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APPLICATION NUMBER:
202344Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 202-344
Supporting document/s: SD #1, #5, #20
Applicant's letter date: December 21, 2010
CDER stamp date: February 15, 2011
Review Date: February 8, 2012
Product: EX101 (alendronate sodium) 70 mg,
effervescent tablet, for solution (BINOSTO™)
Indication: Treatment of osteoporosis in postmenopausal
women. Treatment to increase bone mass in
men with osteoporosis.
Applicant: Efrx Pharmaceuticals SA (Efrx, Inc)
Review Division: DRUP (HFD-580)
Reviewer: Gemma Kuijpers, Ph.D.
Supervisor/Team Leader: Lynnda Reid, Ph.D.
Office Director: Julie Beitz, M.D.
Project Manager: Meredith Alpert

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 202-344 are owned by Efrx or are data for which Efrx has obtained a written right of reference.

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TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	4
1.1	INTRODUCTION	4
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	4
1.3	RECOMMENDATIONS	4
2	BACKGROUND.....	5
2.1	INTRODUCTION	5
2.2	REGULATORY BACKGROUND:	5
3	DRUG INFORMATION	6
3.1	DRUG	6
3.2	RELEVANT INDS, NDAs	6
3.3	DRUG FORMULATION	7
3.3.1	DRUG SUBSTANCE	7
3.3.2	DRUG PRODUCT	8
3.4	EXCIPIENTS	11
3.5	IMPURITIES/DEGRADANTS	12
3.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	14
4	PHARMACOLOGY AND TOXICOLOGY	14
4.1	REFERENCE TO FOSAMAX	14
4.2	FOSAMAX NONCLINICAL	15
5	LABELING.....	15
6	APPENDIX/ATTACHMENTS.....	17

1 Executive Summary

1.1 Introduction

The applicant, Effrx, submitted a 505(b)(2) NDA for EX101, a soluble effervescent tablet containing the equivalent of 70 mg alendronic acid for weekly dose administration (Binosto™). Alendronic acid is a bisphosphonic acid. These acids and/or their salts are anti-hypercalcemics that have been shown to increase bone mass and reduce fracture risk. The applicant is relying on the finding of safety and efficacy of the Fosamax 70 mg tablet (NDA 20-560, alendronate) for NDA approval. Data from clinical studies to demonstrate bioequivalence of EX101 to the 70-mg Fosamax tablet and to evaluate the safety and pharmacodynamic aspects of the EX101 effervescent tablet were also submitted.

1.2 Brief Discussion of Nonclinical Findings

Oral bisphosphonates are associated with esophageal or gastrointestinal toxicity in both animals and humans. The applicant refers to NDA 20-560 and NDA 21-575 for Fosamax 70 mg tablet and oral solution, respectively, for nonclinical information supporting the safety of EX101. No new nonclinical data were submitted.

There were no excipients and no impurities or degradants in drug substance or drug product requiring qualification in nonclinical studies.

1.3 Recommendations

1.3.1 Approvability

Based on bioequivalence of the listed drug (Fosamax, 70 mg tablet) and the 70 mg EX101 effervescent tablet, the Sponsor's referral to NDA 20-560 and NDA 21-575 for nonclinical support of NDA 202-344 is acceptable. Pharmacology/Toxicology recommends approval of the NDA.

1.3.2 Additional Non Clinical Recommendations

N/A

1.3.3 Labeling

The labeling is similar to the Fosamax label. It was submitted in PLR format, with the proposed tradename changed from STEOVESS to BINOSTO on June 21, 2011. In the nonclinical sections of the label, multiples of the 40 mg daily dose, (b) (4)

However, reference to a 40 mg dose can be retained for the purpose of dose comparison.

2 Background

2.1 Introduction

NDA 202-344 is a 505(b)(2) application for EX101 (alendronate sodium), an effervescent tablet containing 70 mg alendronic acid, for once-weekly administration. The proprietary name is BINOSTO™. The indications sought are (1) treatment of osteoporosis in postmenopausal women and (2) treatment to increase bone mass in men with osteoporosis (b) (4)

Alendronate is a bisphosphonate which inhibits osteoclastic bone resorption causing an increase in bone mass and reduction in fracture incidence. Alendronate was first approved in the US in 1995 as a 10 mg daily tablet for the osteoporosis treatment indication (NDA 20-560). Subsequently, 35 mg and 70 mg weekly tablets were approved in 2000 (NDA 20-560, S021 and S022) and a 70 mg weekly oral solution (NDA 21-575) was approved in 2003.

The Binosto™ 70 mg effervescent tablet is to be dissolved in 4 ounces of water, stirred for 10 seconds once effervescence stops, and ingested. Patients should not lie down for at least 30 minutes and until after the first food of the day. For comparison, the Fosamax tablet has to be taken in the morning on an empty stomach at least 30 minutes before breakfast with 6-8 ounces of water and patients have to refrain from lying down for at least 30 minutes after dose ingestion and until after the first food of the day.

