at screening.

11. Subjects who used antacids, H₂ receptor antagonists, or proton pump inhibitors on a chronic basis during the past 3 months.
12. Regular use of any medication within 4 weeks or within less than 10 times the elimination half-life of the respective drug, whatever was longer, prior to the scheduled admission to the first study period (self-medication or prescription. Exception: hormonal contraceptives and hormonal replacement therapy).
13. Single use of any medication (including over-the-counter) that were not expressly permitted within 2 weeks or within less than 10 times the elimination half-life of the respective drug, whatever was longer, prior to the scheduled admission to the first study period (self-medication or prescription).
14. Females only: Pregnant (positive pregnancy test at screening) or nursing women.
15. Females only: Lack of safe contraception in females of childbearing potential (less than 2 years postmenopausal or not surgically sterile) for at least 30 days prior to screening, for the duration of the study, and for at least 30 days following the last dose of study drug using an established treatment with hormonal contraceptives (e.g., combined oral contraceptives, approved implantable or injectable contraceptives) or intrauterine contraceptives.
16. Females only: Women who had a current desire to have a baby.
17. Abuse of alcohol (equivalent to more than 18 units per week, where 1 unit is equivalent to 330 mL beer or 150 mL wine or one 40 mL drink) or caffeine (equivalent to more than 750 mg per day) or tobacco (more than 10 cigarettes per day).
18. A positive alcohol breath test.
19. Drug addiction, positive drug screening in urine.
20. Participation in a clinical investigation or blood donation of more than 250 mL within the previous 8 weeks prior to the scheduled admission to the first study period, as stated by the subject at screening.
21. Planned donation of germ cells, egg cells, blood, organs, or bone marrow during the course of the study.
22. Lack of ability or willingness to give informed consent.
23. Anticipated non-availability for study visits/procedures.
24. Anticipated lack of willingness or inability to cooperate adequately.
25. Vulnerable subjects (e.g., persons kept in detention).
26. Males only: Desire to father a baby.
27. To be in such a precarious financial situation that they no longer considered the
28. possible risks of their participation an

-Treatment Administered

In each period, a single dose of study drug was administered under the supervision of the Investigator or his designee after at least a 12-hour fast. Study drug was administered in the morning of Day 1 of each of the 4 treatment periods. The subjects were in an upright position for all administrations and were not permitted to lie down for 4 hours after dosing.

-Formulation of Binosto

Component	Quantity per Tablet	Reference to Standards	Function
Sodium alendronate trihydrate (b) (4)	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)			

-Selection and Timing of Dose for Each Subject

The treatments were administered under the supervision of the Investigator or his designee in the morning of Day 1 of each of the 4 treatment periods. The subjects were in an upright position for all study drug administrations, and were not permitted to lie down for 4 hours after dosing. The subjects fasted from at least 12 hours before (evening before, Day -1) and until 4 hours after administration of study drug on Day 1. During the fasting periods, only water was allowed. Subjects were asked to drink at least 100 mL of non-sparkling water approximately every 30 minutes from 2 hours prior to dosing to approximately 30 minutes after dosing for a total of approximately 740 mL (including water administered at dosing).

In Study AE-1212-001-EM, a total of 400 mL of water could have been consumed in 100 mL increments at approximately 30-minute intervals over the 2 hour interval before dosing with an alendronate tablet. Considering approximate mean half life of gastric emptying time of water (15 mins³, ⁴), 33 mL of residual water would have been present in the stomach at the time of dosing. Considering the proposed label instructs patients to

³ Coyle EF, Costill DL, Fink WJ, Hoopes DG. Gastric emptying rates for selected athletic drinks. *The Research Quarterly* 1978;42(2):119-24.

⁴ Zeissman HA, Chander A, Clarke JO, Ramos A, Wahl RL. The added diagnostic value of liquid gastric emptying compared with solid emptying alone. *J Nucl Med* 2009;50:726-31.

take the effervescent alendronate tablet in approximately 240 mL (4 ounces) of water, there could have been approximately 14% increase in volume of water when the study was conducted. Since the drug is already fully dissolved on administration, the increased water volume compared to the proposed dosing instructions is not expected to alter dissolution or bioavailability of the drug.

-PK Measurements

The following PK variables were calculated:

- Ae: fractional amount of alendronate excreted during each collection interval
- Ae₀₋₄₈: cumulative amount of alendronate excreted in urine during the entire period of sample collection
- Et: 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}: maximum excretion rate

The primary PK variables for this study were Ae₀₋₄₈ and E_{max}.

-Drug Concentration Measurements

Urine fractions were collected starting from 2 hours before dosing until 48 hours after dosing. The collection intervals were -2 to 0 hours (drug administration at 0 hours) and 0 to 0.5, 0.5 to 1, 1 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 18, 18 to 24, 24 to 30, 30 to 36, 36 to 42, and 42 to 48 hours after dosing. At -2 hours, when the first urine collection period started the subjects were requested to void their bladder. This urine fraction was discarded. The first urine fraction to be analyzed was collected from -2 to 0 hours. The subjects were requested/advised to void their bladders at the end of each interval, i.e., at predose (0 hours) and at 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 30, 36, 42, and 48 hours after dosing.

