CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-710

Name: Alendronate Sodium Tablets, USP
5 mg, 10 mg, 35 mg, 40 mg, and 70 mg

Sponsor: TEVA Pharmaceuticals USA

Approval Date: February 6, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-710

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Microbiology Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-710

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 75-710

TEVA Pharmaceuticals USA
Attention: Philip Erickson
Senior Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 29, 1999, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Alendronate Sodium Tablets USP, 5 mg (base), 10 mg (base), and 40 mg (base) for once-daily dosing and 35 mg (base) and 70 mg (base) for once-weekly dosing.

Reference is also made to the tentative approval letter issued by this office on December 27, 2002, and to your amendments dated December 28, 1999; April 29, 2005; December 12, 2006; October 19, November 20, and December 28, 2007; and January 2, and January 10, 2008.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Alendronate Sodium Tablets USP, 5 mg (base), 10 mg (base), 35 mg (base), 40 mg (base) and 70 mg (base), to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Fosamax Tablets, 5 mg (base), 10 mg (base), 35 mg (base), 40 mg (base) and 70 mg (base), respectively, of Merck and Co., Inc. (Merck). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, Merck's Fosamax Tablets, is subject to periods of patent protection. The following patents with their expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
4,621,077 (the '077 patent)	February 6, 2008*
5,358,941 (the '941 patent)	June 2, 2013*
5,681,590 (the '590 patent)	June 2, 2013*
5,849,726 (the '726 patent)	December 6, 2015*
5,994,329 (the '329 patent)	January 17, 2019*
6,008,207 (the '207 patent)	December 6, 2015*
6,015,801 (the '801 patent)	January 17, 2019*
6,090,410 (the '410 patent)	June 2, 2013*
6,225,294 (the '294 patent)	January 17, 2019*
6,194,004 (the '004 patent)	June 2, 2013*

* with pediatric exclusivity

To each of these 10 patents your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Alendronate Sodium Tablets USP, 5 mg (base), 10 mg (base), 35 mg (base), 40 mg (base) and 70 mg (base), under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against TEVA Pharmaceuticals USA (TEVA) for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. This action must have been brought against TEVA prior to the expiration of 45 days from the date the notice you provided under section 505(j)(2)(B)(i) was received by the NDA/patent holder(s). You have notified the agency that TEVA complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of the '004 patent was brought against TEVA within the statutory 45-day period, but litigation was initiated against TEVA for infringement of the other nine patents[1] in the United States District Court for the District of Delaware [Merck & Co., Inc. v. TEVA Pharmaceuticals USA, Inc., Civil Action Nos. 00-035, 01-675 and 01-728]. You have also notified the agency that the district court upheld the '077 and '329 patents and dismissed the cases with respect to the other seven patents. TEVA

[1] The actions for infringement of the '329, '801, and '294 patents pertained only to the 35 mg and 70 mg strengths.

appealed the ruling on the '329 patent to the United States Court of Appeals for the Federal Circuit [Merck & Co., Inc. v. TEVA Pharmaceuticals USA, Inc., No. 04-1005]. You have notified the agency that the Court of Appeals held the '329 patent to be invalid, unenforceable, or not infringed. Because the pediatric exclusivity period attaching to the'077 patent expired on February 6, 2008, under section 505(j)(5)(B)(iii) of the Act your ANDA is eligible for approval.

With respect to 180-day generic drug exclusivity, we note that TEVA was the first ANDA applicant to submit a substantially complete ANDA with paragraph IV certifications to the '077, '941, '590, '726, '329, '207, '801, and '410 patents. Therefore, with this approval, TEVA is eligible for 180 days of generic drug exclusivity for Alendronate Sodium Tablets USP, 5 mg (base), 10 mg (base), 35 mg (base), and 40 mg (base). With respect to Alendronate Sodium Tablets USP, 70 mg (base), TEVA will share 180-day generic exclusivity with Barr Laboratories Inc. (Barr) because Barr was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the '294 patent. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv).[1] Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in

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[1] Because your ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA)(Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 2070

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
2/6/2008 07:24:15 AM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-710

TENTATIVE APPROVAL LETTER

ANDA 75-710

DEC 27 2002

TEVA Pharmaceuticals USA
Attention: Deborah A. Jaskot
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 29, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Alendronate Sodium Tablets, 5 mg (base), 10 mg (base), 35 mg (base), 40 mg (base) and 70 mg (base).

Reference is also made to your amendment dated July 31, 2002. Reference is also made to your communications dated December 2, 1999; February 9, February 14, March 23, April 18, May 12, September 19, October 17, and December 20, 2000; February 13, February 28, March 21, April 24, May 23, August 27, October 16, October 19, October 23, December 4, December 5, and December 6, 2001 (2 submissions); and June 10, and October 7, 2002 addressing patent and exclusivity issues related to the reference listed drug product.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Although we are unable to grant final approval at this time due to ongoing litigation arising from various patent issues explained below and exclusivity issues pertaining to the reference listed drug, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention. This letter does

not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug product (RLD) upon which you have based your application, Fosamax Tablets of Merck and Co. Inc., is currently subject to periods of patent protection. As currently listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange book"), these patents expire on August 6, 2007, (U.S. Patent No. 4,621,077 [the '077 patent]), December 2, 2012, (U.S. Patent Nos. 5,358,941 [the '941 patent], 5,681,590 [the '590 patent], 6,090,410 [the '410 patent], and 6,194,004 [the '004 patent]), June 6, 2015, (U.S. Patent No. 5,849,726 [the '726 patent] and 6,008,207, [the '207 patent]), and July 17, 2018 (U.S. patent No. 5,994,329 [the '329 patent], 6,015,801 [the '801 patent] and 6,225,294 [the '294 patent]).

Your application contains Paragraph IV patent certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of this drug product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless an action is brought against TEVA Pharmaceuticals USA (TEVA) for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be brought against TEVA prior to the expiration of forty-five (45) days from the date the notices your provided to the patent/NDA holder(s) under paragraph (2)(B)(I) was received. You have notified the agency that TEVA complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, a patent infringement suit was brought against you in the United States District Court for the District of Delaware involving a challenge to the '077, '941, '590, '726, '329, '207, '410 (35 mg and 70 mg strengths only), '801, and '294 patents (Merck & Co., Inc. v. TEVA Pharmaceuticals USA, Inc., Civil Action No. C.A. 00-035, 01-675 and 01-728. You have also informed us that no legal action regarding the '004 patent was brought against TEVA within the statutory 45-day period.

Therefore, final approval of this application cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has

extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

b. the date of court decision [505(j)(5)(B)(iii)(I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,

c. all patents have expired and pending exclusivity issues have been resolved, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED between 60 - 90 days prior to the date you believe your application will be eligible for final approval. This amendment should notify the agency of the legal or regulatory events that may affect the effective date of final approval, and should include:

1. A copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

b. a statement that no such changes have been made to the application since the date of tentative approval.

In addition to, or instead of, the amendment referred to above, the Agency may, at any time prior to the final date of approval, request that you submit an amendment containing the information requested above. Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to Agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to current OGD policy. The submission of multiple amendments prior to final approval is discouraged.

Please note that this drug product may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the "Orange Book".

For further information on the status of this application, or prior to submitting future amendments, Wanda Pamphile, Pharm.D., Project Manager, at 301-827-5848, for further instructions.

Sincerely yours,

Robert L. Lee for

12/27/2002

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-710
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-623/B.Cai/
HFD-623/S.Liu/ S.H.Liu 12/4/02
HFD-617/W.Pamphile/ W. Pam 11/26/02
HFD-613/A.Payne/ Payne 12/03/02
HFD-613/J.Grace/ 12/4/2002

V:\FIRMSNZ\TEVA\LTRS&REV\75710.TA.doc
F/T by: DJ 5/15/02 As revised:RLWest:7/24/02

TENTATIVE APPROVAL

12/16/02

Robert L. West
12/27/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-710

LABELING

NDC 0093-**5140**-56

ALENDRONATE SODIUM Tablets USP **5 mg***

*Each tablet contains 6.53 mg alendronate sodium (5 mg free acid equivalent).

℞ **only**

30 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

L22457 Rev. B 2/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-5140-56 8

02

NDC 0093-**5140**-01

ALENDRONATE SODIUM Tablets USP

5 mg*

*Each tablet contains 6.53 mg alendronate sodium (5 mg free acid equivalent).

℞ **only**

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

L22453 Rev. B 2/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-5140-01 8

02

NDC 0093-**5141**-56

ALENDRONATE SODIUM Tablets USP **10 mg***

*Each tablet contains 13.05 mg alendronate sodium (10 mg free acid equivalent).

℞ **only**

30 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

L22458 Rev. B 2/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-5141-56 02
3 5

NDC 0093-5141-01

ALENDRONATE SODIUM Tablets USP 10 mg*

*Each tablet contains 13.05 mg alendronate sodium (10 mg free acid equivalent).

℞ only

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

L22454 Rev. B 2/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-5141-01 02
3 5

NDC 0093-**5141**-10

ALENDRONATE SODIUM Tablets USP 10 mg*

*Each tablet contains 13.05 mg alendronate sodium (10 mg free acid equivalent).

℞ **only**

1000 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Rev. B 2/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-5141-10 7 02
3

NDC 0093-**5142**-56

ALENDRONATE SODIUM Tablets USP **40 mg***

*Each tablet contains 52.21 mg alendronate sodium (40 mg free acid equivalent).

℞ **only**

30 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

L22459 Rev. B 2/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-5142-56 2 02

NDC 0093-**5142**-01

ALENDRONATE SODIUM Tablets USP

40 mg*

*Each tablet contains 52.21 mg alendronate sodium (40 mg free acid equivalent).

℞ **only**

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Rev. B 2/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-5142-01 2

02

NDC 0093-**5172**-22

Once Weekly

ALENDRONATE SODIUM Tablets USP

35 mg*

℞ **only**

12 TABLETS

TEVA

***Each tablet contains 45.68 mg alendronate sodium (35 mg free acid equivalent).

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss. 12/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

00

0093-5172-22

NDC 0093-**5172**-01

Once Weekly

ALENDRONATE SODIUM Tablets USP

35 mg*

℞ **only**

100 TABLETS

TEVA

***Each tablet contains 45.68 mg alendronate sodium (35 mg free acid equivalent).

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss. 12/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

00

0093-5172-01

NDC 0093-**5171**-22

Once Weekly

ALENDRONATE SODIUM Tablets USP

70 mg*

℞ **only**

12 TABLETS

TEVA

***Each tablet contains 91.37 mg alendronate sodium (70 mg free acid equivalent).

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss. 12/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

00

0093-5171-22

NDC 0093-**5171**-01

Once Weekly

ALENDRONATE SODIUM Tablets USP

70 mg*

℞ **only**

100 TABLETS

TEVA

***Each tablet contains 91.37 mg alendronate sodium (70 mg free acid equivalent).

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Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss. 12/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

00

0093-5171-01

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.

N(01)00300093-5172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.

N(01)00300093-5172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.

N(01)00300093-5172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.

N(01)00300093-5172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
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Sellersville, PA 18960
Lot# Exp.

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NDC 0093-**5172**-19
Once Weekly
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SODIUM Tablet USP
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Sellersville, PA 18960
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Sellersville, PA 18960
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NDC 0093-**5172**-19
Once Weekly
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SODIUM Tablet USP
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Lot# Exp.

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NDC 0093-**5172**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.

N(01)00300093-5172194

NDC 0093-**5172**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
35 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.

N(01)00300093-5172194

NDC 0093-**5171**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
70 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)0030093-5171197

NDC 0093-**5171**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
70 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)0030093-5171197

NDC 0093-**5171**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
70 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)0030093-5171197

NDC 0093-**5171**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
70 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)0030093-5171197

NDC 0093-**5171**-19
Once Weekly
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SODIUM Tablet USP
70 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)0030093-5171197

NDC 0093-**5171**-19
Once Weekly
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TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)0030093-5171197

NDC 0093-**5171**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
70 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)0030093-5171197

NDC 0093-**5171**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
70 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)0030093-5171197

NDC 0093-**5171**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
70 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)0030093-5171197

NDC 0093-**5171**-19
Once Weekly
ALENDRONATE
SODIUM Tablet USP
70 mg (base)
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot# Exp.
N(01)0030093-5171197

NDC 0093-**5172**-19

Once Weekly

ALENDRONATE SODIUM Tablet USP

35 mg (base)

WEEK 1

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Lot#

Exp.

PEEL

N (01) 0 03 0093-5172 19 4

NDC 0093-**5172**-19

Once Weekly

ALENDRONATE SODIUM Tablet USP

35 mg (base)

WEEK 2

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Lot#

Exp.

PEEL

N (01) 0 03 0093-5172 19 4

NDC 0093-**5172**-19

Once Weekly

ALENDRONATE SODIUM Tablet USP

35 mg (base)

WEEK 3

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Lot#

Exp.

PEEL

N (01) 0 03 0093-5172 19 4

NDC 0093-**5172**-19

Once Weekly

ALENDRONATE SODIUM Tablet USP

35 mg (base)

WEEK 4
(Time to refill)

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Lot#

Exp.

PEEL

N (01) 0 03 0093-5172 19 4

NDC 0093-**5171**-19

Once Weekly

ALENDRONATE SODIUM Tablet USP

70 mg (base)

WEEK 1

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Lot#

Exp.

PEEL

N (01) 0 03 0093-5171 19 7

NDC 0093-**5171**-19

Once Weekly

ALENDRONATE SODIUM Tablet USP

70 mg (base)

WEEK 2

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Lot#

Exp.

PEEL

N (01) 0 03 0093-5171 19 7

NDC 0093-**5171**-19

Once Weekly

ALENDRONATE SODIUM Tablet USP

70 mg (base)

WEEK 3

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Lot#

Exp.

PEEL

N (01) 0 03 0093-5171 19 7

NDC 0093-**5171**-19

Once Weekly

ALENDRONATE SODIUM Tablet USP

70 mg (base)

WEEK 4
(Time to refill)

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Lot#

Exp.

PEEL

N (01) 0 03 0093-5171 19 7

GLUE FLAP AREA IS UNVARNISHED

Begin your morning activities... but don't lie down, eat, drink, or take other medication for at least 30 minutes. If you want to lie down after 30 minutes, you must eat breakfast first.

Remember to take one alendronate sodium tablet once each week on that same day for as long as your doctor prescribes it.

If you miss a dose, take only one alendronate sodium tablet on the morning after you remember. *Do not take two tablets on the same day.* Return to taking one tablet once a week, as originally scheduled on your chosen day.

There is important additional information about how to take *Once Weekly* alendronate sodium tablets in the enclosed Patient Information leaflet. Please read it carefully.

Important information:
Please read the enclosed Patient Information leaflet before taking *Once Weekly* alendronate sodium tablets. Keep this and all drugs out of the reach of children.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

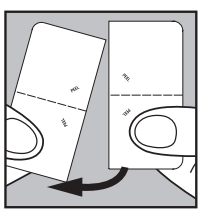
Lot XXXX
Exp XXXX

Mat. No. C22532

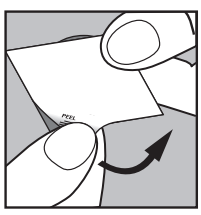
Iss. 12/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

How to remove tablets:



1. Tear blister card at perforation.



2. Peel backing and push tablet through.

Apply Prescription Label Here

NDC 0093-**5171**-44
Once Weekly
Alendronate Sodium Tablets USP, 70 mg*
4 TABLETS

Iss. 12/2007

Mat. No. C22532

N 3 0093-5171-44 9

NDC 0093-**5171**-44

Once Weekly
ALENDRONATE SODIUM Tablets USP
70 mg*

For the treatment of osteoporosis in postmenopausal women

***Each tablet contains 91.37 mg alendronate sodium (70 mg free acid equivalent).**

Osteoporosis is a disease that causes bones to become thin, weak, and easy to break.

That's why it is important you take *Once Weekly* alendronate sodium tablets to help protect your bones.

USUAL ADULT DOSAGE:
ONE 70 mg TABLET ONCE WEEKLY

See accompanying circular for complete dosage information.

Unit-of-Use dispense in original package.