This 505(b)(2) application refers to NDA 20-560 (Fosamax®, alendronate sodium, 70 mg tablets) for clinical safety and efficacy information, and to NDA's 20-560 and 21-575 for nonclinical pharmacology and toxicology information to support their NDA 202-344. The Sponsor submitted three clinical studies including 2 bioavailability/bioequivalence studies, Study SCO 5361 and Study AE-1212-001-EM. The third study, Study BC-118-07, is a gastric imaging and pH telemetry study. No new nonclinical studies were submitted.

2.2 Regulatory Background:

Upon Pharmacology/Toxicology review of the initial IND submission, it was concluded that for a 505(b)(2) submission no additional toxicity testing would be needed if (1) the excipients in the to-be-marketed drug product are the same as described, and (2) the impurities and degradation products in the drug product are present at the same as or lower levels than those specified for the tablet to be used in the proposed IND study (Study-AE-1212-001-EM).

A pre-NDA meeting was held on November 6, 2008. In response to the Sponsor's questions, the Division stated that a single bioequivalence study would be an adequate bridge to the referenced approved product to support a 505(b)(2) submission. The Division also affirmed that additional pharmacology/ toxicology studies would not be required as long as clinical bioequivalence was established and no new excipients or impurities were identified which require qualification.

3 Drug Information

3.1 Drug

CAS Registry Number: 121268-17-5

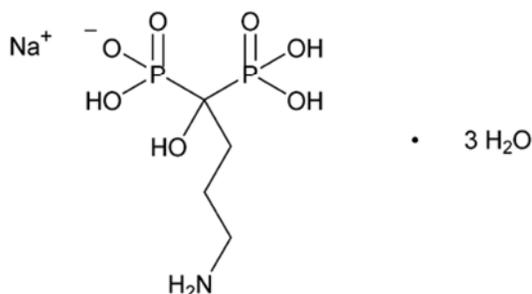
Name (USAN, rINN): Sodium Alendronate

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

Molecular Formula/Weight: $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ / 325.12

Structure:

Figure 1 Structural Formula of Sodium Alendronate Trihydrate



Biochemical Description:

Pharmacologic Class: Bisphosphonate

Manufacturer:

(b) (4)

3.2 Relevant INDs, NDAs

IND 32,033	Alendronate sodium, MK-217, Merck and Co, Inc
IND 103,033	EX101 (alendronate sodium), Effrx Pharmaceuticals SA
NDA 20-560	Fosamax (MK-217, alendronate sodium, tablet), Merck and Co, Inc

NDA 21-575 Fosamax (MK-217, alendronate sodium, oral solution), Merck and Co, Inc

3.3 Drug Formulation

3.3.1 Drug Substance

Alendronate Sodium Trihydrate, USP

Specifications:

Table 1 Specification for Sodium Alendronate Drug Substance

Test	Specification	Analytical Procedure
-------------	----------------------	-----------------------------

Ph. Eur. requirements [include USP requirements – ID, LOD, Heavy metals, Assay, and Purity (Related substances)]



(b) (4)

Test	Specification	Analytical Procedure
(b) (4)		

3.3.2 Drug Product

Effervescent tablets, containing sodium alendronate trihydrate, Na-citrate, citric acid, Na-HCO₃, NaCO₃, strawberry flavor, acesulfame potassium, sucralose.

Quantitative Composition:

Table 1 Quantitative Composition per Tablet of Alendronate Effervescent Tablets 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)	(b) (4)	(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 Pharmacopeia.

(b) (4)

Release and Shelf-Life Specifications of Alendronate Effervescent Tablets:

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

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

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

3.4 Excipients

Excipients in the drug product include sodium citrate, citric acid, sodium bicarbonate, sodium carbonate, sucralose, and acesulfame potassium (Table 1, above). These excipients are either present as inactive ingredients in FDA approved products at equal or higher amounts (on per day basis) or non-toxic food substances. Strawberry flavoring agent (b) (4) is recognized as GRAS by FDA.

The specifications for citric acid anhydrous, sodium hydrogen carbonate, sodium carbonate anhydrous, acesulfame potassium, sucralose, (b) (4) comply with the respective monographs in the compendia shown in Table 1.

Table 1 Standards for Specifications of Compendial Excipients

Compendial Excipient	Reference to Standards
Citric acid anhydrous	United States Pharmacopeia (USP) / European Pharmacopoeia (Ph. Eur.)
Sodium hydrogen carbonate	USP / Ph. Eur.
Sodium carbonate anhydrous	Ph. Eur.
Acesulfame potassium	National Formulary (NF) / Ph. Eur.
Sucralose	NF
(b) (4)	

3.5 Impurities/Degradants

Drug substance

Impurities in the drug substance are (b) (4)



According to the ICH Guidance Q3A, the limit of qualification for impurities in drug substances at daily dosages of $\leq 2\text{g/day} = 0.15\%$ or 1 mg/day .