-Statistical Analysis

- Safety population (115 subjects: 70 females + 45 males):

All subjects who received at least 1 dose of study drug

- Per protocol population (112 subjects: 68 females + 44 males):

All subjects who had no protocol deviations concerning PK and who had evaluable post-dose assessments for both study drugs were to be included in the per protocol population. Subjects who did not participate in all 4 periods were to be included in the per protocol population, as long as they received both the Test and Reference formulations at least once.

- The 3 subjects were excluded from safety population
 - Subjects 009 (female), 039 (female), and 109 (male): completed only one period)
- Reanalysis population following OSI inspection (103 subjects: 62 females + 41 males)
 - Due to the findings (chromatographic interferences from peaks co-eluting near alendronate on chromatograms of study samples) from the OSI reanalysis population was generated for reanalysis of PK results
 - The 9 subjects were excluded from per protocol population.

- Subjects 004 (female), 010 (female), 030 (female), 063 (female), 065 (female), 066 (female), 119 (male), 121 (male), and 140 (male)
- The partial data from following 4 subjects were excluded from the per protocol population.
 - Subject 005 (female): periods 2-4
 - Subject 006 (female): periods 2-4
 - Subject 105 (male): period 1
 - Subject 106 (male): period 1

-Demographics

Parameter		Safety Set (= Full Analysis Set)		Per Protocol Analysis Set (Ae ₀₋₄₈ , E _{max})	
		Female	Female and Male	Female	Female and Male
Age [years]	n	70	115	68	112
	Mean ± SD	58.0 ± 8.0	56.6 ± 7.9	57.9 ± 8.1	56.5 ± 7.9
	Min - Max	45 - 73	45 - 73	45 - 73	45 - 73
Body Height [cm]	n	70	115	68	112
	Mean ± SD	162 ± 5.9	168 ± 9.4	162 ± 6.0	168 ± 9.5
	Min - Max	150 - 178	150 - 191	150 - 178	150 - 191
Body Weight [kg]	n	70	115	68	112
	Mean ± SD	64.3 ± 8.2	70.1 ± 11.4	64.4 ± 8.2	70.2 ± 11.3
	Min - Max	45 - 87	45 - 99	45 - 87	45 - 99
Body Mass Index [kg/m ²]	n	70	115	68	112
	Mean ± SD	24.5 ± 2.5	24.8 ± 2.3	24.5 ± 2.4	24.8 ± 2.3
	Min - Max	19 - 28	19 - 28	19 - 28	19 - 28

-PK results

As described in the overall study design, each subject received the Binosto (Treatment A, Test) and Fosamax (Treatment B, Reference) twice. Due to the replicated cross-over design with 2 sequences ABAB and BABA, the first administration (Treatment A1 or B1) was given in Periods 1 or 2 and the second administration (Treatment A2 or B2) in Periods 3 or 4.

The individual subject cumulative excretion profiles of alendronate in urine following 2 administrations of Binosto (Test) are shown in Figure 3.

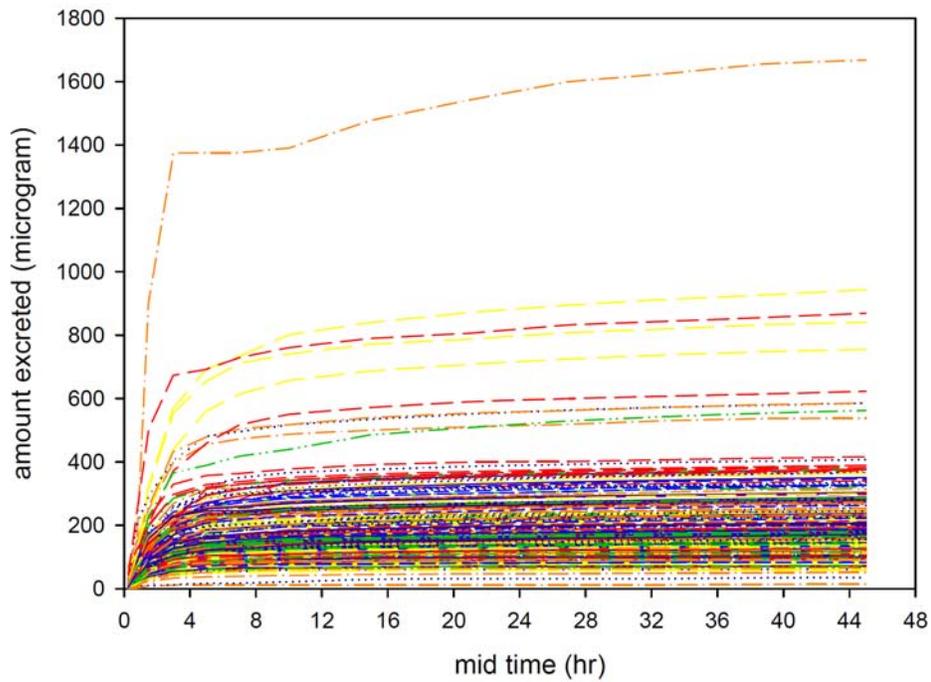


Figure 3 Individual cumulative urinary excretion of alendronate following repetitive doses of Binosto (Test)

The individual subject cumulative excretion profiles of alendronate in urine following 2 administrations of Fosamax (Reference) are shown in Figure 4.