℞ **only**

4 TABLETS

TEVA

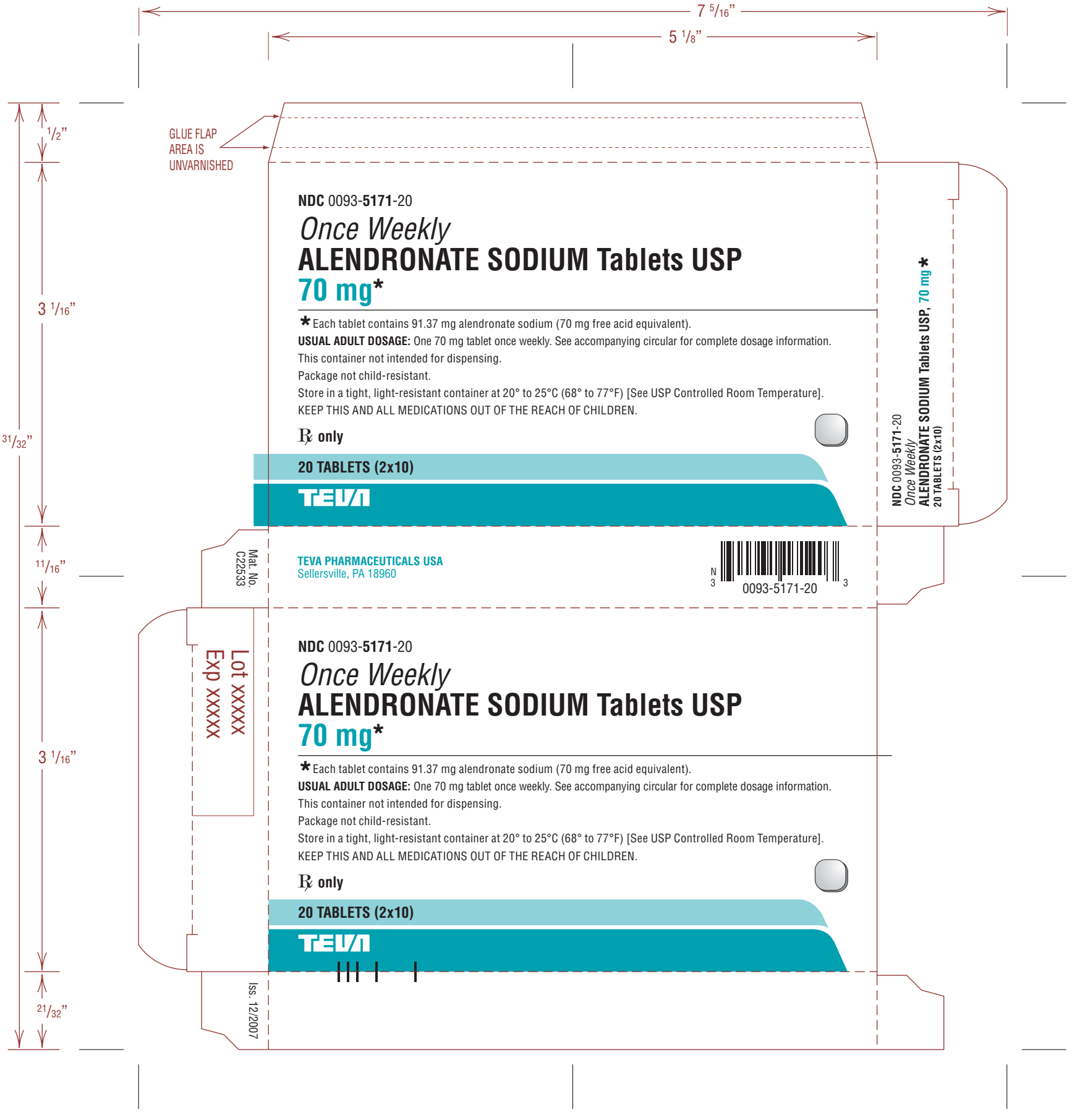
How to take *Once Weekly* alendronate sodium tablets, 70 mg

Choose the day of the week that best fits your schedule.
Every week, take one alendronate sodium tablet on your chosen day.

After getting up for the day on your chosen day of the week, swallow (do not chew or suck) one alendronate sodium tablet with a full glass (6 to 8 oz.) of plain water, on an empty stomach. Do not take alendronate sodium tablets at bedtime or before arising for the day.

Choose your day for taking *Once Weekly* alendronate sodium tablets, 70 mg

SUN	MON	TUE	WED	THU	FRI	SAT


7 5/16"
5 1/8"
1/2"
3 1/16"
7 31/32"
11/16"
3 1/16"
21/32"
GLUE FLAP AREA IS UNVARNISHED
NDC 0093-5171-20
Once Weekly
ALENDRONATE SODIUM Tablets USP
70 mg*
*Each tablet contains 91.37 mg alendronate sodium (70 mg free acid equivalent).
USUAL ADULT DOSAGE: One 70 mg tablet once weekly. See accompanying circular for complete dosage information.
This container not intended for dispensing.
Package not child-resistant.
Store in a tight, light-resistant container at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
℞ only
20 TABLETS (2x10)
TEVA
NDC 0093-5171-20 Once Weekly ALENDRONATE SODIUM Tablets USP, 70 mg* 20 TABLETS (2x10)
Mat. No. C22533
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
N 3 0093-5171-20 3
Lot XXXXX
Exp XXXXX
Iss. 12/2007

6 13/16"
4 5/8"
3 19/32"
11/16"
3 5/8"
23/32"
3 9/16"
15 7/32"
3"

GLUE FLAP AREA IS UNVARNISHED

Begin your morning activities... but don't lie down, eat, drink, or take other medication for at least 30 minutes. If you want to lie down after 30 minutes, you must eat breakfast first.

Remember to take one alendronate sodium tablet once each week on that same day for as long as your doctor prescribes it.

If you miss a dose, take only one alendronate sodium tablet on the morning after you remember. *Do not take two tablets on the same day.* Return to taking one tablet once a week, as originally scheduled on your chosen day.

There is important additional information about how to take *Once Weekly* alendronate sodium tablets in the enclosed Patient Information leaflet. Please read it carefully.

Important information:
Please read the enclosed Patient Information leaflet before taking *Once Weekly* alendronate sodium tablets. Keep this and all drugs out of the reach of children.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

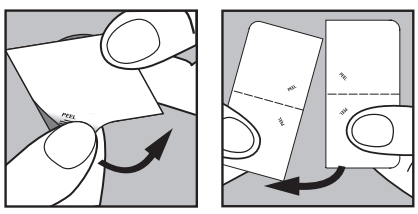
Lot XXXX
Exp XXXX

Mat. No. C22530

Iss. 12/2007

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

How to remove tablets:



1. Tear blister card at perforation.
2. Peel backing and push tablet through.

Apply Prescription Label Here

NDC 0093-**5172**-44
Once Weekly
Alendronate Sodium Tablets USP, 35 mg*
4 TABLETS

Iss. 12/2007

Mat. No. C22530

N 3 0093-5172-44 6

NDC 0093-**5172**-44

Once Weekly
ALENDRONATE SODIUM Tablets USP
35 mg*

For the prevention of osteoporosis in postmenopausal women

***Each tablet contains 45.68 mg alendronate sodium (35 mg free acid equivalent).**

Osteoporosis is a disease that causes bones to become thin, weak, and easy to break.

That's why it is important you take *Once Weekly* alendronate sodium tablets to help protect your bones.

USUAL ADULT DOSAGE:
ONE 35 mg TABLET ONCE WEEKLY

See accompanying circular for complete dosage information.

Unit-of-Use dispense in original package.

℞ **only**

4 TABLETS

TEVA

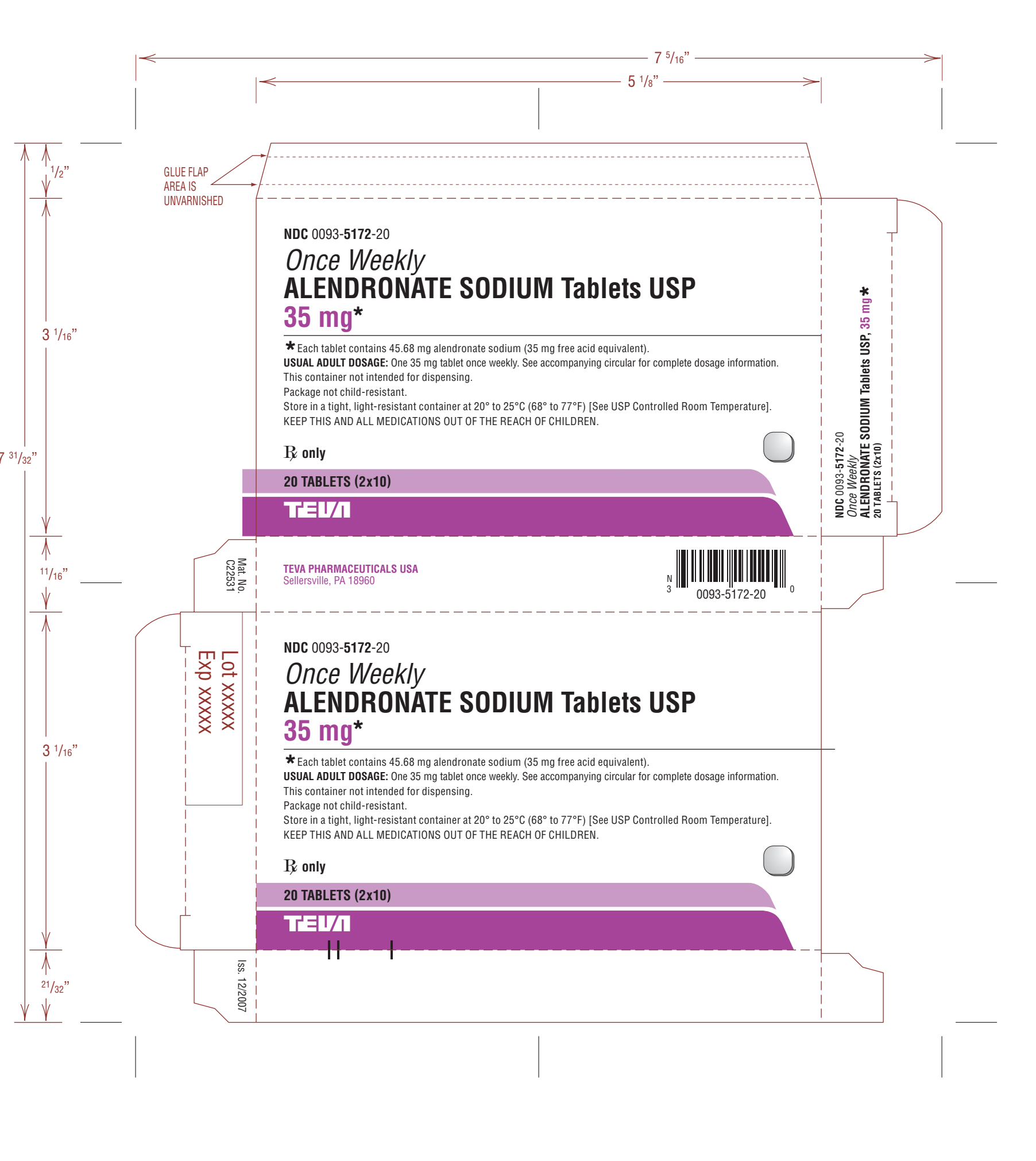
How to take *Once Weekly* alendronate sodium tablets, 35 mg

Choose the day of the week that best fits your schedule.
Every week, take one alendronate sodium tablet on your chosen day.

After getting up for the day on your chosen day of the week, swallow (do not chew or suck) one alendronate sodium tablet with a full glass (6 to 8 oz.) of plain water, on an empty stomach. Do not take alendronate sodium tablets at bedtime or before arising for the day.

Choose your day for taking *Once Weekly* alendronate sodium tablets, 35 mg

SUN	MON	TUE	WED	THU	FRI	SAT


7 5/16"
5 1/8"
1/2"
3 1/16"
7 31/32"
11/16"
3 1/16"
21/32"
GLUE FLAP AREA IS UNVARNISHED
NDC 0093-5172-20
Once Weekly
ALENDRONATE SODIUM Tablets USP
35 mg*
*Each tablet contains 45.68 mg alendronate sodium (35 mg free acid equivalent).
USUAL ADULT DOSAGE: One 35 mg tablet once weekly. See accompanying circular for complete dosage information.
This container not intended for dispensing.
Package not child-resistant.
Store in a tight, light-resistant container at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
℞ only
20 TABLETS (2x10)
TEVA
NDC 0093-5172-20 Once Weekly ALENDRONATE SODIUM Tablets USP, 35 mg* 20 TABLETS (2x10)
Mat. No. C22531
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
N 3 0093-5172-20 0
Lot XXXXX
Exp XXXXX
Iss. 12/2007

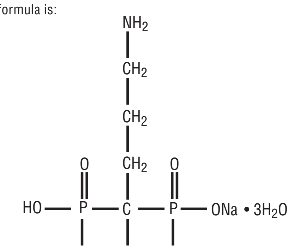
ALENDRONATE
SODIUM TABLETS USP
5140
5141
5172
5142
5171
℞ only
Iss. 12/2007

DESCRIPTION

Alendronate sodium is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The structural formula is:



$C_4H_{12}NNaO_7P_2•3H_2O$ M.W. 325.12

Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Each tablet, for oral administration contains 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

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 [^{3}H]alendronate in bone showed about 10 fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]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.

Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with alendronate sodium (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric

Alendronate is not indicated for use in children. Due to Merck's marketing exclusivity rights, this generic drug product is not approved with descriptive pharmacokinetic information in pediatric patients. Merck's alendronate sodium tablets and oral solution are approved with that descriptive pharmacokinetic information.

Gender

Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric

Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION**).

Race

Pharmacokinetic differences due to race have not been studied.

Renal insufficiency

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). **Alendronate sodium 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.**

Hepatic insufficiency

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.

Drug Interactions

(Also see **PRECAUTIONS**, **Drug Interactions**.)

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

Pharmacodynamics

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in Postmenopausal Women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50 fold and the risk of vertebral fracture 15 to 30 fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with alendronate sodium 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received alendronate sodium 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with alendronate sodium. In osteoporosis treatment studies alendronate sodium 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau after 6 to 12 months. In osteoporosis prevention studies alendronate sodium 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with once weekly alendronate sodium 70 mg for the treatment of osteoporosis and once weekly alendronate sodium 35 mg for the prevention of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with alendronate sodium. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of alendronate sodium 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment; however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with alendronate sodium 5 mg/day. In one-year studies with once weekly alendronate sodium 35 and 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to alendronate sodium but also a decrease in renal phosphate reabsorption.

Osteoporosis in Men

Treatment of men with osteoporosis with alendronate sodium 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly alendronate sodium 70 mg.

Glucocorticoid Induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to two years' duration, alendronate sodium 5 and 10 mg/day reduced cross-linked N-telopeptides of type I collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition of bone resorption, alendronate sodium 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

Paget's Disease of Bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

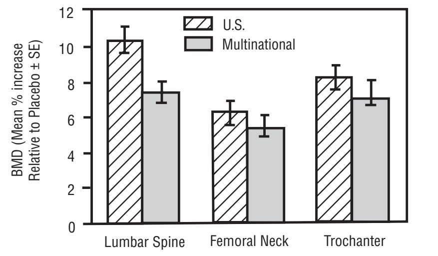
Alendronate sodium decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, alendronate sodium 40 mg once daily for six months produced significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, alendronate sodium induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

Clinical Studies

Treatment of Osteoporosis in Postmenopausal Women

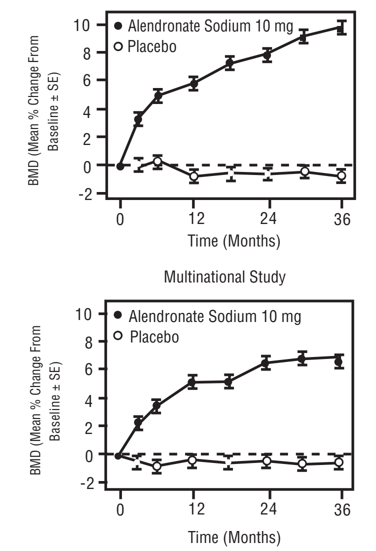
Effect on bone mineral density

The efficacy of alendronate sodium 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving alendronate sodium 10 mg/day relative to placebo-treated patients at three years for each of these studies.



Osteoporosis Treatment Studies in Postmenopausal Women Increase in BMD Alendronate Sodium 10 mg/day at Three Years

At three years significant increases in BMD, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received alendronate sodium 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the three years of treatment. (See figures below for lumbar spine results.) In the two-year extension of these studies, treatment of 147 patients with alendronate sodium 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. Alendronate sodium was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at least 2 standard deviations below the premenopausal mean). Thus, overall alendronate sodium reverses the loss of bone mineral density, a central factor in the progression of osteoporosis.



Osteoporosis Treatment Studies in Postmenopausal Women Time Course of Effect of Alendronate Sodium 10 mg/day Versus Placebo: Lumbar Spine BMD Percent Change From Baseline

In patients with postmenopausal osteoporosis treated with alendronate sodium 10 mg/day for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups. These data indicate that continued treatment with alendronate sodium is required to maintain the effect of the drug.

The therapeutic equivalence of once weekly alendronate sodium 70 mg (n = 519) and alendronate sodium 10 mg daily (n = 370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70 mg once-weekly group (n = 440) and 5.4% (5.0, 5.8%; 95% CI) in the 10 mg daily group (n = 330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Effect on fracture incidence

Data on the effects of alendronate sodium on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

To assess the effects of alendronate sodium on the incidence of vertebral fractures (detected by digitized radiography; approximately one-third of these were clinically symptomatic), the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of alendronate sodium (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients treated with alendronate sodium experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received alendronate sodium had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study); approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial

Three-Year Study (Patients With at Least One Baseline Radiographic Vertebral Fracture)

This randomized, double-blind, placebo-controlled, 2027 patient study (alendronate sodium, n = 1022; placebo, n = 1005) demonstrated that treatment with alendronate sodium resulted in statistically significant reductions in fracture incidence at three years as shown in the table below.

Effect of Alendronate Sodium on Fracture Incidence in the Three-Year Study of FIT (patients with vertebral fracture at baseline)

	Percent of Patients			
	Alendronate Sodium (n = 1022)	Placebo (n = 1005)	Absolute Reduction in Fracture Incidents	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)†				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47***
≥ 2 new vertebral fractures	0.5	4.9	4.4	90***
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	26‡
≥ 1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54**
Hip fracture	1.1	2.2	1.1	51*
Wrist (forearm) fracture	2.2	4.1	1.9	48*

† Number evaluable for vertebral fractures: Alendronate sodium, n = 984; placebo, n = 966

* $p < 0.05$

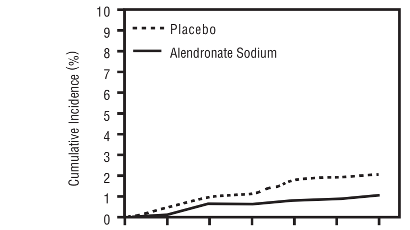
** $p < 0.01$

*** $p < 0.001$

‡ $p = 0.007$

Furthermore, in this population of patients with baseline vertebral fracture, treatment with alendronate sodium significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on alendronate sodium, p = 0.047. The figure below displays the cumulative incidence of hip fractures in this study.