(From: ICH Q3A: Impurities in drug substance:)

Maximum Daily Dose ¹	Reporting Threshold ^{2,3}	Identification Threshold ³	Qualification Threshold ³
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

Thus, the specified levels of impurities in the drug substance are acceptable.

Drug product

Impurities in the drug product are

(b) (4)

According to ICH Guidance Q3B/R2, the qualification threshold for degradation products in drug products to be administered at a daily dose of 10mg-100 mg is <0.5% (see ATTACHMENT 1, from ICH Q3B(R)).

(From: ICH Q3B(R): Impurities (“degradation products”) in drug product:)

ATTACHMENT 1

THRESHOLDS FOR DEGRADATION PRODUCTS IN NEW DRUG PRODUCTS

Reporting Thresholds

Maximum Daily Dose ¹	Threshold ^{2,3}
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

Maximum Daily Dose ¹	Threshold ^{2,3}
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

Qualification Thresholds

Maximum Daily Dose ¹	Threshold ^{2,3}
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

¹ The amount of drug substance administered per day

² Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.

³ Higher thresholds should be scientifically justified.

Thus, the specified levels of alendronate-related degradation products in BINOSTO™ tablets are acceptable.

In conclusion, the qualification thresholds for impurities and degradants in drug substance and drug product, respectively, were not exceeded.

3.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is postmenopausal women and men with osteoporosis.

The dosing regimen is weekly administration of one effervescent tablet 70 mg. The tablet is to be dissolved in 4 oz. of water. When the effervescence has stopped it should be stirred for 10 seconds and ingested.

4 Pharmacology and Toxicology

4.1 Reference to Fosamax

Sponsor is relying on the finding of safety and efficacy for Fosamax and is referring to NDA 20-560 (Fosamax 70 mg tablet) for clinical support and on NDA 20-560 (Fosamax, 70 mg tablet) and NDA 21-575 (Fosamax 70 mg weekly solution for nonclinical support of NDA 202-344.

According to the regulations a 505(b)(2) applicant may rely upon the *finding* of safety and/or effectiveness for a listed drug (not information submitted to the NDA for that listed drug) to the extent that the proposed product in the 505(b)(2) application shares characteristics in common with the listed drug. Since the active ingredient in the 70-mg effervescent tablet (sodium alendronate) is the same as the active ingredient tested in the (nonclinical) development programs for Fosamax tablet and solution, and both dosage forms are oral products, reference to NDA 20-560 for the Fosamax 70 mg listed drug is acceptable.

Thus, the submission of acceptable bioequivalence studies in this (505)(b2) NDA enables the FDA to rely on the finding of safety and efficacy of the 70 mg Fosamax tablet (NDA 20-560) and the 70 mg solution (NDA 21-575). The finding of safety was partly based on the adequacy of the nonclinical information submitted to these NDA's. Hence, referral to FDA's finding of safety for these two NDA's is adequate for nonclinical support of NDA 202-344.

No nonclinical studies were performed by EffRx Inc, to support the current NDA. Gastrointestinal toxicity is a known class effect of bisphosphonates. Clinical data are needed to provide information on esophageal and gastrointestinal safety.

4.2 Fosamax Nonclinical

A comprehensive pharmacology/toxicology program including esophageal irritation studies was conducted with alendronate to support Merck's IND 32,033 and NDA's 20-560 (Fosamax, weekly 70 tablet) and 21-575 (Fosamax, weekly 70 mg oral solution). Nonclinical data submitted to NDA 20-560 included pharmacology studies and general toxicity, genotoxicity, reproductive toxicity, carcinogenicity and special toxicity (esophageal irritation) studies. Additional nonclinical data submitted to NDA 21-575 included esophageal irritation studies in dogs.

Toxicology studies with alendronate conducted for IND 32033 and NDA 20-560 have shown a potential for gastric irritation/injury in rats and dogs and kidney toxicity in dogs. Special esophageal toxicology studies conducted for NDA 20-560 for the weekly dosing regimen (S-021 and S-022; 35 and 70 mg tablet) suggested that weekly dosing with an equivalent total dose of alendronate may be less irritating to esophageal tissue than daily dosing. Local esophageal irritation studies conducted for NDA 21-575 in dogs confirmed that there may be less irritation with weekly than daily dosing but also showed dose-dependent esophageal toxicity with weekly dosing regimens.

Reproductive toxicity studies in rats have shown postimplantation loss, decreased pup weight gain, incomplete fetal ossification, as well as dystocia and protracted parturition possibly due to hypocalcemia. Fosamax is labeled Pregnancy Category C and the label described the fetal abnormalities and parturition findings. As with all bisphosphonates, the label also includes a statement about the theoretical risk for fetal harm, predominantly skeletal (Precautions/Pregnancy section).