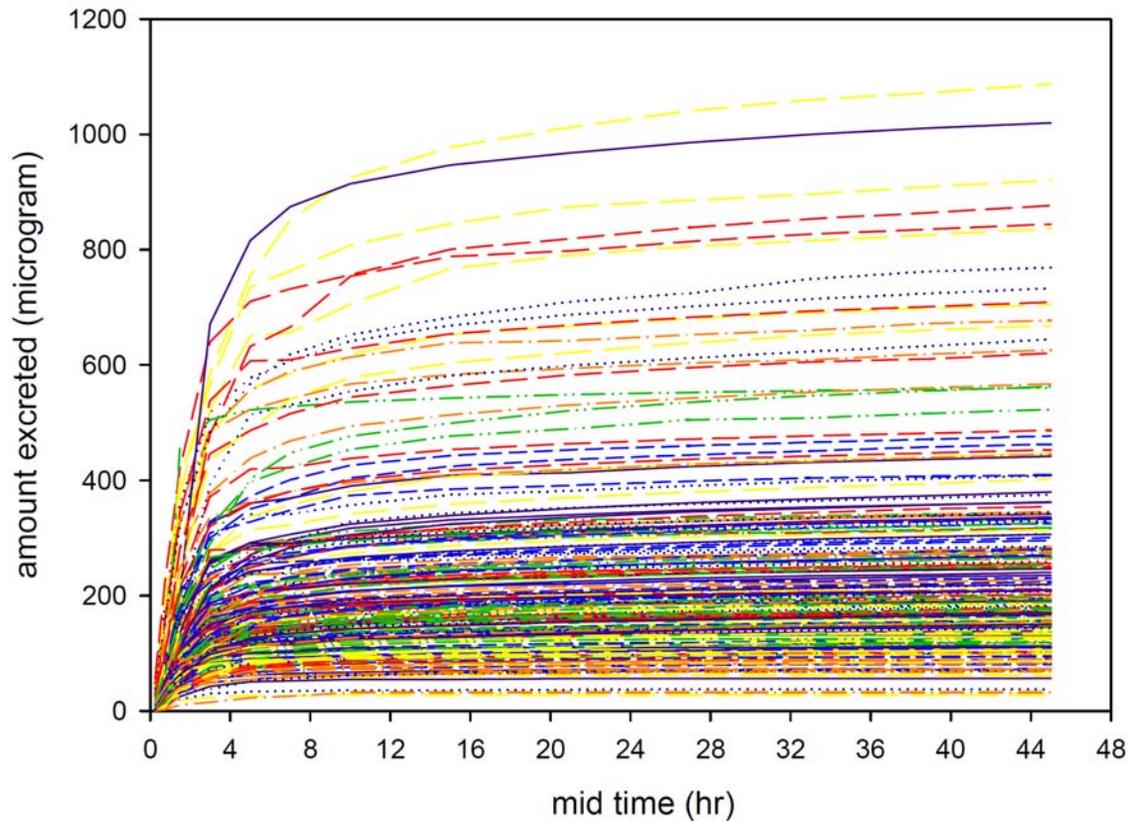


Figure 4 Individual cumulative urinary excretion of alendronate following repetitive doses of 70 mg alendronate as Fosamax (Reference)

Geometric mean (68% range) cumulative urinary excretion profiles of alendronate from the 2 administrations of Binosto or the 2 administrations of Fosamax are shown in Figure 5.

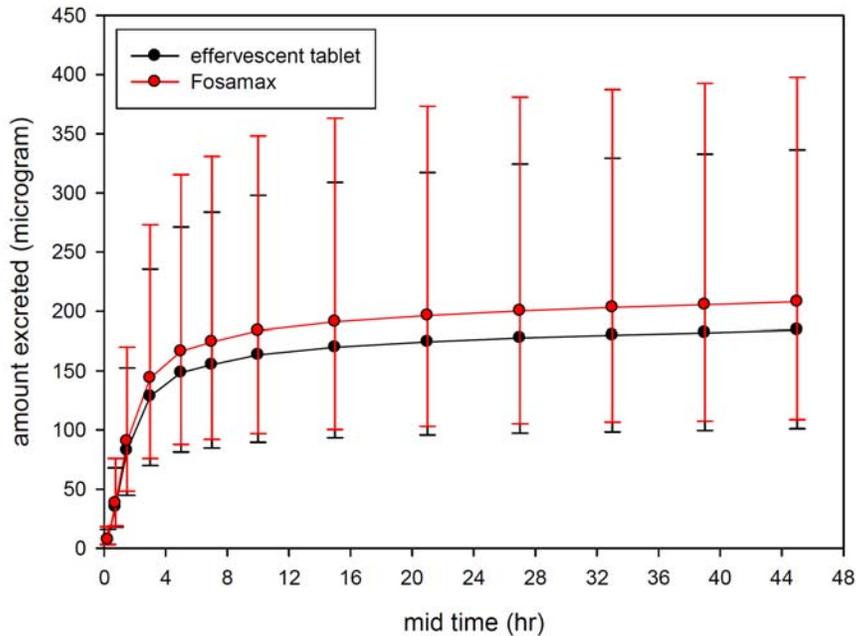


Figure 5 Geometric mean (68% range) cumulative urinary excretion of alendronate following repetitive doses of Binosto (Test) or Fosamax (Reference)

Geometric mean (68% range) profiles of the urinary excretion rate, E_t , of alendronate from the 2 combined administrations of Binosto or the 2 combined administrations of Fosamax are shown in Figure 6 using a linear Y-scale.