Cumulative Incidence of Hip Fractures in the Three-Year Study of FIT (patients with radiographic vertebral fracture at baseline)

Fracture Intervention Trial

Four-Year Study (Patients With Low Bone Mass but Without a Baseline Radiographic Vertebral Fracture)

This randomized, double-blind, placebo-controlled, 4432-patient study (alendronate sodium, n = 2214; placebo, n = 2218) further investigated the reduction in fracture incidence due to alendronate sodium. The intent of the study was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

Effect of Alendronate Sodium on Fracture Incidence in Osteoporotic† Patients in the Four-Year Study of FIT (patients without vertebral fracture at baseline)

	Percent of Patients			
	Alendronate Sodium (n = 1545)	Placebo (n = 1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (%)
Patients with:				
Vertebral fractures (diagnosed by X-ray)††				
≥ 1 new vertebral fracture	2.5	4.8	2.3	48***
≥ 2 new vertebral fractures	0.1	0.6	0.5	78*
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22**
≥ 1 clinical (symptomatic) vertebral fracture	1.0	1.6	0.6	41 (NS)†††
Hip fracture	1.0	1.4	0.4	29 (NS)†††
Wrist (forearm) fracture	3.9	3.8	-0.1	NS†††

† Baseline femoral neck BMD at least 2 SD below the mean for young adult women

†† Number evaluable for vertebral fractures: Alendronate sodium, n = 1426; placebo, n = 1428

††† Not significant. This study was not powered to detect differences at these sites.

* $p = 0.035$

** $p = 0.01$

*** $p < 0.001$

Fracture results across studies

In the Three-Year Study of FIT, alendronate sodium reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, p < 0.001); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction, p = 0.001); and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, p = 0.034).

Alendronate sodium reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, p < 0.001) in the combined U.S./Multinational studies and from 4.9% to 0.5% (90% relative risk reduction, p < 0.001) in the Three-Year Study of FIT. In the Four-Year Study of FIT, alendronate sodium reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, p = 0.035).

Thus, alendronate sodium reduced the incidence of radiographic vertebral fractures in osteoporotic women whether or not they had a previous radiographic vertebral fracture.

Alendronate sodium, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.

Bone Histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with alendronate sodium at doses ranging from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed during therapy with alendronate is of normal quality.

Men

The efficacy of alendronate sodium in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.

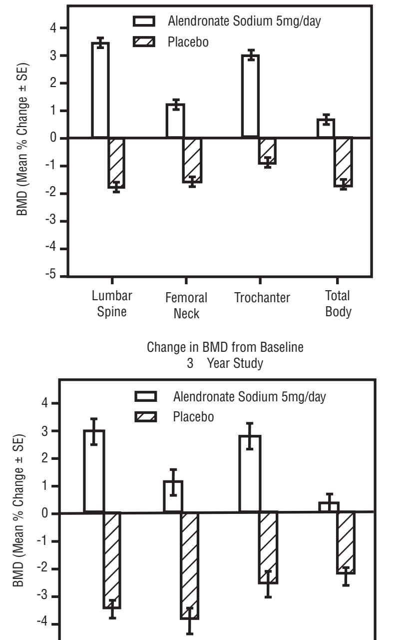
A two-year, double-blind, placebo-controlled, multicenter study of alendronate sodium 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score ≤ -2 at the femoral neck and ≤ -1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score ≤ -1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving alendronate sodium 10 mg/day were significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with alendronate sodium also reduced height loss (alendronate sodium, -0.6 mm vs. placebo, -2.4 mm).

A one-year, double-blind, placebo-controlled, multicenter study of once weekly alendronate sodium 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤ -2 at the femoral neck and ≤ -1 at the lumbar spine, 2) a BMD T-score ≤ -2 at the lumbar spine and ≤ -1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤ -1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving alendronate sodium 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

In both studies, BMD responses were similar regardless of age (≥ 65 years vs. < 65 years), gonadal function (baseline testosterone < 9 ng/dL vs. ≥ 9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤ -2.5 vs. > -2.5).

Prevention of Osteoporosis in Postmenopausal Women

Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40 to 60 years of age. One thousand six hundred nine patients (alendronate sodium 5 mg/day; n = 498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (alendronate sodium 5 mg/day; n = 88), who were between six months and three years postmenopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, alendronate sodium 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). In addition, alendronate sodium 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. Alendronate sodium 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.



Osteoporosis Prevention Studies in Postmenopausal Women

The therapeutic equivalence of once weekly alendronate sodium 35 mg (n = 362) and alendronate sodium 5 mg daily (n = 361) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35 mg once-weekly group (n = 307) and 3.2% (2.9, 3.5%; 95% CI) in the 5 mg daily group (n = 298). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Bone Histology

Bone histology was normal in the 28 patients biopsied at the end of three years who received alendronate sodium at doses of up to 10 mg/day.

Concomitant Use With Estrogen/Hormone Replacement Therapy (HRT)

The effects on BMD of treatment with alendronate sodium 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized postmenopausal osteoporotic women (n = 425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or alendronate sodium alone (both 6.0%).

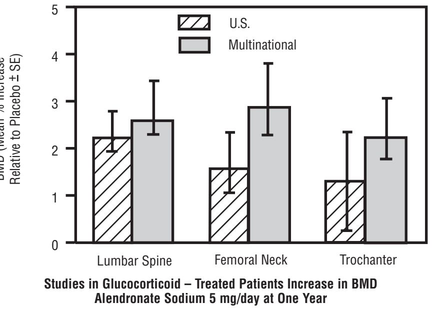
The effects on BMD when alendronate sodium was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n = 428). The addition of alendronate sodium 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with alendronate sodium and HRT, 94% on alendronate sodium alone, and 78% on HRT alone. The long-term effects of combined alendronate sodium and HRT on fracture occurrence and fracture healing have not been studied.

Glucocorticoid Induced Osteoporosis

The efficacy of alendronate sodium 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multicenter studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included alendronate sodium 2.5 mg/day]). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving alendronate sodium 5 mg/day for each study.



Studies in Glucocorticoid – Treated Patients Increase in BMD Alendronate Sodium 5 mg/day at One Year

After one year, significant increases relative to placebo in BMD were seen in the combined studies at each of these sites in patients who received alendronate sodium 5 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with alendronate sodium 5 mg/day. The increases in BMD with alendronate 10 mg/day were similar to those with alendronate sodium 5 mg/day in all patients except for postmenopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with alendronate sodium 10 mg/day were greater than those with alendronate sodium 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. Alendronate sodium was effective regardless of dose or duration of glucocorticoid use. In addition, alendronate sodium was similarly effective regardless of age (< 65 vs. ≥ 65 years), race (Caucasian vs. other races), gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

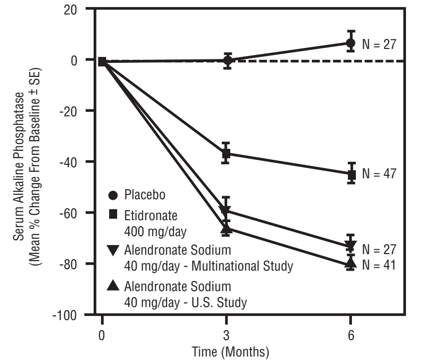
Bone histology was normal in the 49 patients biopsied at the end of one year who received alendronate sodium at doses of up to 10 mg/day.

Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with alendronate sodium 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

After one year, 2.3% of patients treated with alendronate sodium 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with alendronate sodium (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (alendronate sodium 0.7% vs. placebo 6.8%).

Paget's Disease of Bone

The efficacy of alendronate sodium 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled, multinational study and a U.S. comparative study with etidronate disodium 400 mg/day. The following figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.



Studies in Paget's Disease of Bone Effect on Serum Alkaline Phosphatase of Alendronate Sodium 40 mg/day Versus Placebo or Etidronate 400 mg/day

At six months the suppression in alkaline phosphatase in patients treated with alendronate sodium was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline ≥ 60%) occurred in approximately 85% of patients treated with alendronate sodium in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. Alendronate sodium was similarly effective regardless of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with alendronate sodium 40 mg/day for 6 months. As in patients treated for osteoporosis (see **Clinical Studies**, ***Treatment of Osteoporosis in Postmenopausal Women***, ***Bone Histology***), alendronate sodium did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with alendronate sodium, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with alendronate sodium is of normal quality.

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000 fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE

Alendronate sodium tablets are indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women
  - For the treatment of osteoporosis, alendronate sodium tablets increase bone mass and reduce the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture (see **CLINICAL PHARMACOLOGY**, **Pharmacodynamics**).
  - For the prevention of osteoporosis, alendronate sodium tablets may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture. Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of alendronate sodium for prevention of osteoporosis.
- Treatment to increase bone mass in men with osteoporosis
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see **PRECAUTIONS**, ***Glucocorticoid-induced osteoporosis***). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.
- Treatment of Paget's disease of bone in men and women
  - Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Hypersensitivity to any component of this product
- Hypocalcemia (see **PRECAUTIONS**, **General**)

WARNINGS

Alendronate sodium, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with alendronate sodium. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue alendronate sodium and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking alendronate sodium and/or who fail to swallow it with the recommended amount of water, and/or who continue to take alendronate sodium after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see **DOSAGE AND ADMINISTRATION**). In patients who cannot comply with dosing instructions due to mental disability, therapy with alendronate sodium should be used under appropriate supervision.

Because of possible irritant effects of alendronate sodium on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when alendronate sodium is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

There have been postmarketing reports of gastric and duodenal ulcers, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with alendronate sodium (see **CONTRAINDICATIONS**). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with alendronate sodium.

Presumably due to the effects of alendronate sodium on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see **ADVERSE REACTIONS**). However, such reports have been infrequent. This category of drugs includes alendronate sodium. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of alendronate sodium, the percentages of patients with these symptoms were similar in the alendronate sodium and placebo groups.

Dental

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., preexisting dental disease, anemia, and coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Renal insufficiency

Alendronate sodium is not recommended for patients with renal insufficiency (creatinine clearance < 35 mL/min) (see **DOSAGE AND ADMINISTRATION**).

Glucocorticoid-induced osteoporosis

The risk versus benefit of alendronate sodium for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see **INDICATIONS AND USAGE**). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined alendronate sodium and glucocorticoid treatment.

The efficacy of alendronate sodium for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of alendronate sodium has been established in studies of two years' duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of alendronate sodium beyond two years has not been studied.

The efficacy of alendronate sodium in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

Physicians should instruct their patients to read the patient package insert before starting therapy with alendronate sodium and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of alendronate sodium may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of alendronate sodium (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**, ***Absorption***).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of alendronate sodium with a full glass of water (6 to 8 oz). Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take alendronate sodium at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking alendronate sodium and consult their physician.

Patients should be instructed that if they miss a dose of once weekly alendronate sodium, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Drug Interactions

(Also see **CLINICAL PHARMACOLOGY, Pharmacokinetics**, ***Drug Interactions***.)

Estrogen/Hormone Replacement Therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and alendronate sodium was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined alendronate sodium and HRT on fracture occurrence have not been studied (see **CLINICAL PHARMACOLOGY**, **Clinical Studies**, ***Concomitant Use With Estrogen/Hormone Replacement Therapy (HRT)*** and **ADVERSE REACTIONS**, **Clinical Studies**, ***Concomitant use with estrogen/hormone replacement therapy***).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of alendronate sodium. Therefore, patients must wait at least one-half hour after taking alendronate sodium 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 alendronate sodium greater than 10 mg and aspirin-containing products.

PATIENT INFORMATION ABOUT ONCE DAILY ALENDRONATE SODIUM TABLETS USP

℞ only

Read this information before you start taking alendronate sodium tablets USP. Also, read the leaflet each time you refill your prescription, just in case anything has changed. This leaflet does not take the place of discussions with your doctor. You and your doctor should discuss alendronate sodium tablets USP when you start taking your medicine and at regular checkups.

What is the most important information I should know about alendronate sodium tablets USP?

- **You must take alendronate sodium tablets USP exactly as directed to help make sure they work and to help lower the chance of problems in your esophagus (the tube that connects your mouth and stomach). (See "How should I take alendronate sodium tablets USP?".)**
- **If you have chest pain, new or worsening heartburn, or have trouble or pain when you swallow, stop taking alendronate sodium tablets USP and call your doctor. (See "What are the possible side effects of alendronate sodium tablets USP?".)**

What are alendronate sodium tablets USP?

Alendronate sodium tablets USP are a prescription medicine for:

- The treatment or prevention of osteoporosis (thinning of bone) in women after menopause. They reduce the chance of having a hip or spinal fracture (break).
- Treatment to increase bone mass in men with osteoporosis.
- The treatment of osteoporosis in either men or women who are taking corticosteroid medicines (for example, prednisone).

Improvement in bone density may be observed as early as 3 months after you start taking alendronate sodium tablets USP even though you won't see or feel a difference. For alendronate sodium tablets USP to continue to work, you need to keep taking them.

Alendronate sodium tablets USP are not hormones.

There is more information about osteoporosis at the end of this leaflet.

Who should not take alendronate sodium tablets USP?

Do not take alendronate sodium tablets USP if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in your blood
- Are allergic to alendronate sodium tablets USP or any of their ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before using alendronate sodium tablets USP?

Tell your doctor about all of your medical conditions, including if you:

- **have problems with swallowing**
- **have stomach or digestive problems**
- **have kidney problems**
- **are pregnant or planning to become pregnant.** It is not known if alendronate sodium tablets USP can harm your unborn baby.
- **are breastfeeding.** It is not known if alendronate sodium tablets USP pass into your milk and if they can harm your baby.

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take alendronate sodium tablets USP?

- Take 1 alendronate sodium tablet USP once a day, every day **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take alendronate sodium tablets USP while you are sitting or standing.
- Swallow your alendronate sodium tablet USP with a full glass (6 to 8 oz) of plain water only.

Do **not** take alendronate sodium tablets USP with:

Mineral water

Coffee or tea

Juice

Alendronate sodium tablets USP work only if taken on an empty stomach.

Do not chew or suck on an alendronate sodium tablet USP.

After swallowing your alendronate sodium tablet USP, wait at least 30 minutes:

- before you lie down. You may sit, stand or walk, and do normal activities like reading.
- before you take your first food or drink except for plain water.
- before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down until after first food of the day.

- It is important that you keep taking alendronate sodium tablets USP for as long as your doctor says to take them. For alendronate sodium tablets USP to continue to work, you need to keep taking them.

What should I do if I miss a dose of alendronate sodium tablets USP or if I take too many?

- If you miss a dose, do not take it later in the day. Continue your usual schedule of 1 tablet once a day the next morning.
- If you think you took more than the prescribed dose of alendronate sodium tablets USP, drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

What should I avoid while taking alendronate sodium tablets USP?

- Do not eat, drink, or take other medicines or supplements **before** taking alendronate sodium tablets USP.
- Wait for at least 30 minutes **after** taking alendronate sodium tablets USP to eat, drink, or take other medicines or supplements.
- Do not lie down for at least 30 minutes **after** taking alendronate sodium tablets USP. Do not lie down until **after** your first food of the day.

What are the possible side effects of alendronate sodium tablets USP?

Alendronate sodium tablets USP may cause problems in your esophagus (the tube that connects the mouth and stomach). (See "**What is the most important information I should know about alendronate sodium tablets USP?**".) These problems include irritation, inflammation, or ulcers of the esophagus, which may sometimes bleed. This may occur especially if you do not drink a full glass of water with alendronate sodium tablets USP or if you lie down in less than 30 minutes or before your first food of the day.

- **Stop taking alendronate sodium tablets USP and call your doctor right away if you get any of these signs of possible serious problems of the esophagus:**
  - **Chest pain**
  - **New or worsening heartburn**
  - **Trouble or pain when swallowing**
- Esophagus problems may get worse if you continue to take alendronate sodium tablets USP.
- Mouth sores (ulcers) may occur if the alendronate sodium tablets USP are chewed or dissolved in the mouth.
- You may get flu-like symptoms typically at the start of treatment with alendronate sodium tablets USP.
- You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.
- Alendronate sodium tablets USP may cause jaw-bone problems in some people. Jaw-bone problems may include infection, and delayed healing after teeth are pulled.
- The most common side effect is stomach area (abdominal) pain. Less common side effects are nausea, vomiting, a full or bloated feeling in the stomach, constipation, diarrhea, black or bloody stools (bowel movements), gas, eye pain, rash that may be made worse by sunlight, headache, dizziness, a changed sense of taste, joint swelling or swelling in the hands or legs, and bone, muscle, or joint pain.
- **Call your doctor if you develop severe bone, muscle, or joint pain.**

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects with alendronate sodium tablets USP. Ask your doctor or pharmacist for more information.

How do I store alendronate sodium tablets USP?

- Store alendronate sodium tablets USP at room temperature, 68° to 77°F (20° to 25°C).
- Safely discard alendronate sodium tablets USP that are out-of-date or no longer needed.
- **Keep alendronate sodium tablets USP and all medicines out of the reach of children.**

General information about using alendronate sodium tablets USP safely and effectively

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use alendronate sodium tablets USP for a condition for which they were not prescribed. Do not give alendronate sodium tablets USP to other people, even if they have the same symptoms you have. It may harm them.