Carcinogenicity studies have shown increases in Harderian gland adenomas in female mice and parafollicular cell (C-cell) adenomas in male rats. Carcinogenicity data are included in the Fosamax label (Precautions/ Carcinogenesis, Mutagenesis, Impairment of Fertility).

Alendronate was not genotoxic and had no effect on fertility in rats. This is mentioned in the Fosamax label (Precautions/Carcinogenesis, Mutagenesis, Impairment of fertility).

5 Labeling

Labeling including the proprietary name BINOSTO™ was submitted in PLR format. Labeling revisions were submitted on several dates. The PLR format of the Fosamax label was approved on February 6, 2012.

The nonclinical sections of the BINOSTO label include:

Section 8 (Use in specific populations)

- 8.1. Pregnancy

Section 13 Nonclinical toxicology

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In these nonclinical sections, the daily administered doses in the animal studies are given as multiples of the maximum recommended daily dose of 40 mg (b) (4) based on dose per surface area (mg/m²). (b) (4)

(b) (4) should be deleted from the label. However, reference to a 40 mg daily dose can be retained for the purpose of dose comparison (APPENDIX).

2 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/

GEMMA KUIJPERS
02/08/2012

LYNNDA L REID
02/09/2012
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202-344

Applicant: Effrx, Inc.

Stamp Date: Dec 21, 2010

Drug Name: STEOVESSTTM
(alendronate sodium) 70-mg
Effervescent Tablets

NDA Type: 505(b)(2)

NDA 202-344 is a 505(b)(2) application for STEOVESSTTM, 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. The reference listed drug for the application is Fosamax[®] (alendronate sodium) 70 mg tablets. The product is intended for once-weekly administration for the treatment of osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis.

The drug product is a conventionally manufactured effervescent tablet. The goal of this product development was to allow for administering sodium alendronate as an oral solution wherein the drug substance is completely dissolved.

The applicant refers to Merck's NDA 20-560 (alendronate sodium, tablet) for nonclinical pharmacology and toxicology data and NDA 21-575 (alendronate sodium, oral solution) for additional nonclinical safety data. NDA 20-560 is referenced for clinical efficacy and safety data.

The application is based on a bioequivalence study comparing the Effrx effervescent alendronate product with Fosamax (Study AE-1212-001-EM). The applicant contends that the results from this study show that STEOVESSTTM 70 mg tablets are bioequivalent to Fosamax 70 mg tablets. In addition, a pharmacodynamic scintigraphic study (Study BC-118-07) was conducted to investigate in vivo pH and gastric emptying following administration of the 3 different sodium alendronate formulations.

A complete pharmacology/toxicology program including pharmacology, PK, general toxicity, carcinogenicity, reprotoxicity and special esophageal irritation toxicity studies was conducted by Merck for NDA 20-560 in support of daily and weekly oral administration of alendronate sodium tablets (Fosamax[®]). Additional esophageal irritation studies were conducted for Merck NDA 21-575 in support of weekly oral administration of alendronate sodium solution. Effrx did not perform any additional nonclinical studies on alendronate and refers to NDA 20-560 and NDA 21-575 for nonclinical information on alendronate.

At the pre-NDA meeting on 1 September 2010, the Division stated that no new nonclinical studies were needed if there are no new excipients or impurities identified and if the limits for impurities in the drug product do not exceed the qualification threshold levels specified in ICH guidance Q3B(R2) *Impurities in New Drug Products*. Applicant confirms in the Nonclinical Overview of NDA 202-344 that this is the case for the new product.

It is acceptable that no new nonclinical studies were performed for this NDA 505(b)(2) application.

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
	begin?			
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	N/A		The applicant refers to Merck's NDA 20-560 (Fosamax, alendronate sodium, tablet) for nonclinical pharmacology and toxicology data and NDA 21-575 (Fosamax, alendronate sodium, oral solution) for additional nonclinical safety data. Bridging to these NDA's is based on a BA/BE study showing bioequivalence of the Effic product and Fosamax. Bridging is also based on the fact that the route of administration for the Effic product (oral, tablet) is the same as for the Fosamax products (oral, tablet or solution) and Merck's nonclinical data are in support of dosing by this administration route.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	N/A		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	N/A		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	N/A		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
	with 201.57?			
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?	N/A		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	N/A		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE?

-YES

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- No issues

Gemma Kuijpers, Ph.D.

March 28, 2011

Reviewing Pharmacologist

Date

Lynnda Reid, Ph.D.

March 28, 2011

Team Leader/Supervisor

Date

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

/s/

GEMMA A KUIJPERS
03/28/2011

LYNNDA L REID
03/30/2011