Figures 1-3 show that the major part of alendronate excreted in urine occurs during the first 6 hours after dosing, with relatively small additional amounts excreted from 6 to 48 hours after dosing. Also, they demonstrate the interindividual variability of alendronate excretion in urine.

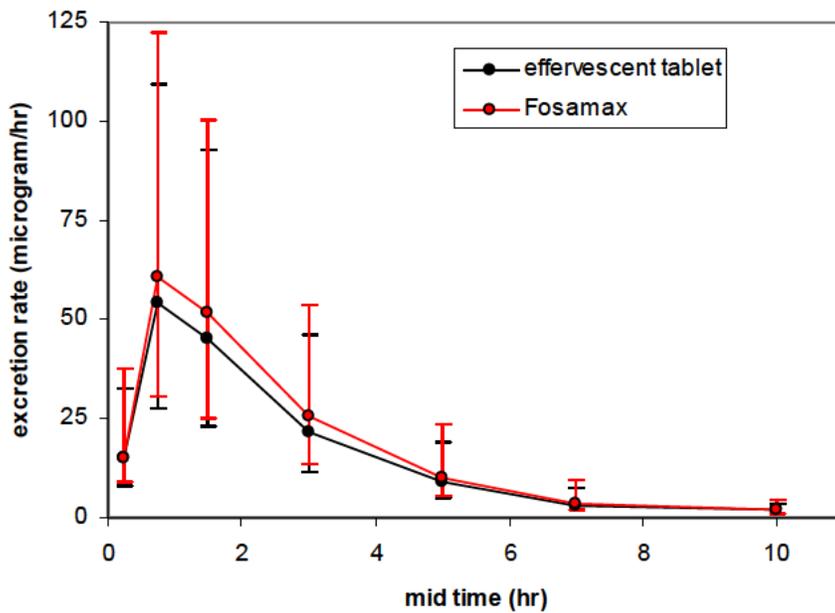


Figure 6 Geometric mean (68% range) of the urinary excretion rate of alendronate following repetitive doses of Binosto (Test) or as Fosamax (Reference), linear Y-scale; n = 103

Figure 6 again shows that the major part of the absorbed fraction of alendronate is excreted in urine within approximately 6 to 8 hours after dosing. Geometric mean (68%-range) profiles of the urinary excretion rate, E_t , of alendronate from the 2 combined administrations of Binosto or the 2 combined administrations of Fosamax to the combined group of female and male subjects are shown in Figure 7 using a logarithmic Y-scale.

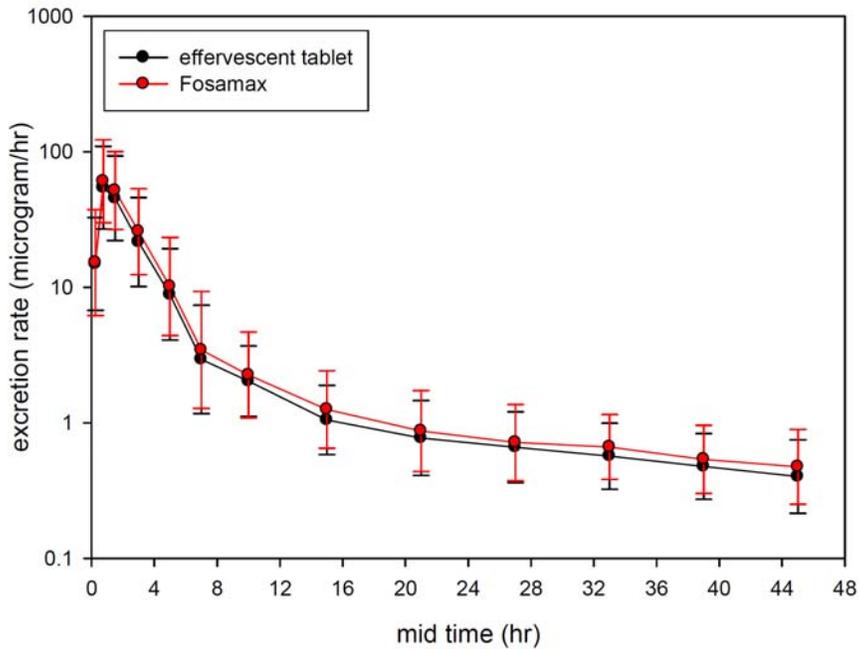


Figure 7 Geometric mean (68% range) of the urinary excretion rate of alendronate following repetitive doses of Binosto (Test) or as Fosamax (Reference), logarithmic Y-scale; n = 103

Figure 7 indicates a biphasic pattern of excretion with a more rapid phase lasting until 8 hours after dosing, which is followed by a second phase with a slower excretion rate from 8 until 48 hours after dosing. The pharmacokinetic parameters following single 70 mg administrations of either Binosto or Fosamax are summarized in Table 5.