Alendronate sodium tablets USP are not indicated for use in children.

This leaflet is a summary of information about alendronate sodium tablets USP. If you have any questions or concerns about alendronate sodium tablets USP or osteoporosis, talk to your doctor, pharmacist, or other health care provider. You can ask your doctor or pharmacist for information about alendronate sodium tablets USP written for health care providers. For more information, call 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in alendronate sodium tablets USP?

Alendronate sodium tablets USP contain alendronate sodium as the active ingredient and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.

At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, your spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who:

- Are going through or who are past menopause

Men who:

- Are elderly

People who:

- Are white (Caucasian) or oriental (Asian)
- Are thin
- Have family member with osteoporosis
- Do not get enough calcium or vitamin D
- Do not exercise
- Smoke
- Drink alcohol often
- Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help prevent or treat osteoporosis?

In addition to alendronate sodium tablets USP, your doctor may suggest one or more of the following lifestyle changes:

- **Stop smoking.** Smoking may increase your chance of getting osteoporosis.
- **Reduce the use of alcohol.** Too much alcohol may increase the risk of osteoporosis and injuries that can cause fractures.
- **Exercise regularly.** Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.
- **Eat a balanced diet.** Having enough calcium in your diet is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements, such as calcium or vitamin D.

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Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Alendronate sodium 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 alendronate sodium 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 alendronate sodium.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p = 0.003) in a 92 week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p = 0.003) in a 2 year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy
Teratogenic Effects
Pregnancy category C
Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

There are no studies in pregnant women. Alendronate sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers
It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when alendronate sodium is administered to nursing women.

Pediatric Use
The efficacy and safety of alendronate sodium were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4 to 18 years, with severe osteogenesis imperfecta. One hundred-and-nine patients were randomized to 5 mg alendronate sodium daily (weight < 40 kg) or 10 mg alendronate sodium daily (weight ≥ 40 kg) and 30 patients to placebo. The mean baseline lumbar spine 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 alendronate sodium treated patients and 0.1 in the placebo-treated patients. Treatment with alendronate sodium did not reduce the risk of fracture. Sixteen percent of the alendronate sodium 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 alendronate sodium-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 alendronate sodium and placebo groups in reduction of bone pain.

Alendronate sodium tablets are not indicated for use in children. (For clinical adverse experiences in children, see **ADVERSE REACTIONS**, **Clinical Studies**, ***Osteogenesis Imperfecta***.*)*

Geriatric Use
Of the patients receiving alendronate sodium 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 alendronate sodium in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see **CLINICAL PHARMACOLOGY, Clinical 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.

ADVERSE REACTIONS
Clinical Studies
In clinical studies of up to five years in duration adverse experiences associated with alendronate sodium usually were mild, and generally did not require discontinuation of therapy.

Alendronate sodium has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of Osteoporosis
Postmenopausal women
In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n = 994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with alendronate sodium 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n = 6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with alendronate sodium 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: alendronate sodium, 3.2%; placebo, 2.7%. In these study populations, 49 to 54% had a history of gastrointestinal disorders at baseline and 54 to 89% used non-steroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients treated with either alendronate sodium or placebo are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	United States/Multinational Studies		Fracture Intervention Trial	
	Alendronate Sodium* % (n = 196)	Placebo % (n = 397)	Alendronate Sodium** % (n = 3236)	Placebo % (n = 3223)
Gastrointestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle, or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
(continued)				
Nervous System/ Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

* 10 mg/day for three years
** 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred.

One patient treated with alendronate sodium (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and alendronate sodium were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of alendronate sodium in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of alendronate sodium in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with alendronate sodium 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly alendronate sodium 70 mg and alendronate sodium 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients in either treatment group are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	Once Weekly Alendronate Sodium 70 mg % (n = 519)	Alendronate Sodium 10 mg/day % (n = 370)
Gastrointestinal		
abdominal pain	3.7	3.0
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distention	1.0	1.4
constipation	0.8	1.6
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle, joint) pain	2.9	3.2
muscle cramp	0.2	1.1

Men
In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of alendronate sodium 10 mg/day and a one-year study of once weekly alendronate sodium 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for alendronate sodium 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly alendronate sodium 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥ 2% of patients treated with either alendronate sodium or placebo are presented in the following table.

Osteoporosis Studies in Men Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 2% of Patients

	Two-year Study		One-year Study	
	Alendronate Sodium 10 mg/day % (n = 146)	Placebo % (n = 95)	Once Weekly Alendronate Sodium 70 mg % (n = 109)	Placebo % (n = 58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

Prevention of Osteoporosis in Postmenopausal Women
The safety of alendronate sodium 5 mg/day in postmenopausal women 40 to 60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive alendronate sodium for either two or three years. In these studies the overall safety profiles of alendronate sodium 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with alendronate sodium 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly alendronate sodium 35 mg and alendronate sodium 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients treated with either once weekly alendronate sodium 35 mg, alendronate sodium 5 mg/day or placebo are presented in the following table.

Osteoporosis Prevention Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	Two/Three-Year Studies		One-Year Study	
	Alendronate Sodium 5 mg/ day % (n = 642)	Placebo % (n = 648)	Alendronate Sodium 5 mg/day % (n = 361)	Once Weekly Alendronate Sodium 35 mg % (n = 362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Concomitant use with estrogen/hormone replacement therapy
In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n = 853), the safety and tolerability profile of combined treatment with alendronate sodium 10 mg once daily and estrogen ± progestin (n = 354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis
In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of alendronate sodium 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients treated with either alendronate sodium 5 or 10 mg/day or placebo are presented in the following table:

One-Year Studies in Glucocorticoid-Treated Patients Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	Alendronate Sodium 10 mg/day % (n = 157)	Alendronate Sodium 5 mg/day % (n = 161)	Placebo % (n = 159)
Gastrointestinal			
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (alendronate sodium: n = 147) was consistent with that observed in the first year.

Paget's Disease of Bone
In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking alendronate sodium 40 mg/day for 3 to 12 months were similar to those in postmenopausal women treated with alendronate sodium 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking alendronate sodium 40 mg/day (17.7% alendronate sodium vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with alendronate sodium 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with alendronate sodium 40 mg/day and 2.4% of patients treated with placebo.

Osteogenesis Imperfecta
Alendronate sodium tablets are not indicated for use in children.

The overall safety profile of alendronate sodium in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with alendronate sodium. However, there was an increased occurrence of vomiting in OI patients treated with alendronate sodium compared to placebo. During the 24 month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with alendronate sodium and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of alendronate sodium 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates, including alendronate sodium. See **ADVERSE REACTIONS**, **Postmarketing Experience**, ***Body as a Whole***.

Laboratory Test Findings
In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking alendronate sodium versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dL (2.0 mM) and serum phosphate to ≤ 2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Postmarketing Experience
The following adverse reactions have been reported in postmarketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with alendronate sodium, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see **WARNINGS, PRECAUTIONS, Information for Patients**, and **DOSAGE AND ADMINISTRATION**).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see **PRECAUTIONS**, **Dental).**

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see **PRECAUTIONS**, ***Musculoskeletal Pain***); joint swelling.

Nervous system: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE
Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with alendronate sodium. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION
Alendronate sodium tablets must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see **PRECAUTIONS, Information for Patients**). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of alendronate sodium tablets (see **PRECAUTIONS, Drug Interactions**). Waiting less than 30 minutes, or taking alendronate sodium tablets with food, beverages (other than plain water) or other medications will lessen the effect of alendronate sodium tablets by decreasing its absorption into the body.

Alendronate sodium tablets should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, an alendronate sodium tablet should be swallowed with a full glass of water (6 to 8 oz). Patients should not lie down for at least 30 minutes and until after their first food of the day. Alendronate sodium tablets should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see **WARNINGS, PRECAUTIONS, Information for Patients**).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see **PRECAUTIONS, General**).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). Alendronate sodium tablets are not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min) due to lack of experience.

Treatment of Osteoporosis in Postmenopausal Women
(See **INDICATIONS AND USAGE**.)

The recommended dosage is:

- one 70 mg tablet once weekly

or

- one 10 mg tablet once daily

Treatment to Increase Bone Mass in Men With Osteoporosis
The recommended dosage is:

- one 70 mg tablet once weekly

or

- one 10 mg tablet once daily

Prevention of Osteoporosis in Postmenopausal Women
(See **INDICATIONS AND USAGE**.)

The recommended dosage is:

- one 35 mg tablet once weekly

or

- one 5 mg tablet once daily

The safety of treatment and prevention of osteoporosis with alendronate sodium has been studied for up to 7 years.

Treatment of Glucocorticoid-Induced Osteoporosis in Men and Women
The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's Disease of Bone in Men and Women
The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's Disease
In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with alendronate sodium tablets. Specific retreatment data are not available, although responses to alendronate sodium tablets were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with alendronate sodium tablets may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED
Alendronate sodium tablets USP, for oral administration, are available as:

5 mg - white to off-white, round flat-faced beveled-edge, unscored tablet debossed with "93" on one side and "5140" on the other side, in bottles of 30 and 100.

10 mg - white to off-white, round, convex, unscored tablet debossed with "93" on one side and "5141" on the other side, in bottles of 30, 100, and 1000.

35 mg – white to off-white, pillow-shaped, convex, unscored tablet debossed with "93" on one side and "5172" on the other side, in bottles of 12 and 100, unit-of-use blister package of 4, and unit dose packages of 20 (2x10).

40 mg - white to off-white, oval convex, unscored tablet debossed with "93" on one side and "5142" on the other side, in bottles of 30 and 100.

70 mg - white to off-white, pillow-shaped, convex, unscored tablet debossed with "93" on one side and "5171" on the other side, in bottles of 12 and 100, unit-of-use blister package of 4, and unit dose packages of 20 (2x10).

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

PATIENT INFORMATION ABOUT ONCE DAILY ALENDRONATE SODIUM TABLETS USP
Read this information before you start taking alendronate sodium tablets USP. Also, read the leaflet each time you refill your prescription, just in case anything has changed. This leaflet does not take the place of discussions with your doctor. You and your doctor should discuss alendronate sodium tablets USP when you start taking your medicine and at regular checkups.

What is the most important information I should know about alendronate sodium tablets USP?

- **You must take alendronate sodium tablets USP exactly as directed to help make sure they work and to help lower the chance of problems in your esophagus (the tube that connects your mouth and stomach). (See "How should I take alendronate sodium tablets USP?".)**
- **If you have chest pain, new or worsening heartburn, or have trouble or pain when you swallow, stop taking alendronate sodium tablets USP and call your doctor. (See "What are the possible side effects of alendronate sodium tablets USP?".)**

What are alendronate sodium tablets USP?

Alendronate sodium tablets USP are a prescription medicine for:

- The treatment or prevention of osteoporosis (thinning of bone) in women after menopause. They reduce the chance of having a hip or spinal fracture (break).
- Treatment to increase bone mass in men with osteoporosis.
- The treatment of osteoporosis in either men or women who are taking corticosteroid medicines (for example, prednisone).

Improvement in bone density may be observed as early as 3 months after you start taking alendronate sodium tablets USP even though you won't see or feel a difference. For alendronate sodium tablets USP to continue to work, you need to keep taking them.

Alendronate sodium tablets USP are not hormones.

There is more information about osteoporosis at the end of this leaflet.

Who should not take alendronate sodium tablets USP?

Do not take alendronate sodium tablets USP if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in your blood
- Are allergic to alendronate sodium tablets USP or any of their ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before using alendronate sodium tablets USP?

Tell your doctor about all of your medical conditions, including if you:

- **have problems with swallowing**
- **have stomach or digestive problems**
- **have kidney problems**
- **are pregnant or planning to become pregnant.** It is not known if alendronate sodium tablets USP can harm your unborn baby.
- **are breastfeeding.** It is not known if alendronate sodium tablets USP pass into your milk and if they can harm your baby.

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take alendronate sodium tablets USP?

- Take 1 alendronate sodium tablet USP once a day, every day **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take alendronate sodium tablets USP while you are sitting or standing.
- Swallow your alendronate sodium tablet USP with a full glass (6 to 8 oz) of plain water only.

Do **not** take alendronate sodium tablets USP with:

Mineral water

Coffee or tea

Juice

Alendronate sodium tablets USP work only if taken on an empty stomach.

Do not chew or suck on an alendronate sodium tablet USP.

After swallowing your alendronate sodium tablet USP, wait at least 30 minutes:

- before you lie down. You may sit, stand or walk, and do normal activities like reading.
- before you take your first food or drink except for plain water.
- before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down until after first food of the day.

- It is important that you keep taking alendronate sodium tablets USP for as long as your doctor says to take them. For alendronate sodium tablets USP to continue to work, you need to keep taking them.

What should I do if I miss a dose of alendronate sodium tablets USP or if I take too many?

- If you miss a dose, do not take it later in the day. Continue your usual schedule of 1 tablet once a day the next morning.
- If you think you took more than the prescribed dose of alendronate sodium tablets USP, drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

What should I avoid while taking alendronate sodium tablets USP?

- Do not eat, drink, or take other medicines or supplements **before** taking alendronate sodium tablets USP.
- Wait for at least 30 minutes **after** taking alendronate sodium tablets USP to eat, drink, or take other medicines or supplements.
- Do not lie down for at least 30 minutes **after** taking alendronate sodium tablets USP. Do not lie down until **after** your first food of the day.

What are the possible side effects of alendronate sodium tablets USP?

Alendronate sodium tablets USP may cause problems in your esophagus (the tube that connects the mouth and stomach). (See "**What is the most important information I should know about alendronate sodium tablets USP?**".) These problems include irritation, inflammation, or ulcers of the esophagus, which may sometimes bleed. This may occur especially if you do not drink a full glass of water with alendronate sodium tablets USP or if you lie down in less than 30 minutes or before your first food of the day.

- **Stop taking alendronate sodium tablets USP and call your doctor right away if you get any of these signs of possible serious problems of the esophagus:**
  - **Chest pain**
  - **New or worsening heartburn**
  - **Trouble or pain when swallowing**
- Esophagus problems may get worse if you continue to take alendronate sodium tablets USP.
- Mouth sores (ulcers) may occur if the alendronate sodium tablets USP are chewed or dissolved in the mouth.
- You may get flu-like symptoms typically at the start of treatment with alendronate sodium tablets USP.
- You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.
- Alendronate sodium tablets USP may cause jaw-bone problems in some people. Jaw-bone problems may include infection, and delayed healing after teeth are pulled.
- The most common side effect is stomach area (abdominal) pain. Less common side effects are nausea, vomiting, a full or bloated feeling in the stomach, constipation, diarrhea, black or bloody stools (bowel movements), gas, eye pain, rash that may be made worse by sunlight, headache, dizziness, a changed sense of taste, joint swelling or swelling in the hands or legs, and bone, muscle, or joint pain.
- **Call your doctor if you develop severe bone, muscle, or joint pain.**

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects with alendronate sodium tablets USP. Ask your doctor or pharmacist for more information.

How do I store alendronate sodium tablets USP?

- Store alendronate sodium tablets USP at room temperature, 68° to 77°F (20° to 25°C).
- Safely discard alendronate sodium tablets USP that are out-of-date or no longer needed.
- **Keep alendronate sodium tablets USP and all medicines out of the reach of children.**

General information about using alendronate sodium tablets USP safely and effectively

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use alendronate sodium tablets USP for a condition for which they were not prescribed. Do not give alendronate sodium tablets USP to other people, even if they have the same symptoms you have. It may harm them.

Alendronate sodium tablets USP are not indicated for use in children.

This leaflet is a summary of information about alendronate sodium tablets USP. If you have any questions or concerns about alendronate sodium tablets USP or osteoporosis, talk to your doctor, pharmacist, or other health care provider. You can ask your doctor or pharmacist for information about alendronate sodium tablets USP written for health care providers. For more information, call 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in alendronate sodium tablets USP?

Alendronate sodium tablets USP contain alendronate sodium as the active ingredient and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.

At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, your spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who:

- Are going through or who are past menopause

Men who:

- Are elderly

People who:

- Are white (Caucasian) or oriental (Asian)
- Are thin
- Have family member with osteoporosis
- Do not get enough calcium or vitamin D
- Do not exercise
- Smoke
- Drink alcohol often
- Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help prevent or treat osteoporosis?

In addition to alendronate sodium tablets USP, your doctor may suggest one or more of the following lifestyle changes:

- **Stop smoking.** Smoking may increase your chance of getting osteoporosis.
- **Reduce the use of alcohol.** Too much alcohol may increase the risk of osteoporosis and injuries that can cause fractures.
- **Exercise regularly.** Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.
- **Eat a balanced diet.** Having enough calcium in your diet is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements, such as calcium or vitamin D.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 12/2007

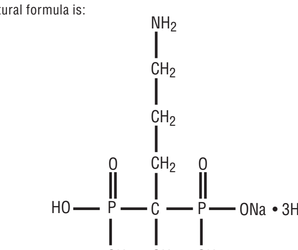
ALENDRONATE SODIUM TABLETS USP
5140
5141
5172
5142
5171
℞ only
Iss. 12/2007

DESCRIPTION

Alendronate sodium is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The structural formula is:



$C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ M.W. 325.12

Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Each tablet, for oral administration contains 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

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 [^{3}H]alendronate in bone showed about 10 fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]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.

Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with alendronate sodium (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric

Alendronate is not indicated for use in children. Due to Merck's marketing exclusivity rights, this generic drug product is not approved with descriptive pharmacokinetic information in pediatric patients. Merck's alendronate sodium tablets and oral solution are approved with that descriptive pharmacokinetic information.