Table 5 PK parameters (geometric mean, 68% range) of alendronate excreted in urine

PK-Parameter	Formulation	1 st dose (A ₁ or B ₁) (Periods 1 or 2)	2 nd dose (A ₂ or B ₂) (Periods 3 or 4)	both doses (A ₁ +A ₂ , B ₁ +B ₂) (Periods 1 - 4)
Ae₀₋₄₈ (µg) (primary)	Effervescent tablet (A)	187.07 (100.85, 347.02) (N=101)	181.45 (101.02, 325.94) (N=96)	184.31 (101.04, 336.21) (N=197)
	Fosamax (B)	199.26 (101.92, 389.55) (N=101)	217.26 (116.29, 405.90) (N=99)	207.97 (108.77, 397.65) (N=200)
E_{max} (µg/h) (primary)	Effervescent tablet (A)	63.69 (34.08, 119.03) (N=99)	62.41 (36.06, 108.02) (N=95)	63.06 (35.04, 113.48) (N=194)
	Fosamax (B)	67.63 (35.88, 127.49) (N=100)	71.18 (36.97, 137.06) (N=98)	69.37 (36.45, 132.00) (N=198)
t(E_{max}) (h) (secondary) Median (min/max)	Effervescent tablet (A)	0.75 (0.70, 2.94) (N=99)	0.74 (0.28, 1.49) (N=95)	0.75 (0.28, 2.94) (N=194)
	Fosamax (B)	0.74 (0.67, 2.94) (N=100)	0.74 (0.69, 4.90) (N=98)	0.74 (0.67, 4.90) (N=198)
t_{1/2} (h) (secondary)	Effervescent tablet (A)	19.10 (13.55, 26.91) (N=101)	20.36 (15.65, 26.49) (N=96)	19.70 (14.48, 26.80) (N=197)
	Fosamax (B)	18.36 (12.85, 26.22) (N=101)	21.16 (16.73, 26.77) (N=99)	19.70 (14.44, 26.86) (N=200)

Table 6 gives a summary of the BE analysis.

Table 6 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

A summary of Binosto and Fosamax PK parameter values and bioequivalence evaluation is provided in Table 6. The 90% CIs for the difference between the Test and Reference least squares means for the parameters Ae₀₋₄₈ and E_{max} were within the 80 to 125% bioequivalence limits, hence confirmed the bioequivalence between Binosto and Fosamax.

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

3 pages of Appendix 4.3 have been Withheld in Full immediately following this page as a duplicate copy of the OSI Site Inspection Report dated September 26, 2011 which is located in the Other Reviews of this package

6 pages of Appendix 4.4 have been Withheld in Full immediately following this page as a duplicate copy of the Clinical Pharmacology and Biopharmaceutics Filing Checklist dated 04/15/2011 which can be found in this review

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/s/

HYUNJIN KIM
02/08/2012

LAI M LEE
02/09/2012

ONDQA BIOPHARMACEUTICS REVIEW ADDENDUM

NDA#:	202-344/N-000
Submission Dates:	12/21/10 (Review clock started on 02/15/11) and 09/29/11
Brand Name:	Steovess
Generic Name:	Alendronate Sodium
Formulation:	Effervescent Tablets
Strength:	70 mg
Applicant:	EffRx
Type of submission:	Original (Standard, 10 months)
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

EffRx submitted NDA 202-344 as a 505(b)(2) submission for Steovess, an effervescent tablet 70 mg, referencing Fosamax for the same indications. This document is an Addendum to the original ONDQA-Biopharmaceutics Review for NDA 202-344 dated 9/19/11 in DARRTS. In the original review the proposed disintegration method for Steovess tablets was accepted, however, the Agency recommended a revision to the disintegration time at release. On 09/21/11 the Agency's sent an Advice Letter to the applicant recommending that the disintegration time at release be revised as follows.

Change from:

At Release:

(b) (4)

Stability:

To: **At Release and Stability:**

(b) (4)

On 09/29/11, the Applicant agreed to the Agency's recommendation and the specifications table for the drug product in Section M32P51 was updated. Please see the copy of the revised section M32P51 in Appendix 1.

RECOMMENDATION

This Addendum to the original ONDQA-Biopharmaceutics Review is to document that EffRx accepted the Agency's recommendation for the disintegration acceptance criterion and Section M32P51 was updated accordingly.

ONDQA-Biopharmaceutics recommends approval of NDA 202-344 for Steovess (Alendronate Sodium) Effervescent Tablets.

Tien-Mien Chen, Ph.D.
Reviewer, ONDQA Biopharmaceutics

10/21/11

Date

Angelica Dorantes, Ph.D.
Team Leader, ONDQA Biopharmaceutics

10/21/11

Date

CC: NDA, Tien-Mien Chen, Rebecca Mc Knight

**NDA 202-344 for Steovess (Alendronate Sodium)
Effervescent Tablet, 70 mg**

Appendix 1

Revised Disintegration Acceptance Criterion

3.2.P.5.1 SPECIFICATIONS (ALENDRONATE, EFFERVESCENT TABLET)

The revised release and stability (shelf-life) specifications and list of analytical procedures for Alendronate Effervescent Tablets 70 mg (effective 27 september 2011) are provided in Table 1.