Gender

Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric

Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION**).

Race

Pharmacokinetic differences due to race have not been studied.

Renal insufficiency

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). **Alendronate sodium 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.**

Hepatic insufficiency

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.

Drug Interactions

(Also see **PRECAUTIONS**, **Drug Interactions**.)

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

Pharmacodynamics

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in Postmenopausal Women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50 fold and the risk of vertebral fracture 15 to 30 fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with alendronate sodium 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received alendronate sodium 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with alendronate sodium. In osteoporosis treatment studies alendronate sodium 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau after 6 to 12 months. In osteoporosis prevention studies alendronate sodium 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with once weekly alendronate sodium 70 mg for the treatment of osteoporosis and once weekly alendronate sodium 35 mg for the prevention of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with alendronate sodium. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of alendronate sodium 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment; however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with alendronate sodium 5 mg/day. In one-year studies with once weekly alendronate sodium 35 and 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to alendronate sodium but also a decrease in renal phosphate reabsorption.

Osteoporosis in Men

Treatment of men with osteoporosis with alendronate sodium 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly alendronate sodium 70 mg.

Glucocorticoid Induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to two years' duration, alendronate sodium 5 and 10 mg/day reduced cross-linked N-telopeptides of type I collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition of bone resorption, alendronate sodium 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

Paget's Disease of Bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

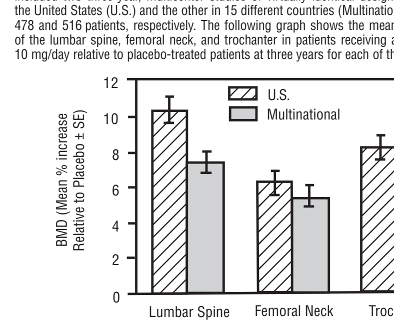
Alendronate sodium decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, alendronate sodium 40 mg once daily for six months produced significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, alendronate sodium induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

Clinical Studies

Treatment of Osteoporosis in Postmenopausal Women

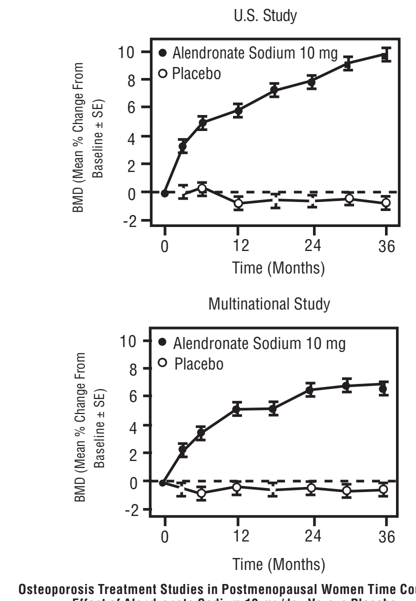
Effect on bone mineral density

The efficacy of alendronate sodium 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving alendronate sodium 10 mg/day relative to placebo-treated patients at three years for each of these studies.



Osteoporosis Treatment Studies in Postmenopausal Women Increase in BMD Alendronate Sodium 10 mg/day at Three Years

At three years significant increases in BMD, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received alendronate sodium 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the three years of treatment. (See figures below for lumbar spine results.) In the two-year extension of these studies, treatment of 147 patients with alendronate sodium 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. Alendronate sodium was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at least 2 standard deviations below the premenopausal mean). Thus, overall alendronate sodium reverses the loss of bone mineral density, a central factor in the progression of osteoporosis.



Osteoporosis Treatment Studies in Postmenopausal Women Time Course of Effect of Alendronate Sodium 10 mg/day Versus Placebo: Lumbar Spine BMD Percent Change From Baseline

In patients with postmenopausal osteoporosis treated with alendronate sodium 10 mg/day for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups. These data indicate that continued treatment with alendronate sodium is required to maintain the effect of the drug.

The therapeutic equivalence of once weekly alendronate sodium 70 mg (n = 519) and alendronate sodium 10 mg daily (n = 370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70 mg once-weekly group (n = 440) and 5.4% (5.0, 5.8%; 95% CI) in the 10 mg daily group (n = 330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Effect on fracture incidence

Data on the effects of alendronate sodium on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

To assess the effects of alendronate sodium on the incidence of vertebral fractures (detected by digitized radiography; approximately one-third of these were clinically symptomatic), the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of alendronate sodium (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients treated with alendronate sodium experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received alendronate sodium had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study); approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial

Three-Year Study (Patients With at Least One Baseline Radiographic Vertebral Fracture)

This randomized, double-blind, placebo-controlled, 2027 patient study (alendronate sodium, n = 1022; placebo, n = 1005) demonstrated that treatment with alendronate sodium resulted in statistically significant reductions in fracture incidence at three years as shown in the table below.

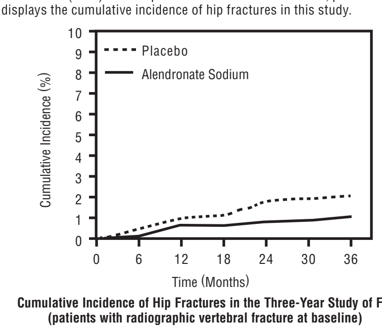
Effect of Alendronate Sodium on Fracture Incidence in the Three-Year Study of FIT (patients with vertebral fracture at baseline)

	Percent of Patients			
	Alendronate Sodium (n = 1022)	Placebo (n = 1005)	Absolute Reduction in Fracture Incidents	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)†				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47***
≥ 2 new vertebral fractures	0.5	4.9	4.4	90***
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	26‡
≥ 1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54**
Hip fracture	1.1	2.2	1.1	51*
Wrist (forearm) fracture	2.2	4.1	1.9	48*

† Number evaluable for vertebral fractures: Alendronate sodium, n = 984; placebo, n = 966
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$
‡ $p = 0.007$

Furthermore, in this population of patients with baseline vertebral fracture, treatment with alendronate sodium significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on alendronate sodium, p = 0.047. The figure below displays the cumulative incidence of hip fractures in this study.



Cumulative Incidence of Hip Fractures in the Three-Year Study of FIT (patients with radiographic vertebral fracture at baseline)

Fracture Intervention Trial

Four-Year Study (Patients With Low Bone Mass but Without a Baseline Radiographic Vertebral Fracture)

This randomized, double-blind, placebo-controlled, 4432-patient study (alendronate sodium, n = 2214; placebo, n = 2218) further investigated the reduction in fracture incidence due to alendronate sodium. The intent of the study was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

Effect of Alendronate Sodium on Fracture Incidence in Osteoporotic† Patients in the Four-Year Study of FIT (patients without vertebral fracture at baseline)

	Percent of Patients			
	Alendronate Sodium (n = 1545)	Placebo (n = 1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (%)
Patients with:				
Vertebral fractures (diagnosed by X-ray)††				
≥ 1 new vertebral fracture	2.5	4.8	2.3	48***
≥ 2 new vertebral fractures	0.1	0.6	0.5	78*
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22**
≥ 1 clinical (symptomatic) vertebral fracture	1.0	1.6	0.6	41 (NS)†††
Hip fracture	1.0	1.4	0.4	29 (NS)†††
Wrist (forearm) fracture	3.9	3.8	-0.1	NS†††

† Baseline femoral neck BMD at least 2 SD below the mean for young adult women
†† Number evaluable for vertebral fractures: Alendronate sodium, n = 1426; placebo, n = 1428
††† Not significant. This study was not powered to detect differences at these sites.
* $p = 0.035$
** $p = 0.01$
*** $p < 0.001$

Fracture results across studies

In the Three-Year Study of FIT, alendronate sodium reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, p < 0.001); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction, p = 0.001); and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, p = 0.034).

Alendronate sodium reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, p < 0.001) in the combined U.S./Multinational studies and from 4.9% to 0.5% (90% relative risk reduction, p < 0.001) in the Three-Year Study of FIT. In the Four-Year Study of FIT, alendronate sodium reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, p = 0.035).

Thus, alendronate sodium reduced the incidence of radiographic vertebral fractures in osteoporotic women whether or not they had a previous radiographic vertebral fracture.

Alendronate sodium, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.

Bone Histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with alendronate sodium at doses ranging from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed during therapy with alendronate is of normal quality.

Men

The efficacy of alendronate sodium in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.

A two-year, double-blind, placebo-controlled, multicenter study of alendronate sodium 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score ≤ -2 at the femoral neck and ≤ -1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score ≤ -1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving alendronate sodium 10 mg/day were significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with alendronate sodium also reduced height loss (alendronate sodium, -0.6 mm vs. placebo, -2.4 mm).

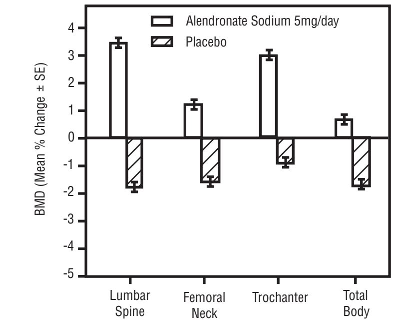
A one-year, double-blind, placebo-controlled, multicenter study of once weekly alendronate sodium 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤ -2 at the femoral neck and ≤ -1 at the lumbar spine, 2) a BMD T-score ≤ -2 at the lumbar spine and ≤ -1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤ -1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving alendronate sodium 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

In both studies, BMD responses were similar regardless of age (≥ 65 years vs. < 65 years), gonadal function (baseline testosterone < 9 ng/dL vs. ≥ 9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤ -2.5 vs. > -2.5).

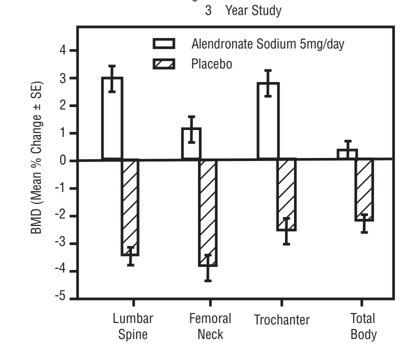
Prevention of Osteoporosis in Postmenopausal Women

Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40 to 60 years of age. One thousand six hundred nine patients (alendronate sodium 5 mg/day; n = 498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (alendronate sodium 5 mg/day; n = 88), who were between six months and three years postmenopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, alendronate sodium 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). In addition, alendronate sodium 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. Alendronate sodium 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.

Change in BMD from Baseline
2 Year Study



Change in BMD from Baseline
3 Year Study



Osteoporosis Prevention Studies in Postmenopausal Women

The therapeutic equivalence of once weekly alendronate sodium 35 mg (n = 362) and alendronate sodium 5 mg daily (n = 361) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35 mg once-weekly group (n = 307) and 3.2% (2.9, 3.5%; 95% CI) in the 5 mg daily group (n = 298). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Bone Histology

Bone histology was normal in the 28 patients biopsied at the end of three years who received alendronate sodium at doses of up to 10 mg/day.

Concomitant Use With Estrogen/Hormone Replacement Therapy (HRT)

The effects on BMD of treatment with alendronate sodium 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized postmenopausal osteoporotic women (n = 425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or alendronate sodium alone (both 6.0%).

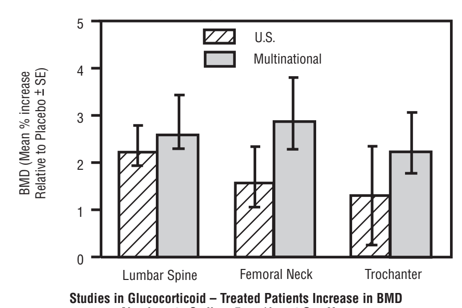
The effects on BMD when alendronate sodium was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n = 428). The addition of alendronate sodium 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with alendronate sodium and HRT, 94% on alendronate sodium alone, and 78% on HRT alone. The long-term effects of combined alendronate sodium and HRT on fracture occurrence and fracture healing have not been studied.

Glucocorticoid Induced Osteoporosis

The efficacy of alendronate sodium 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multicenter studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included alendronate sodium 2.5 mg/day]). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving alendronate sodium 5 mg/day for each study.



Studies in Glucocorticoid – Treated Patients Increase in BMD Alendronate Sodium 5 mg/day at One Year

After one year, significant increases relative to placebo in BMD were seen in the combined studies at each of these sites in patients who received alendronate sodium 5 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with alendronate sodium 5 mg/day. The increases in BMD with alendronate 10 mg/day were similar to those with alendronate sodium 5 mg/day in all patients except for postmenopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with alendronate sodium 10 mg/day were greater than those with alendronate sodium 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. Alendronate sodium was effective regardless of dose or duration of glucocorticoid use. In addition, alendronate sodium was similarly effective regardless of age (< 65 vs. ≥ 65 years), race (Caucasian vs. other races), gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

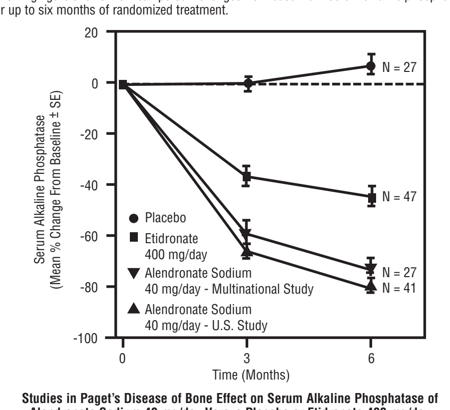
Bone histology was normal in the 49 patients biopsied at the end of one year who received alendronate sodium at doses of up to 10 mg/day.

Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with alendronate sodium 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

After one year, 2.3% of patients treated with alendronate sodium 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with alendronate sodium (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (alendronate sodium 0.7% vs. placebo 6.8%).

Paget's Disease of Bone

The efficacy of alendronate sodium 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled, multinational study and a U.S. comparative study with etidronate disodium 400 mg/day. The following figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.



Studies in Paget's Disease of Bone Effect on Serum Alkaline Phosphatase of Alendronate Sodium 40 mg/day Versus Placebo or Etidronate 400 mg/day

At six months the suppression in alkaline phosphatase in patients treated with alendronate sodium was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline ≥ 60%) occurred in approximately 85% of patients treated with alendronate sodium in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. Alendronate sodium was similarly effective regardless of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with alendronate sodium 40 mg/day for 6 months. As in patients treated for osteoporosis (see **Clinical Studies**, ***Treatment of Osteoporosis in Postmenopausal Women***, ***Bone Histology***), alendronate sodium did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with alendronate sodium, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with alendronate sodium is of normal quality.

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000 fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE

Alendronate sodium tablets are indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women
  - For the treatment of osteoporosis, alendronate sodium tablets increase bone mass and reduce the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture (see **CLINICAL PHARMACOLOGY**, **Pharmacodynamics**).
  - For the prevention of osteoporosis, alendronate sodium tablets may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture. Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of alendronate sodium for prevention of osteoporosis.
- Treatment to increase bone mass in men with osteoporosis
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see **PRECAUTIONS**, ***Glucocorticoid-induced osteoporosis***). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.
- Treatment of Paget's disease of bone in men and women
  - Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Hypersensitivity to any component of this product
- Hypocalcemia (see **PRECAUTIONS**, **General**)

WARNINGS

Alendronate sodium, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with alendronate sodium. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue alendronate sodium and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking alendronate sodium and/or who fail to swallow it with the recommended amount of water, and/or who continue to take alendronate sodium after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see **DOSAGE AND ADMINISTRATION**). In patients who cannot comply with dosing instructions due to mental disability, therapy with alendronate sodium should be used under appropriate supervision.

Because of possible irritant effects of alendronate sodium on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when alendronate sodium is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

There have been postmarketing reports of gastric and duodenal ulcers, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with alendronate sodium (see **CONTRAINDICATIONS**). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with alendronate sodium.

Presumably due to the effects of alendronate sodium on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see **ADVERSE REACTIONS**). However, such reports have been infrequent. This category of drugs includes alendronate sodium. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of alendronate sodium, the percentages of patients with these symptoms were similar in the alendronate sodium and placebo groups.

Dental

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., preexisting dental disease, anemia, and coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Renal insufficiency

Alendronate sodium is not recommended for patients with renal insufficiency (creatinine clearance < 35 mL/min) (see **DOSAGE AND ADMINISTRATION**).

Glucocorticoid-induced osteoporosis

The risk versus benefit of alendronate sodium for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see **INDICATIONS AND USAGE**). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined alendronate sodium and glucocorticoid treatment.

The efficacy of alendronate sodium for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of alendronate sodium has been established in studies of two years' duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of alendronate sodium beyond two years has not been studied.

The efficacy of alendronate sodium in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

Physicians should instruct their patients to read the patient package insert before starting therapy with alendronate sodium and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of alendronate sodium may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of alendronate sodium (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**, ***Absorption***).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of alendronate sodium with a full glass of water (6 to 8 oz). Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take alendronate sodium at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking alendronate sodium and consult their physician.

Patients should be instructed that if they miss a dose of once weekly alendronate sodium, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Drug Interactions

(Also see **CLINICAL PHARMACOLOGY, Pharmacokinetics**, ***Drug Interactions***.)

Estrogen/Hormone Replacement Therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and alendronate sodium was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined alendronate sodium and HRT on fracture occurrence have not been studied (see **CLINICAL PHARMACOLOGY**, **Clinical Studies**, ***Concomitant Use With Estrogen/Hormone Replacement Therapy (HRT)*** and **ADVERSE REACTIONS**, **Clinical Studies**, ***Concomitant use with estrogen/hormone replacement therapy***).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of alendronate sodium. Therefore, patients must wait at least one-half hour after taking alendronate sodium 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 alendronate sodium greater than 10 mg and aspirin-containing products.

PATIENT INFORMATION ABOUT ONCE WEEKLY ALENDRONATE SODIUM TABLETS USP

℞ only

Read this information before you start taking alendronate sodium tablets USP. Also, read the leaflet each time you refill your prescription, just in case anything has changed. This leaflet does not take the place of discussions with your doctor. You and your doctor should discuss alendronate sodium tablets USP when you start taking your medicine and at regular checkups.

What is the most important information I should know about once weekly alendronate sodium tablets USP?

- **You must take once weekly alendronate sodium tablets USP exactly as directed to help make sure they work and to help lower the chance of problems in your esophagus (the tube that connects your mouth and stomach). (See "How should I take once weekly alendronate sodium tablets USP?".)**
- **If you have chest pain, new or worsening heartburn, or have trouble or pain when you swallow, stop taking alendronate sodium tablets USP and call your doctor. (See "What are the possible side effects of alendronate sodium tablets USP?".)**

What are alendronate sodium tablets USP?

Alendronate sodium tablets USP are a prescription medicine for:

- The treatment or prevention of osteoporosis (thinning of bone) in women after menopause. They reduce the chance of having a hip or spinal fracture (break).
- Treatment to increase bone mass in men with osteoporosis.
- Alendronate sodium tablets USP are for treatment and prevention of osteoporosis.

Improvement in bone density may be observed as early as 3 months after you start taking alendronate sodium tablets USP even though you won't see or feel a difference. For alendronate sodium tablets USP to continue to work, you need to keep taking them.

Alendronate sodium tablets USP are not hormones.

There is more information about osteoporosis at the end of this leaflet.

Who should not take alendronate sodium tablets USP?

Do not take alendronate sodium tablets USP if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in your blood
- Are allergic to alendronate sodium tablets USP or any of their ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before using alendronate sodium tablets USP?

Tell your doctor about all of your medical conditions, including if you:

- **have problems with swallowing**
- **have stomach or digestive problems**
- **have kidney problems**
- **are pregnant or planning to become pregnant.** It is not known if alendronate sodium tablets USP can harm your unborn baby.
- **are breastfeeding.** It is not known if alendronate sodium tablets USP pass into your milk and if they can harm your baby.

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take once weekly alendronate sodium tablets USP?

- Choose the day of the week that best fits your schedule.
- Take 1 dose of alendronate sodium tablets USP every week on your chosen day **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take alendronate sodium tablets USP while you are sitting or standing.
- Take your alendronate sodium tablets USP with plain water only as follows:
  - Swallow one tablet with a full glass (6 to 8 oz) of plain water.

Do **not** take alendronate sodium tablets USP with:

Mineral water
Coffee or tea
Juice

Alendronate sodium tablets USP work only if they are taken on an empty stomach.

Do not chew or suck on an alendronate sodium tablet USP.

After taking your alendronate sodium tablets USP, wait at least 30 minutes:

- before you lie down. You may sit, stand or walk, and do normal activities like reading.
- before you take your first food or drink except for plain water.
- before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down until after your first food of the day.

- It is important that you keep taking alendronate sodium tablets USP for as long as your doctor says to take them. For alendronate sodium tablets USP to continue to work, you need to keep taking them.

What should I do if I miss a dose of alendronate sodium tablets USP or if I take too many?

- If you miss a dose, take only 1 dose of alendronate sodium tablets USP on the morning after you remember. Do not take 2 doses on the same day. Continue your usual schedule of 1 dose once a week on your chosen day.
- If you think you took more than the prescribed dose of alendronate sodium tablets USP, drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

What should I avoid while taking alendronate sodium tablets USP?

- Do not eat, drink, or take other medicines or supplements **before** taking alendronate sodium tablets USP.
- Wait for at least 30 minutes **after** taking alendronate sodium tablets USP to eat, drink, or take other medicines or supplements.
- Do not lie down for at least 30 minutes **after** taking alendronate sodium tablets USP. Do not lie down until **after** your first food of the day.

What are the possible side effects of alendronate sodium tablets USP?

Alendronate sodium tablets USP may cause problems in your esophagus (the tube that connects the mouth and stomach). (See "**What is the most important information I should know about once weekly alendronate sodium tablets USP?**".) These problems include irritation, inflammation, or ulcers of the esophagus, which may sometimes bleed. This may occur especially if you do not drink a full glass of water with alendronate sodium tablets USP or if you lie down in less than 30 minutes or before your first food of the day.

- **Stop taking alendronate sodium tablets USP and call your doctor right away if you get any of these signs of possible serious problems of the esophagus:**
  - **Chest pain**
  - **New or worsening heartburn**
  - **Trouble or pain when swallowing**
- Esophagus problems may get worse if you continue to take alendronate sodium tablets USP.
- Mouth sores (ulcers) may occur if the alendronate sodium tablet USP is chewed or dissolved in the mouth.
- You may get flu-like symptoms, typically at the start of treatment with alendronate sodium tablets USP.
- You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.
- Alendronate sodium tablets USP may cause jaw-bone problems in some people. Jaw-bone problems may include infection, and delayed healing after teeth are pulled.
- The most common side effect is stomach area (abdominal) pain. Less common side effects are nausea, vomiting, a full or bloated feeling in the stomach, constipation, diarrhea, black or bloody stools (bowel movements), gas, eye pain, rash that may be made worse by sunlight, headache, dizziness, a changed sense of taste, joint swelling or swelling in the hands or legs, and bone, muscle, or joint pain.
- **Call your doctor if you develop severe bone, muscle, or joint pain.**

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects with alendronate sodium tablets USP. Ask your doctor or pharmacist for more information.

How do I store alendronate sodium tablets USP?

- Store at room temperature, 68° to 77°F (20° to 25°C).
- Safely discard alendronate sodium tablets USP that are out-of-date or no longer needed.
- **Keep alendronate sodium tablets USP and all medicines out of the reach of children.**

General information about using alendronate sodium tablets USP safely and effectively

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use alendronate sodium tablets USP for a condition for which they were not prescribed. Do not give alendronate sodium tablets USP to other people, even if they have the same symptoms you have. It may harm them.

Alendronate sodium tablets USP are not indicated for use in children.

This leaflet is a summary of information about alendronate sodium tablets USP. If you have any questions or concerns about alendronate sodium tablets USP or osteoporosis, talk to your doctor, pharmacist, or other health care provider. You can ask your doctor or pharmacist for information about alendronate sodium tablets USP written for health care providers. For more information, call 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in alendronate sodium tablets USP?

Alendronate sodium tablets USP contain alendronate sodium as the active ingredient and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.

At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, your spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who:

- Are going through or who are past menopause

Men who:

- Are elderly

People who:

- Are white (Caucasian) or oriental (Asian)
- Are thin
- Have family member with osteoporosis
- Do not get enough calcium or vitamin D
- Do not exercise
- Smoke
- Drink alcohol often
- Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help prevent or treat osteoporosis?

In addition to alendronate sodium tablets USP, your doctor may suggest one or more of the following lifestyle changes:

- **Stop smoking.** Smoking may increase your chance of getting osteoporosis.
- **Reduce the use of alcohol.** Too much alcohol may increase the risk of osteoporosis and injuries that can cause fractures.
- **Exercise regularly.** Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.
- **Eat a balanced diet.** Having enough calcium in your diet is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements, such as calcium or vitamin D.

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Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Alendronate sodium 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 alendronate sodium 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 alendronate sodium.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p = 0.003) in a 92 week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p = 0.003) in a 2 year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy
Teratogenic Effects
Pregnancy category C
Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

There are no studies in pregnant women. Alendronate sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers
It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when alendronate sodium is administered to nursing women.

Pediatric Use
The efficacy and safety of alendronate sodium were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4 to 18 years, with severe osteogenesis imperfecta. One hundred-and-nine patients were randomized to 5 mg alendronate sodium daily (weight < 40 kg) or 10 mg alendronate sodium daily (weight ≥ 40 kg) and 30 patients to placebo. The mean baseline lumbar spine 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 alendronate sodium treated patients and 0.1 in the placebo-treated patients. Treatment with alendronate sodium did not reduce the risk of fracture. Sixteen percent of the alendronate sodium 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 alendronate sodium-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 alendronate sodium and placebo groups in reduction of bone pain.

Alendronate sodium tablets are not indicated for use in children. (For clinical adverse experiences in children, see **ADVERSE REACTIONS**, **Clinical Studies**, ***Osteogenesis Imperfecta***.*)*

Geriatric Use
Of the patients receiving alendronate sodium 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 alendronate sodium in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see **CLINICAL PHARMACOLOGY, Clinical 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.

ADVERSE REACTIONS
Clinical Studies
In clinical studies of up to five years in duration adverse experiences associated with alendronate sodium usually were mild, and generally did not require discontinuation of therapy.

Alendronate sodium has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of Osteoporosis
Postmenopausal women
In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n = 994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with alendronate sodium 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n = 6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with alendronate sodium 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: alendronate sodium, 3.2%; placebo, 2.7%. In these study populations, 49 to 54% had a history of gastrointestinal disorders at baseline and 54 to 89% used non-steroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients treated with either alendronate sodium or placebo are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	United States/Multinational Studies		Fracture Intervention Trial	
	Alendronate Sodium* % (n = 196)	Placebo % (n = 397)	Alendronate Sodium** % (n = 3236)	Placebo % (n = 3223)
Gastrointestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle, or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1

(continued)

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	United States/Multinational Studies		Fracture Intervention Trial	
	Alendronate Sodium* % (n = 196)	Placebo % (n = 397)	Alendronate Sodium** % (n = 3236)	Placebo % (n = 3223)
(continued)				
Nervous System/ Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

* 10 mg/day for three years
** 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred.

One patient treated with alendronate sodium (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and alendronate sodium were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of alendronate sodium in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of alendronate sodium in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with alendronate sodium 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly alendronate sodium 70 mg and alendronate sodium 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients in either treatment group are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	Once Weekly Alendronate Sodium 70 mg % (n = 519)	Alendronate Sodium 10 mg/day % (n = 370)
Gastrointestinal		
abdominal pain	3.7	3.0
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distention	1.0	1.4
constipation	0.8	1.6
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle, joint) pain	2.9	3.2
muscle cramp	0.2	1.1

Men
In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of alendronate sodium 10 mg/day and a one-year study of once weekly alendronate sodium 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for alendronate sodium 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly alendronate sodium 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥ 2% of patients treated with either alendronate sodium or placebo are presented in the following table.

Osteoporosis Studies in Men Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 2% of Patients

	Two-year Study		One-year Study	
	Alendronate Sodium 10 mg/day % (n = 146)	Placebo % (n = 95)	Once Weekly Alendronate Sodium 70 mg % (n = 109)	Placebo % (n = 58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

Prevention of Osteoporosis in Postmenopausal Women
The safety of alendronate sodium 5 mg/day in postmenopausal women 40 to 60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive alendronate sodium for either two or three years. In these studies the overall safety profiles of alendronate sodium 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with alendronate sodium 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly alendronate sodium 35 mg and alendronate sodium 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients treated with either once weekly alendronate sodium 35 mg, alendronate sodium 5 mg/day or placebo are presented in the following table.

Osteoporosis Prevention Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	Two/Three-Year Studies		One-Year Study	
	Alendronate Sodium 5 mg/ day % (n = 642)	Placebo % (n = 648)	Alendronate Sodium 5 mg/day % (n = 361)	Once Weekly Alendronate Sodium 35 mg % (n = 362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Concomitant use with estrogen/hormone replacement therapy
In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n = 853), the safety and tolerability profile of combined treatment with alendronate sodium 10 mg once daily and estrogen ± progestin (n = 354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis
In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of alendronate sodium 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients treated with either alendronate sodium 5 or 10 mg/day or placebo are presented in the following table:

One-Year Studies in Glucocorticoid-Treated Patients Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	Alendronate Sodium 10 mg/day % (n = 157)	Alendronate Sodium 5 mg/day % (n = 161)	Placebo % (n = 159)
Gastrointestinal			
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (alendronate sodium: n = 147) was consistent with that observed in the first year.

Paget's Disease of Bone
In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking alendronate sodium 40 mg/day for 3 to 12 months were similar to those in postmenopausal women treated with alendronate sodium 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking alendronate sodium 40 mg/day (17.7% alendronate sodium vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with alendronate sodium 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with alendronate sodium 40 mg/day and 2.4% of patients treated with placebo.

Osteogenesis Imperfecta
Alendronate sodium tablets are not indicated for use in children.

The overall safety profile of alendronate sodium in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with alendronate sodium. However, there was an increased occurrence of vomiting in OI patients treated with alendronate sodium compared to placebo. During the 24 month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with alendronate sodium and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of alendronate sodium 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates, including alendronate sodium. See **ADVERSE REACTIONS**, **Postmarketing Experience**, ***Body as a Whole***.

Laboratory Test Findings
In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking alendronate sodium versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dL (2.0 mM) and serum phosphate to ≤ 2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Postmarketing Experience
The following adverse reactions have been reported in postmarketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with alendronate sodium, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see **WARNINGS, PRECAUTIONS, Information for Patients**, and **DOSAGE AND ADMINISTRATION**).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see **PRECAUTIONS**, **Dental).**

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see **PRECAUTIONS**, ***Musculoskeletal Pain***); joint swelling.

Nervous system: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE
Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with alendronate sodium. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION
Alendronate sodium tablets must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see **PRECAUTIONS, Information for Patients**). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of alendronate sodium tablets (see **PRECAUTIONS, Drug Interactions**). Waiting less than 30 minutes, or taking alendronate sodium tablets with food, beverages (other than plain water) or other medications will lessen the effect of alendronate sodium tablets by decreasing its absorption into the body.

Alendronate sodium tablets should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, an alendronate sodium tablet should be swallowed with a full glass of water (6 to 8 oz). Patients should not lie down for at least 30 minutes and until after their first food of the day. Alendronate sodium tablets should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see **WARNINGS, PRECAUTIONS, Information for Patients**).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see **PRECAUTIONS, General**).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). Alendronate sodium tablets are not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min) due to lack of experience.

Treatment of Osteoporosis in Postmenopausal Women
(See **INDICATIONS AND USAGE**.)

The recommended dosage is:

- one 70 mg tablet once weekly

or

- one 10 mg tablet once daily

Treatment to Increase Bone Mass in Men With Osteoporosis
The recommended dosage is:

- one 70 mg tablet once weekly

or

- one 10 mg tablet once daily

Prevention of Osteoporosis in Postmenopausal Women
(See **INDICATIONS AND USAGE**.)

The recommended dosage is:

- one 35 mg tablet once weekly

or

- one 5 mg tablet once daily

The safety of treatment and prevention of osteoporosis with alendronate sodium has been studied for up to 7 years.

Treatment of Glucocorticoid-Induced Osteoporosis in Men and Women
The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's Disease of Bone in Men and Women
The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's Disease
In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with alendronate sodium tablets. Specific retreatment data are not available, although responses to alendronate sodium tablets were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with alendronate sodium tablets may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED
Alendronate sodium tablets USP, for oral administration, are available as:

5 mg - white to off-white, round flat-faced beveled-edge, unscored tablet debossed with "93" on one side and "5140" on the other side, in bottles of 30 and 100.

10 mg - white to off-white, round, convex, unscored tablet debossed with "93" on one side and "5141" on the other side, in bottles of 30, 100, and 1000.

35 mg – white to off-white, pillow-shaped, convex, unscored tablet debossed with "93" on one side and "5172" on the other side, in bottles of 12 and 100, unit-of-use blister package of 4, and unit dose packages of 20 (2x10).

40 mg - white to off-white, oval convex, unscored tablet debossed with "93" on one side and "5142" on the other side, in bottles of 30 and 100.

70 mg - white to off-white, pillow-shaped, convex, unscored tablet debossed with "93" on one side and "5171" on the other side, in bottles of 12 and 100, unit-of-use blister package of 4, and unit dose packages of 20 (2x10).

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

PATIENT INFORMATION ABOUT ONCE WEEKLY ALENDRONATE SODIUM TABLETS USP
Read this information before you start taking alendronate sodium tablets USP. Also, read the leaflet each time you refill your prescription, just in case anything has changed. This leaflet does not take the place of discussions with your doctor. You and your doctor should discuss alendronate sodium tablets USP when you start taking your medicine and at regular checkups.

What is the most important information I should know about once weekly alendronate sodium tablets USP?

- **You must take once weekly alendronate sodium tablets USP exactly as directed to help make sure they work and to help lower the chance of problems in your esophagus (the tube that connects your mouth and stomach). (See "How should I take once weekly alendronate sodium tablets USP?".)**
- **If you have chest pain, new or worsening heartburn, or have trouble or pain when you swallow, stop taking alendronate sodium tablets USP and call your doctor. (See "What are the possible side effects of alendronate sodium tablets USP?".)**

What are alendronate sodium tablets USP?

Alendronate sodium tablets USP are a prescription medicine for:

- The treatment or prevention of osteoporosis (thinning of bone) in women after menopause. They reduce the chance of having a hip or spinal fracture (break).
- Treatment to increase bone mass in men with osteoporosis.
- Alendronate sodium tablets USP are for treatment and prevention of osteoporosis.

Improvement in bone density may be observed as early as 3 months after you start taking alendronate sodium tablets USP even though you won't see or feel a difference. For alendronate sodium tablets USP to continue to work, you need to keep taking them.

Alendronate sodium tablets USP are not hormones.