Table 1 Release and Shelf-life Specifications for Alendronate Effervescent Tablets 70 mg

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

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/s/

TIEN MIEN CHEN
10/23/2011

ANGELICA DORANTES
10/23/2011

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	202-344 (N-000)
Submission Date:	12/21/10 (Review clock started on 02/15/11)
Brand Name:	Steovess
Generic Name:	Alendronate Sod.
Formulation:	Effervescent Tablets
Strength:	70 mg
Applicant:	EffRx
Type of submission:	Original (10 months)
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Background: Merck's original NDA (20-560) for the bisphosphonate Fosamax (alendronate sodium) 5, 10, 35, 40, and 70 mg oral tablets was approved in the US on 09/29/95. Fosamax is indicated for the treatment of osteoporosis in postmenopausal women and the treatment to increase bone mass in men with osteoporosis. Alendronate sodium has known side effects (esophageal irritation) when administered orally as a standard uncoated swallowable tablet.

(b)(4) EffRx Pharmaceuticals SA developed a soluble buffered effervescent tablet containing an equivalent of 70 mg alendronic acid (as 91.37 mg of alendronate sodium trihydrate) as a new dosage form, effervescent tablet (named Steovess). Steovess has the same active pharmaceutical ingredient as Fosamax and belongs to the same drug class (bisphosphonate).

Submission: On 12/21/10, EffRx submitted a 505(b)(2) NDA for Steovess referencing Fosamax for the same indications. The review clock started on 02/15/11. The applicant reported that Steovess formulation has demonstrated to be bioequivalent to the 70-mg dosage strength of Fosamax in a bioequivalence study which is currently under review by the Office of Clinical Pharmacology (OCP).

Review: The Biopharmaceutics review is focused on the evaluation of the data supporting the proposed disintegration method and acceptance criterion.

RECOMMENDATION

From the Biopharmaceutics perspective, the proposed disintegration method was found acceptable to support the NDA approval, however, the disintegration acceptance criterion needs to be revised and implemented. The following comment needs to be conveyed to the applicant.

COMMENT (Needs to be sent to the sponsor)

Your proposed disintegration method (in water, 20°C) is acceptable; however, we recommend that the proposed disintegration acceptance criteria be revised as follows:

Change from:
At Release: [REDACTED] (b) (4)
Stability: [REDACTED]

To: **At Release and Stability:** [REDACTED] (b) (4)

Tien-Mien Chen, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

09/19/11

Date

Angelica Dorantes, Ph.D.
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09/19/11

Date

CC: NDA
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BACKGROUND

Merck's original NDA (NDA 20-560) for the bisphosphonate Fosamax (alendronate sodium) 5, 10, 35, 40, and 70 mg oral tablets was approved in the US on 09/29/95. Fosamax is indicated for the treatment of osteoporosis in postmenopausal women and the treatment to increase bone mass in men with osteoporosis.

Alendronate sodium has known side effects (esophageal irritation) when administered orally as a standard uncoated swallowable tablet. Therefore, patients are instructed to drink approximately 200 mL of water and remain in an upright position for 30 minutes after swallowing the tablet.

Given the above restrictions, the concept of pre-dissolving the active ingredient in a buffered solution has a potential for improvement. Sodium alendronate is soluble in water up to approximately 10 mg/mL. Therefore, an effervescent formulation is an appropriate pharmaceutical form for the drug delivery system since it contains acids, as well as salts of the acids, working as a buffer system.

CURRENT SUBMISSION

EffRx Pharmaceuticals SA developed a soluble buffered effervescent tablet containing an equivalent of 70 mg alendronic acid (as 91.37 mg of alendronate sodium trihydrate) as a new dosage form (named Steovess). Steovess has the same active pharmaceutical ingredient as Fosamax and belongs to the same drug class (bisphosphonate).

On 12/21/10, EffRx submitted a 505(b)(2) NDA for Steovess referencing Fosamax for the same indications. The review clock started on 02/12/11. The applicant reported that Steovess formulation is bioequivalent to the 70-mg dosage strength of Fosamax in a bioequivalence study which is currently being reviewed by OCP. Included in the NDA submission are the proposed disintegration method and disintegration data which are reviewed here.

BIOPHARMACEUTICS EVALUATION

FORMULATION

The composition of the formulation for the Steovess effervescent tablets is shown below in Table 1.

Table 1. Quantitative Composition per Tablet of Steovess (Sod. Alendronate) Effervescent Tablet 70 mg

Component	Quantity per Tablet	Reference to Standards	Function			
Sodium alendronate trihydrate (b) (4)	91.37 mg	USP / Ph. Eur.	Active ingredient			
Monosodium citrate anhydrous	(b) (4)					
Citric acid anhydrous						
Sodium hydrogen carbonate						
Sodium carbonate anhydrous						
Strawberry flavor, (b) (4)						
Acesulfame potassium						
Sucralose						
(b) (4)						
Total tablet weight				4,050.00 mg		

DAC = Deutscher Arzneimittel Codex; NF = Current edition of the National Formulary; Ph. Eur. = Current edition of the European Pharmacopoeia; USP = Current edition of the United States Pharmacopoeia.

(b) (4)

PROPOSED DISINTEGRATION METHOD AND ACCEPTANCE CRITERIA

The effervescent tablet, by definition, is intended to be dissolved or dispersed in water before administration. The applicant proposed a disintegration method (b) (4). The procedure is described below.

(b) (4)

The manufacturing information on the stability batches is shown below in Table 2.