There is more information about osteoporosis at the end of this leaflet.

Who should not take alendronate sodium tablets USP?

Do not take alendronate sodium tablets USP if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in your blood
- Are allergic to alendronate sodium tablets USP or any of their ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before using alendronate sodium tablets USP?

Tell your doctor about all of your medical conditions, including if you:

- **have problems with swallowing**
- **have stomach or digestive problems**
- **have kidney problems**
- **are pregnant or planning to become pregnant.** It is not known if alendronate sodium tablets USP can harm your unborn baby.
- **are breastfeeding.** It is not known if alendronate sodium tablets USP pass into your milk and if they can harm your baby.

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take once weekly alendronate sodium tablets USP?

- Choose the day of the week that best fits your schedule.
- Take 1 dose of alendronate sodium tablets USP every week on your chosen day **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take alendronate sodium tablets USP while you are sitting or standing.
- Take your alendronate sodium tablets USP with plain water only as follows:
  - Swallow one tablet with a full glass (6 to 8 oz) of plain water.

Do **not** take alendronate sodium tablets USP with:

Mineral water
Coffee or tea
Juice

Alendronate sodium tablets USP work only if they are taken on an empty stomach.

Do not chew or suck on an alendronate sodium tablet USP.

After taking your alendronate sodium tablets USP, wait at least 30 minutes:

- before you lie down. You may sit, stand or walk, and do normal activities like reading.
- before you take your first food or drink except for plain water.
- before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down until after your first food of the day.

- It is important that you keep taking alendronate sodium tablets USP for as long as your doctor says to take them. For alendronate sodium tablets USP to continue to work, you need to keep taking them.

What should I do if I miss a dose of alendronate sodium tablets USP or if I take too many?

- If you miss a dose, take only 1 dose of alendronate sodium tablets USP on the morning after you remember. Do not take 2 doses on the same day. Continue your usual schedule of 1 dose once a week on your chosen day.
- If you think you took more than the prescribed dose of alendronate sodium tablets USP, drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

What should I avoid while taking alendronate sodium tablets USP?

- Do not eat, drink, or take other medicines or supplements **before** taking alendronate sodium tablets USP.
- Wait for at least 30 minutes **after** taking alendronate sodium tablets USP to eat, drink, or take other medicines or supplements.
- Do not lie down for at least 30 minutes **after** taking alendronate sodium tablets USP. Do not lie down until **after** your first food of the day.

What are the possible side effects of alendronate sodium tablets USP?

Alendronate sodium tablets USP may cause problems in your esophagus (the tube that connects the mouth and stomach). (See "**What is the most important information I should know about once weekly alendronate sodium tablets USP?**".) These problems include irritation, inflammation, or ulcers of the esophagus, which may sometimes bleed. This may occur especially if you do not drink a full glass of water with alendronate sodium tablets USP or if you lie down in less than 30 minutes or before your first food of the day.

- **Stop taking alendronate sodium tablets USP and call your doctor right away if you get any of these signs of possible serious problems of the esophagus:**
  - **Chest pain**
  - **New or worsening heartburn**
  - **Trouble or pain when swallowing**
- Esophagus problems may get worse if you continue to take alendronate sodium tablets USP.
- Mouth sores (ulcers) may occur if the alendronate sodium tablet USP is chewed or dissolved in the mouth.
- You may get flu-like symptoms, typically at the start of treatment with alendronate sodium tablets USP.
- You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.
- Alendronate sodium tablets USP may cause jaw-bone problems in some people. Jaw-bone problems may include infection, and delayed healing after teeth are pulled.
- The most common side effect is stomach area (abdominal) pain. Less common side effects are nausea, vomiting, a full or bloated feeling in the stomach, constipation, diarrhea, black or bloody stools (bowel movements), gas, eye pain, rash that may be made worse by sunlight, headache, dizziness, a changed sense of taste, joint swelling or swelling in the hands or legs, and bone, muscle, or joint pain.
- **Call your doctor if you develop severe bone, muscle, or joint pain.**

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects with alendronate sodium tablets USP. Ask your doctor or pharmacist for more information.

How do I store alendronate sodium tablets USP?

- Store at room temperature, 68° to 77°F (20° to 25°C).
- Safely discard alendronate sodium tablets USP that are out-of-date or no longer needed.
- **Keep alendronate sodium tablets USP and all medicines out of the reach of children.**

General information about using alendronate sodium tablets USP safely and effectively

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use alendronate sodium tablets USP for a condition for which they were not prescribed. Do not give alendronate sodium tablets USP to other people, even if they have the same symptoms you have. It may harm them.

Alendronate sodium tablets USP are not indicated for use in children.

This leaflet is a summary of information about alendronate sodium tablets USP. If you have any questions or concerns about alendronate sodium tablets USP or osteoporosis, talk to your doctor, pharmacist, or other health care provider. You can ask your doctor or pharmacist for information about alendronate sodium tablets USP written for health care providers. For more information, call 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in alendronate sodium tablets USP?

Alendronate sodium tablets USP contain alendronate sodium as the active ingredient and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.

At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, your spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who:

- Are going through or who are past menopause

Men who:

- Are elderly

People who:

- Are white (Caucasian) or oriental (Asian)
- Are thin
- Have family member with osteoporosis
- Do not get enough calcium or vitamin D
- Do not exercise
- Smoke
- Drink alcohol often
- Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help prevent or treat osteoporosis?

In addition to alendronate sodium tablets USP, your doctor may suggest one or more of the following lifestyle changes:

- **Stop smoking.** Smoking may increase your chance of getting osteoporosis.
- **Reduce the use of alcohol.** Too much alcohol may increase the risk of osteoporosis and injuries that can cause fractures.
- **Exercise regularly.** Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.
- **Eat a balanced diet.** Having enough calcium in your diet is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements, such as calcium or vitamin D.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 12/2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-710

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
LABELING REVIEW BRANCH

ANDA Number: 75-710 **Date of Submission: September 29, 1999**
Applicant's Name: Teva Pharmaceuticals
Established Name: Alendronate Sodium Tablets 5 mg, 10 mg, and 40 mg

Labeling Deficiencies:

1. CONTAINER (5 mg- 100's, 10 mg- 100's & 1000's, 40 mg- 100's)

   a. We encourage you to differentiate product strengths using color or shading as does the reference listed drug.

   b. Ensure that the established name and strength are the most prominent information appearing on the label.

2. INSERT

   a. GENERAL COMMENT

   Due to significant changes in the insert labeling of the listed drug (Fosamax – Merck Research Laboratories; approved in draft June 8, 1999), please revise your package insert labeling as follows:

   i. CLINICAL PHARMACOLOGY

   A) Pharmacodynamics (Osteoporosis in postmenopausal women)

   1. Revise the first sentence of the fourth paragraph to read, "Long-term treatment of osteoporosis with alendronate 10 mg/day (for up to five years) ...bone resorption, deoxypyridinoline...by approximately 50% and 70%, respectively.

   2. Revise the 4th sentence of the fourth paragraph to read, ...osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau...

   3. Revise the 5th sentence of the fourth paragraph to read, ...decreased osteocalcin and total serum alkaline phosphatase by approximately...

   4. The 2nd and 3rd sentences of the fifth paragraph should read, ...initiation of alendronate sodium 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment, however, serum phosphate returned toward prestudy levels during years three through five.

   B) Clinical Studies (Treatment of osteoporosis in postmenopausal women)

   1. Effect on bone mineral density

   a) Revise the 1st sentence of the second paragraph to read, "At three years...".

   b) The 5th and 6th sentence of the second paragraph should read as follows:

   In the two-year extension of these studies, treatment of 147 patients with alendronate sodium 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained.

c) The ultimate sentence of the second paragraph should read, "Thus, overall alendronate sodium reverses the loss of bone mineral density, a central factor in the progression of osteoporosis."

2. Effect on fracture incidence

The last 2 sentences of the first paragraph should read,

In the two-year extension of these studies, patients who continued treatment with alendronate sodium 5 or 10 mg continued to lose height at approximately the same rate, losing an additional 1.9 mm in stature. There was no placebo group in the extension study.

ii. WARNINGS

Revise the first sentence of the second paragraph to read, ...with bleeding and rarely followed by esophageal stricture, have been...

iii. ADVERSE REACTIONS

A) Clinical Studies – The first paragraph should read, "In clinical studies of up to five years in duration adverse...

B) Treatment of osteoporosis – The fourth paragraph should read as follows:

The adverse experience...studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 doses of alendronate sodium in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with alendronate sodium 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

C) Post-Marketing Experience

1. Gastrointestinal – Revise to read, ...esophageal ulcers, rarely esophageal stricture, and oropharyngeal ulceration.

2. Skin – Include this category as the ultimate category with the following text:

rash, (occasionally with photosensitivity)

iv. DOSAGE AND ADMINISTRATION (Prevention of osteoporosis in postmenopausal women)

The ultimate sentence should read, ...for longer than five years...

In addition, make the following changes:

v. TITLE - We encourage the inclusion of "Rx only" in this section.

vi. DESCRIPTION

A) We note that in this section you list "alendronate monosodium salt trihydrate" as the active ingredient, but in you components/composition statement you list "alendronate sodium trihydrate" as the active ingredient. Please revise to be consistent.

B) Revise to describe alendronate sodium as a "bisphosphonate" rather than "an aminobisphosphonate" to be

consistent with the innovator labeling.

3. PATIENT INFORMATION LEAFLET (What are the possible side effects of alendronate sodium?)

   Change the 2nd sentence of the penultimate paragraph to read, "Rarely, a rash (occasionally made worse by sunlight) has occurred.

Please revise your labels and labeling, as instructed above, and submit in final print, or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed labeling with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (5 mg- 100's, 10 mg- 100's & 1000's, 40 mg- 100's)
Professional Package Insert Labeling:
Patient Package Insert Labeling:

Revisions needed post-approval:
BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: FOSAMAX®

NDA Number: 20-560/S-014
NDA Drug Name: Alendronate Sodium Tablets
NDA Firm: Merck

Date of Approval of NDA Insert and supplement #: March 19, 1999
Has this been verified by the MIS system for the NDA? Yes
NOTE: S-012 was approved on June 16, 1999. This is an efficacy supplement for the treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density. The RLD has received exclusivity until June 16, 2002.
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	

Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. The reference listed drug for this product is FOSAMAX® (Merck; NDA#20-560/S-014; approved March 19, 1999). NOTE: S-012 was approved on June 16, 1999. This is an efficacy supplement for the treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density. The RLD has received exclusivity until June 16, 2002.

2. The following patents are in effect for this product

   #5849726 – Expires June 6, 2015
   #5358941 – Expires December 2, 2012
   #4621077 – Expires August 6, 2007
   #5681590 – Expires December 2, 2012
   #5804570 – Expires February 17, 2015
   #6008202 – Expires June 6, 2015

   Patents held but not filed in Orange Book
   #5882656 – issued March 16, 1999
   The applicant has certified Paragraph IV for all patents.

   The following Exclusivities are in effect for this product
   New Chemical Entity – Expires September 29, 2000
   I-272- for the treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density. Expires June 16, 2002.
   M-3 – Efficacy and safety info in which Fosamax was used concomitantly with estrogen alone or with HRT. Expires November 24, 2002.
   The applicant certifies it will not market until the expiration of the New Chemical Entity Exclusivity on September 29, 2000.
   See Vol. 1.1, page 11 and 12.

3. The product will be manufactured by TEVA Pharmaceuticals USA, 650 Cathill Road, Sellersville, PA, 18960. See Vol. 1.14, page 6047.

4. Outside facilities are utilized for testing only. See Vol. 1.14, page 054.

5. Container/Closure
Bottle: 40 cc (100 count)
Cap: CRC w/ (b) (4) **OR** (b) (4) screw Cap w (b) (4)
Closure: (b) (4)
Bottle: 250 cc (1,000 count)
Cap: (b) (4) Screw Cap w/ (b) (4)
Closure: (b) (4)
See Vol. 1.1, page 6296.

6. Finished product - Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform. See Vol. 1.1, page 29.

7. Product Line
5 mg- white to off-white, round flat-faced beveled-edge tablet debossed with "93" on one side and "5140" on the other side. Supplied in bottles of 100.
10 mg- white to off-white, round, convex tablet debossed with "93" on one side and "5141" on the other side. Supplied in bottles of 100 and 1000.
40 mg- white to off-white, oval convex tablet debossed with "93" on one side and "5142" on the other side. Supplied in bottles of 100.
See Vol. 1.1, page 48.

8. Components/Composition
Innovator:
Active: Alendronate monosodium salt trihydrate equivalent to (5, 10, and 40 mg base)
Inactive: microcrystalline cellulose
Anhydrous lactose
Croscarmellose sodium
Magnesium stearate
Applicant:
Active: Alendronate sodium salt trihydrate equivalent to (5, 10, and 40 mg base)
Inactive: Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
See Vol. 1.14, page 5943.

9. Storage/Dispensing
NDA: Store in a well-closed container at room temperature, 15-30°C (59-86°F).
ANDA: (b) (4)
See Vol. 1.1, page 48.

Date of Review: May 30, 2000
Date of Submission: September 29, 1999

Reviewer: **Date:** 6/2/00

Team Leader: **Date:** 6/5/2000

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cc: ANDA: 75-710
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\75710na1.l
Review

FIRST GENERIC
REVIEW OF PROFESSIONAL LABELING
LABELING REVIEW BRANCH

ANDA Number: 75-710 **Date of Submission: October 23, 2000 (Amendment)**
Applicant's Name: Teva Pharmaceuticals
Established Name: Alendronate Sodium Tablets, 70 mg

Labeling Deficiencies:

1. CONTAINER (12s and 100s)

   a. We encourage you to differentiate product strengths using color or shading as does the reference listed drug.

   b. Ensure that the established name and strength are the most prominent information appearing on the label.

2. INSERT - GENERAL COMMENT

   Please note that Merck has been granted marketing exclusivity for the 70 mg product strength and its once weekly dosing interval until October 20, 2003. Since you cannot market your product until after this date, please revise your labeling to be in accord with the innovator labeling for the 70 mg product located at http://www.fda.gov/cder/ogd/rld/20560s21.pdf.

3. PATIENT INFORMATION LEAFLET - Please note that there is a separate patient information leaflet for the once weekly dosing regimen. Please submit labeling to be in accord with the attached patient information leaflet approved for Fosamax.

Please revise your labels and labeling, as instructed above, and submit final printed container labels four draft copies of insert labeling for tentative approval. If draft labeling provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed labeling with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (70 mg – 12s and 100s)
Professional Package Insert Labeling:
Patient Package Insert Labeling:

Revisions needed post-approval:
BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: FOSAMAX®

NDA Number: 20-560/S-021 and 022
NDA Drug Name: Alendronate Sodium Tablets
NDA Firm: Merck

Date of Approval of NDA Insert and supplement #: October 20, 2000
Has this been verified by the MIS system for the NDA? Yes
NOTE: Marketing exclusivity for once weekly dosing of the 70 mg tablet granted until October 20, 2003.
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	

Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTE TO CHEMIST: The RLD packages its 70 mg product in unit dose blisters of 4 and 20. The applicant is proposing to package its product in bottles of 12 and 100. (b) (4) (b) (4) **of Fosamax following a teleconference with HFD-510. Do you concur with this proposal.**

FOR THE RECORD:

1. The reference listed drug for this product is FOSAMAX® (Merck; NDA#20-560/S-021 and 022; approved October 20, 2000).
   NOTE: Although the June 16, 1999 labeling is being used for the 5, 10 and 40 mg tablets, this submission is for the 70 mg tablet which includes a once weekly dosing regimen. Marketing exclusivity has been granted for both the strength and the dosing regimen until October 20, 2003.

2. The following patents are in effect for this product

Patent Data – NDA 20-560

No	Expiration	Use Code	Use	File
4621077	Aug 06, 2007	U-114	Inhibiting bone resorption	P-IV
5681590	Dec 02, 2012		Dry mix formulation w/biphosponic acid	P-IV
5358941	Dec 02, 2012		Dry mix formulation with biphosphoric acids w/lactose	P-IV
5804570	Feb 17, 2015		Method of lessening risk of nonvertebral bone fractures	P-IV
6008207	June 06, 2015	U-303	Method of treating osteoporosis, Paget's Disease prevention & treatment of glucocorticoid-induced osteopososis	P-IV
5849726	June 06, 2015		Salt formulation	P-IV
5994329	June 17, 2018		Method of inhibiting bone resorption	P-IV
6015801	June 17, 2018	U-353	Prevention and treatment of osteoporosis	P-IV

Exclusivity Data– NDA 20-560

Code	Reference	Expiration
I-272	Treatment of glucocorticoid induced osteoporosis in men and women receiving daily doses of glucocorticoids ≥ 7.5 mg prednisone & who have low bone mineral density	June 16, 2002
M-3	Efficacy and safety information in which alendronate was used concomitantly with estrogen alone or with estrogen plus progestin	Nov 24, 2002
NS	Introduction of 35 mg and 70 mg strengths	Oct. 20, 2003
D-61	Once weekly dosing for the treatment of postmenopausal osteoporosis	Oct. 20, 2003
D-62	Once weekly dosing for prevention of postmenopausal osteoporosis	Oct. 20, 2003
I-309	Increase bone mass in men with osteoporosis	Sept. 29, 2003

Patents held but not filed in Orange Book
#5882656 – issued March 16, 1999

3. The product will be manufactured by TEVA Pharmaceuticals USA, 650 Cathill Road, Sellersville, PA, 18960. See Vol. 1.14, page 6047.