Table 2. Manufacturing Information on the Stability Batches Submitted

Batch	Date of Manuf.	Batch Size	Storage Conditions	Time Period	Drug Substance
2046-09501	Mar 2009	(b) (4)	25°C / 60% RH	18 months	(b) (4)
2046-09501	Mar 2009		30°C / 75% RH	18 months	
2046-09502	Mar 2009		25°C / 60% RH	18 months	
2046-09502	Mar 2009		30°C / 75% RH	18 months	
2046-09503	Mar 2009		25°C / 60% RH	18 months	
2046-09503	Mar 2009		30°C / 75% RH	18 months	

The disintegration data for the three stability batches under the storage conditions of 25°C/relative humidity (RH) of 60% are shown below in Table 3.

Table 3. Disintegration Time for the Three Stability Batches of Steovess (in Water, 20°C) Under Storage Conditions: 25°C/RH 60%

Batch No.	Initial (Time Zero)	3 Months	6 Months	9 Months	12 Months	18 Months
2046-0951	(b) (4)					
2046-0952	(b) (4)					
2046-0953	(b) (4)					

The applicant's proposed acceptance criteria for the disintegration test are as follows:

At Release: (b) (4)
Stability: (b) (4)

REVIEWER'S COMMENT:

The proposed disintegration method was reviewed and found acceptable. In general, the acceptance criteria at release and stability should be the same. Note that the disintegration time up to 18 months for the Steovess tablets is (b) (4). Therefore, it is recommended that the acceptance criteria be revised to (b) (4) for both testing times, "At Release" and "Stability".

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/s/

TIEN MIEN CHEN
09/19/2011

ANGELICA DORANTES
09/19/2011

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NDA Number: 202344

Applicant: EffRx, Inc.

Stamp Date: 12/22/2010

**Drug Name: Steovess
(alendronate sodium) 70 mg
effervescent tablet**

NDA Type: Original

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	A pivotal BE study of to-be-marketed product and Fosamax IR 70 mg was conducted.
2	Has the applicant provided metabolism and drug-drug interaction (DDI) information?			X	505(b)(2) relying on NDA 020560, Fosamax for safety and efficacy information including DDI
Criteria for Assessing Quality of an NDA					
Data					
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	A BE approach to Fosamax 70 mg
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X			
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			X	A BE approach to Fosamax 70 mg
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	A BE approach to Fosamax 70 mg
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Request for pediatric study waiver
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Request for pediatric study waiver
11	Is the appropriate pharmacokinetic information	X			

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	submitted?				
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X			
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X			
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
17	Was the translation from another language important or needed for publication?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

Background

Sponsor submitted a 505(b)(2) NDA for a 70 mg alendronate effervescent tablet relying on NDA 020560 (Fosamax, alendronate sodium) 70 mg for clinical efficacy/safety and nonclinical safety data. The sponsor is seeking the following indications: 1) Treatment of osteoporosis in postmenopausal women and 2) Treatment to increase bone mass in men with osteoporosis. The proposed dosing instruction is to take one 70 mg tablet effervescent tablet by dissolving it in half a glass (4 ounces) of water. (b) (4)

In the current submission, the sponsor submitted the following three clinical studies including two bioequivalence (BE) studies:

- o Study SCO 5361: A BE and food effect study comparing a 70 mg effervescent alendronate tablet to a 70 mg Fosamax tablet
- o Study AE-1212-001-EM: A BE study comparing a 70 mg effervescent alendronate tablet to a 70 mg Fosamax tablet

- o Study BC-118-07: A gastric imaging and pH telemetry study

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There is no pharmacokinetic component in this study. Therefore, study BC-118-07 will not be reviewed by Clinical Pharmacology discipline.

Clinical studies

Study SCO 5361, “An open, randomized, single dose, three-period, crossover study to assess the BE of an 70 mg effervescent alendronate tablet versus a standard oral formulation followed by a standard breakfast and under fasting conditions in healthy women aged 45 to 75 years”

- Objective
 - To assess the BE between 70 mg alendronate effervescent tablet and 70 mg Fosamax tablet by measuring alendronate excretion in urine (Ae_{0-48} : cumulative amount of alendronate excreted in urine up to 48 hours, E_{max} : maximum excretion rate)
- Study design
 - This study enrolled 134 healthy Caucasian women with age between 45 to 75 years without any medical history. Subjects were divided into three treatment groups as following with 14-day wash-out period between each treatment:
 - Treatment A: a single dose of the effervescent alendronate 70 mg tablet, administered after at least 12 hours of fasting, followed by 4 hours fasting periods
 - Treatment B: a single dose of the effervescent alendronate 70 mg tablet, administered after at least 12 hours of fasting, followed by a breakfast 15 minutes after administration
 - Treatment C: a single dose of Fosamax immediate release tablet administered after at least 12 hours of fasting, followed by 4 hours of fasting periods
- Result
 - While the 90% confidence interval (CI) of E_{max} ratio met the BE criteria of 80 – 125%, that of Ae_{0-48} ratio did not meet the BE criteria, (b) (4)
 - Table 1 describe the PK parameters (Ae_{0-48} , E_{max} , $t_{1/2}$) comparison of Fosamax, effervescent alendronate tablet while fasting, and effervescent alendronate tablet with breakfast. The larger Ae_{0-48} and E_{max} of Fosamax compared to those of the effervescent tablet while fasting. (b) (4)

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Table 1. Summary of BE analysis; A: effervescent alendronate 70 mg under fasting, B: effervescent alendronate 70 mg under fed, C: Fosamax 70 mg under fasting; SCO 5361

PK-VARIABLE	METHOD	TRANS	COMP	PE [%]	LL90 [%]	UL90 [%]	ANOVA-CV [%]
Ae ₀₋₄₈							
E _{max}							
t _{1/2}							

(b) (4)

Study AE-1212-001-EM, “Single-site, open label, four period cross-over replicate trial after single dose administration of a new alendronate 70 mg formulation, a buffered effervescent soluble tablet, under fasting conditions, to assess the BE versus Fosamax 70 mg in healthy volunteers”

- Objective
 - To assess the BE between 70 mg alendronate effervescent tablet and 70 mg Fosamax tablet by measuring alendronate excretion in urine (Ae₀₋₄₈: cumulative amount of alendronate excreted in urine up to 48 hours, E_{max}: maximum excretion rate)
- Study design
 - This was a single site, single dose, open label, 4-period with at least 14-day wash-out period, replicate design, cross-over trial in 70 females and 45 males under fasting conditions.
- Result
 - 90% CI for both Ae₀₋₄₈ and E_{max} met the 80-125% BE range in two analyses (females only-Tablet 2 AND females and males combined-Table 3)

Table 2: Summary of BE analysis for females only; Test: effervescent tablet, Reference: Fosamax; AE-1212-001-EM

PK-parameter		Geometric LSM ^a		Ratio ^b Test/ Ref. [%]	Lower 90%CI [%]	Upper 90%CI [%]	Inter- Individ. CV [%] ^c	Intra- Individ. CV [%] ^c
		Test	Reference					
Ae ₀₋₄₈ [µg]	primary	176.46	200.83	87.87	80.57	95.82	60.9/60.6	33.0/41.6
E _{max} [µg/h]	secondary	60.63	69.33	87.44	80.11	95.44	54.9/58.5	38.0/49.8
t _{1/2} [h]	secondary	19.73	19.79	99.68	94.75	104.87	18.0/18.7	24.0/20.6

Table 3: Summary of BE analysis for females and males; Test: effervescent tablet, Reference: Fosamax; AE-1212-001-EM

PK-parameter		Geometric LSM ^a		Ratio ^b Test/ Ref. [%]	Lower 90%CI [%]	Upper 90%CI [%]	Inter- Individ. CV [%] ^c	Intra- Individ. CV [%] ^c
		Test	Reference					
Ae ₀₋₄₈ [µg]	primary	185.27	210.21	88.14	82.92	93.69	55.9/54.5	32.0/42.1
E _{max} [µg/h]	primary	62.79	69.42	90.44	84.85	96.41	49.0/53.7	37.5/45.6
t _{1/2} [h]	secondary	19.63	19.87	98.78	94.61	103.13	15.7/18.6	28.1/24.7

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Internal notes

- Per “*Guidance for Industry; Food-Effect Bioavailability and Fed BE Studies, December, 2002,*” water can be allowed as desired except for one hour before and after drug administration for fasting conditions.” However, the subjects in the study AE-1212-001-EM were instructed to drink at least 100 ml of water approximately every 30 minutes from 2 hours prior to dosing to 30 minutes after dosing.
- The prescribing information for approved Fosamax instructs patients not to lie down for at least 30 minutes, whereas subjects in the study AE-1212-001-EM were instructed not to lie down for 4 hours. This will be a review issue.

Request for Waiver of Pediatric Studies

Sponsor requested a waiver of pediatric studies since the pathophysiology of osteoporosis is such that the disease occurs for the most part in adults.

Formulation

The formulation of the effervescent alendronate tablet used in the pivotal BE study, AE-1212-001-EM is same as the to-be-marketed product.

Division of Scientific Investigations (DSI) Inspection Request

Due to the importance of the study AE-1212-001-EM in addressing the approvability of the current NDA, Clinical Pharmacology will request a DSI inspection for the site (Clinical Research Services, Germany) [REDACTED] (b)(4) [REDACTED] conducted for the study AE-1212-001-EM.

PDUFA goal date and waiver of user fee

The current NDA was submitted on December 22, 2010 with request for waiver of user fee. On February 15, 2011, the small business user fee wavier was granted which started the Prescription Drug User Fee Act (PDUFA) clock. Therefore, PDUFA goal date for the current submission is December 15, 2011.

Comments to be conveyed to the sponsor in a 74-day letter:

1. In study AE-1212-001-EM, study subjects were instructed to drink at least 100 mL of Volvic (non-sparkling water) approximately every 30 minutes from 2 hours prior to dosing to approximately 30 minutes after dosing for a total of 740 mL when taking effervescent alendronate sodium tablet or Fosamax. However, the prescribing information of the approved Fosamax label instructs patients to take Fosamax with a full glass of water (6-8 ounces). Address the effect of difference in the total amount of water consumption (740 mL vs. 6-8 ounces) while taking Fosamax on the safety and efficacy of Fosamax.
2. The current proposed label for effervescent alendronate sodium tablet instructs patients to take effervescent alendronate sodium tablet by dissolving it in 4 ounces of water. Address the effect of difference in the total amount of water consumption (740 mL vs. 4 ounces) while taking effervescent alendronate sodium tablet on the bioavailability of effervescent alendronate sodium tablet.

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Reviewing Pharmacologist

Date

Myong-Jin Kim

Team Leader/Supervisor

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/s/

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04/15/2011

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