4. Outside facilities are utilized for testing only. See Vol. 1.14, page 054.

5. Container/Closure
The innovator will package its 70 mg product in unit dose blisters of 4 and 20. Product will not be packed in bottles. The decision to only package in unit dose blisters was not based on safety issues, according to the PM, Randy Hedin.

   The applicant is proposing to package its product in bottles of 12 and 100.

6. Finished product - Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform. See Vol. 1.1, page 29.

7. Product Line

8. Components/Composition
Innovator:
Active: Alendronate monosodium salt trihydrate equivalent to (70 mg base)
Inactive: microcrystalline cellulose
Anhydrous lactose
Croscarmellose sodium
Magnesium stearate
Applicant:
Active: Alendronate sodium salt trihydrate equivalent to (5, 10, and 40 mg base)
Inactive: Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
See Vol. 3.1, page 11A.

9. Storage/Dispensing
NDA: Store in a well-closed container at room temperature, 15-30°C (59-86°F).
ANDA: (b) (4)
See Vol. 1.1, page 48.

Date of Review: January 14, 2001 **Date of Submission: October 23, 2000 (Amendment)**

Reviewer: **Date:** 1/16/01

Team Leader: **Date:** 1/18/2001

cc: ANDA: 75-710
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\75710na3.I
Review

Following this page, 4 pages withheld in full-RLD labeling

No labeling review #3 was located. It is believed to be a numbering error.

REVIEW OF PROFESSIONAL LABELING #4
LABELING REVIEW BRANCH

ANDA Number: **75-710**
Date of Submission: August 20, 2001 unsolicited (35 mg strength) & March 9, 2001 submission.
Applicant's Name: Teva Pharmaceuticals
Established Name: **Alendronate Sodium Tablets, 5 mg, 10 mg, 40 mg, 35 mg and 70 mg**

Labeling Deficiencies: Comments based on the August 20, 2001 submission.

1. CONTAINER - 35 mg (12s and 100s)

   We defer a complete comment on your **once weekly** container labels at this time. We will inform you if there are any other changes needed to your labels. Please note the following :

   a. We encourage you to differentiate product strengths using color or shading as does the reference listed drug.

   b. Ensure that the established name and strength are the most prominent information appearing on the label.

   c. We note your proposed 5 mg, 10 mg, and 40 mg strengths draft container labels submitted in September 29, 1999 were statisfactory.

2. PROFESSIONAL PACKAGE INSERT LABELING - A combined labeling (daily and weekly dosing)

   a. GENERAL COMMENT - Throughout your labeling, delete "sodium" when using the established name "alendronate" except in the insert title, DESCRIPTION section, the first line of the INDICATIONS AND USAGE section, and in the HOW SUPPLIED section.
   b. CLINICAL PHARMACOLOGY
      Clinical Studies, Fracture results across studies (Men) - Add the following as the last sentence:

      The safety and efficacy of once weekly alendronate 70 mg in men with osteoporosis are currently being studied, but data are not yet available.
   c. PRECAUTIONS
      (1) Carcinogenesis, Mutagenesis, Impairment of Fertility - The first sentence of the first Paragraph should read, ...92-week oral carcinogenicity study... (Add "oral")
      (2) Use in the Elderly
         i. Change this subsection heading to "Geriatric Use".
         ii. Add the following as the first sentence:

         Of the patients receiving alendronate in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age.
   d. DOSAGE AND ADMINISTRATION (Treatment to increase bone-mass in men with Osteoporosis) - Add the following as the last sentence:

      Alternatively, one 70 mg tablet once weekly may be considered.

   e. HOW SUPPLIED- Please state whether or not your tablets are scored.

3. PATIENT INFORMATION LEAFLETs: Two separate leaflets

   a. Daily - Revise your leaflet submitted on October 23, 2000 for daily dosing to be in accord with the attached patient information leaflet.

   b. Once weekly - Satisfactory in draft submitted March 9, 2001.

Please revise your labeling, as instructed above, and submit four draft copies of insert labeling and patient leaflet for tentative approval. If draft labeling provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your once weekly container labels and labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your previous labeling and the enclosed fosomax labeling with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachments:
Fosomax labels and
Daily patient leaflet.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No. This is a tentative approval. Firm has up to 60 days prior to the expiration of patents and exclusivity (October 20, 2003) to submit final printed labeling.

CONTAINER LABELS:

5 mg (100s), 10 mg (100s and 100s), 40 mg (100s) - Satisfactory **in draft** as of September 29, 1999 submission (Vol. 1.1, Section V.1, Pages 25 - 28).

35 mg and 70 mg -

PROFESSIONAL PACKAGE INSERT LABELING -

PATIENT PACKAGE INSERT LABELING:

1. Daily Dosing - as of October 23, 2000 submission. Vol 3.1 blue page 38, changes are requested see current review.

2. Weekly Dosing - Satisfactory **in draft** as of March 9, 2001 submission

Revisions needed Pre-approval:

BASIS OF APPROVAL:

Patent Data – NDA 20-560*

No	Expiration	Use Code	Use	How file	Labeling Impact
4621077	Aug 06, 2007	U-114	Inhibiting bone resorption	P-IV	Same as
5358941	Dec 02, 2012		Dry mix formulation with biphosphoric acids w/lactose	P-IV	Same as
5681590	Dec 02, 2012		Dry mix formulation w/biphosphoric acid	P-IV	No impact on labeling
5804570	Feb 17, 2015		Method of lessening risk of nonvertebral bone fractures	P-IV	Same as
5849726	Jun 06, 2015		Salt formulation	P-IV	No impact
6008207	Jun 06, 2015	U-303	Method of treating osteoporosis, Paget's Disease prevention & treatment of glucocorticoid-induced osteopososis	P-IV	Same as
6090410	Dec 02,2012		Dry mix formulation w/biphosphoric acid	P-IV	No impact on labeling
6194004	Dec 02,2012		Dry mix formulation w/biphosphoric acid	P-IV	No impact on labeling
5994329	Jun 17, 2018		Method of inhibiting bone resorption	P-IV	Same as
6225294	Jul 17, 2018		Method of inhibiting bone resorption	P-IV	
6015801	Jun 17, 2018	U-353	Prevention and treatment of osteoporosis	P-IV	Same as

*Black print =5,10,40,35 and 70 mg strengths; Blue print = 5, 10, 40 mg strengths, Brown print = 35 mg and 70 mg (once weekly) strengths.

Exclusivity Data– NDA 20-560*

Code	Reference	Expiration	Labeling impact
I-272	Treatment of glucocorticoid induced osteoporosis in men and women receiving daily doses of glucocorticoids ≥ 7.5 mg prednisone & who have low bone mineral density	June 16, 2002	In labeling
I-309	Increase bone mass in men with osteoporosis	Sept. 29, 2003	In labeling
M-3	Efficacy and safety information in which alendronate was used concomitantly with estrogen alone or with estrogen plus progestin	Nov 24, 2002	In labeling
NS	Introduction of 35 mg and 70 mg strengths	Oct. 20, 2003	In labeling
D-61	Once weekly dosing for the treatment of postmenopausal osteoporosis	Oct. 20, 2003	In labeling
D-62	Once weekly dosing for prevention of postmenopausal osteoporosis	Oct. 20, 2003	In labeling

* Blue print = 5, 10, 40 mg strengths, Brown print = 35 mg and 70 mg (once weekly) strengths.Created 10/12/01 amp. C:data/my document/alendronate P&E

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Fosamax® Tablets

NDA Number: 20-560

NDA Drug Name: Alendronate Sodium Tablets

NDA Firm: Merck

Date of Approval of NDA Insert and supplement #s 024 and 025: January 31, 2001

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

Other Comments: None

NOTES/QUESTIONS TO THE CHEMIST: None

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	

Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). .		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTE TO CHEMIST: The RLD packages its 70 mg product in unit of use blisters of 4 and unit dose packages of 20. The applicant is proposing to package its product in bottles of 12 and 100. (b) (4) (b) (4) of Fosamax following a teleconference with HFD-510. Do you concur with this proposal?

FOR THE RECORD:

1. MODEL LABELING:

   The labeling review was based on the labeling for the reference listed drug, FOSAMAX® (Merck; NDA#20-560/S-024 and 025; approved January 31, 2001).

2. PATENTS/EXCLUSIVITIES. Current submission of August 20, 2001 page 11 cites PIV for all patents. And the feb. 2, 28, 2001 exclusivities certifies that firm will not market the 70 and 35 mg strengths until after the expiration of the patients. Since this is a combined insert for the 5 mg, 10 mg , 40 mg strengths then, firm cannot go to market until 2003. See chart above.

3. MANUFACTURING FACILITY (Vol. 1.14, page 6047)

   TEVA Pharmaceuticals USA
   650 Cathill Road
   Sellersville, PA, 18960

4. SCORING/PRODUCT DESCRIPTION

   NDA: 5 mg - white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other.

   10 mg - white, round, uncoated tablets with a bone image and code MRK 936 on one side and a bone image and FOSAMAX on the other.

   40 mg - white, triangular-shaped, uncoated tablets with code MRK 212 on one side and FOSAMAX on the other.

   70 mg - white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other.
   35 mg - white, oval, uncoated tablets with code 77 on one side and an outline of a bone image on the other.

   ANDA: 5 mg - white to off-white, round flat-faced beveled-edge tablets debossed with "93" on one side and "5140" on the other side.

   10 mg - white to off-white, round, convex tablets debossed with "93" on one side and "5141" on the other side.

   40 mg - white to off-white, oval convex tablets debossed with "93" on one side and "5142" on the other side.

   70 mg - white to off-white, pillow shaped, convex tablets debossed with "93" on one side and "5171" on the other side.

   35 mg strength. white to off-white, pillow shaped, convex tablets debossed with "93" on one side and "5172" on the other side.

5. STORAGE RECOMMENDATIONS:

   NDA: Store in a well-closed container at room temperature, 15-30°C (59-86°F).

   ANDA: Store at [redacted] (b) (4)

   USP: Not applicable

6. DISPENSING RECOMMENDATIONS:

   NDA: None

   ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

7. INACTIVE INGREDIENTS (Vol. 3.1, Section V, page 11A)

   There is no discrepancy between the listing in the DESCRIPTION section of the insert labeling and the

Components and Composition Statements for the 5 mg, 10 mg, and 40 mg products. However at the time this amendment was submitted, the 35 mg and 70 mg products were not on the market and were unavailable to Teva. Teva, therefore, compared its 70 mg product with the 10 mg product .

8. PRODUCT LINE:

RLD: 5 mg tablets - unit of use bottles of 30 and 100

10 mg tablets - unit of use bottles of 30 and 100; unit dose packages of 100; bottles of 1000; UNIBLISTER cards of 31 tablets

40 mg tablets - unit of use bottles of 30

70 mg tablets - unit of use blister package of 4 tablets; unit dose packages of 20

35 mg tablets - unit of use blister package of 4 tablets; unit dose packages of 20

ANDA: 5 mg tablets - bottles of 100

10 mg tablets - bottles of 100 and 1000

40 mg tablets - bottles of 100

70 mg tablets - bottles of 12 and 100
35 mg tablets - bottles of 12 and 100

The innovator will package its 70 mg and 35 mg product in unit dose blisters of 4 and 20. Product will not be packed in bottles. The decision to only package in unit dose blisters **was not** based on safety issues according to the PM, Randy Hedin. We will allow bottles at this time. (b) (4)

(b) (4)

The applicant is proposing to package its product in bottles of 12 and 100.

9. Regulatory will determine if the inclusion of the 35 mg strength will hold up approval of the 5 mg, 10, 40 mg. As for now the insert models the reference listed drug is all respects based on the exclusivity expiration for the 35 mg once weekly strength. Regulatory has stated that the product can get a TA until April 2003 when the exclusivity expires for the once weekly dosing 35 mg and 70 mg strengths.

Date of Review: Jan. 15, 2002 **Date of Submission: August 20, 2001 & March 9, 2001**

cc: ANDA: 75-710
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\75710na4.l
Review

1/15/01

1/30/02

(minor)

REVIEW OF PROFESSIONAL LABELING #5
LABELING REVIEW BRANCH

ANDA Number: **75-710**
Date of Submission: April 26, 2002 unsolicited (unit dose once weekly) & January 14, 2002 submission.
Applicant's Name: Teva Pharmaceuticals
Established Name: **Alendronate Sodium Tablets 35 mg and 70 mg (once weekly)**

Labeling Deficiencies: Comments based on the April 26, 2002 submission.

1. GENERAL COMMENT- Revise and relocate "(Once Weekly)" so that it is in parenthesis and follows the product name. Make this change on all labels and labeling.

2. UNIT-DOSE BLISTERS - 35 mg and 70 mg

   a. Please include the city, state, zip code, lot # and expiration date as seen on your carton labeling.
   b. We encourage you to differentiate your product strengths by using color or shading as does the reference listed drug.

3. UNIT-DOSE CARTONS- (1X 4s) and (20s)

1 x 4s

   a. We note your comment that the carton is a (b) (4) carton. Will this ensure the child resistant concept for unit-of- use cartons? Please comment.
   b. Panel 2, Delete the following " Remember to take one alendronate Sodium tablets once each week on that same day for as long as your doctor prescribes It. ". It does not appear in the reference listed drug label.
   c. Panel 2, If you miss a dose, 2nd paragraph revise to read "There is important additional information about... " (Note insert additional).
   d. Relocate " (Once weekly)" so that it follows the product name
   e. Unit-of-Use- dispense in original package.

20s

   f. We note your comment that 20s are (b) (4) cartons and are not (b) (4). Therefore, please include a statement as to whether or not the unit-dose package carton is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be in a child resistant container. We offer the following example:

      This unit-dose package is not-child-resistant. If dispensed for outpatient use, a child-resistant container should be used. [Note: the second sentence is optional]

   g. Add - Keep out of reach of children.
   h. Please cite the card configuration. It is not clear weather the cards are 5 cards of 4 tabs, 2 cards of 10 tabs, or 4 cards of 5 tabs. Revise 20 tablets to read "20 tablets (? X ?)" .

4. PROFESSIONAL PACKAGE INSERT LABELING - The combined labeling is satisfactory in draft with one minor correction cited in the HOW SUPPLIED section. Revise "unit of dose" to "unit dose" and See comment 3h above.

5. PATIENT INFORMATION LEAFLETs: **We make the following comments again** (two separate leaflets):

   a. Daily - Revise your leaflet submitted on January 14, 2002 for daily dosing to be in accord with the attached patient information leaflet.
   b. Once weekly - Satisfactory in draft submitted March 9, 2001.

Please revise your labels and labeling, as instructed above, and submit 12 copies of container and carton blister labeling, four draft copies of patient leaflet for tentative approval. If draft labeling provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your once weekly container labels and labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your previous labeling and the enclosed fosamax patient leaflet labeling with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Daily patient leaflet.

Following this page, 3 pages withheld in full- RLD labeling

~~Tentative APPROVAL~~ SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	75-710
Date of Submission	
Applicant	Teva Pharmaceuticals
Drug Name	Alendronate Sodium Tablets,
Strength(s)	5 mg, 10 mg, 40 mg, 35 mg and 70 mg

Draft Approval Summary		
Container Labels		**Submitted**
5 mg, 10 mg, and 40 mg	100s	Jan 14, 2002 vol. 7.1, FPL
10 mg	1000s	Jan 14, 2002 vol. 7.1, FPL
35 mg and 70 mg	12s and 100s	Aug 20, 2001 vol. X.X Draft
Blister labels		
35 mg and 70 mg	4s and 20s	
Blister Carton labeling		
35 mg and 70 mg	4s and 20s	
Package Insert Labeling	Rev. 3/2002*	Apr 26, 2002 vol. 8.1 Draft with 35 &70 mg included.
Patient Daily leaflet	#XXXXXRev.	
Patient weekly leaflet	#XXXXRev.	Mar 9, 2001 vol. X.X Draft

BASIS OF APPROVAL : Patent Data – NDA 20-560*

No	Expiration	Use Code	Use	How file	Labeling Impact
4621077	Aug 06, 2007	U-114	Inhibiting bone resorption	MOU	Carved Out
5358941	Dec 02, 2012		Dry mix formulation with biphosphoric acids w/lactose	PIV	
5681590	Dec 02, 2012		Dry mix formulation w/biphosphoric acid	PIV	
5804570	Feb 17, 2015		Method of lessening risk of nonvertebral bone fractures	PIV	Same as
5849726	Jun 06, 2015		Salt formulation	PIV	
6008207	Jun 06, 2015	U-303	Method of treating osteoporosis, Paget's Disease prevention & treatment of glucocorticoid-induced osteopososis	MOU changed to PIV	Same as
6090410	Dec 02,2012		Dry mix formulation w/biphosphoric acid	PIV	
6194004	Dec 02,2012		Dry mix formulation w/biphosphoric acid	PIV	
5994329	Jun 17, 2018		Method of inhibiting bone resorption	PIV	Same as
6225294	Jul 17, 2018		Method of inhibiting bone resorption	PIV	Same as
6015801	Jun 17, 2018	U-353	Prevention and treatment of osteoporosis	PIV	Same as

*Black print =5,10,40,35 and 70 mg strengths; Blue print = 5, 10, 40 mg strengths, Brown print = 35 mg and 70 mg (once weekly) strengths.

Exclusivity Data– NDA 20-560*

Code	Reference	Expiration	Labeling impact
I-272	Treatment of glucocorticoid induced osteoporosis in men and women receiving daily doses of glucocorticoids ≥ 7.5 mg prednisone & who have low bone mineral density	June 16, 2002	Same As
I-309	Increase bone mass in men with osteoporosis	Sept. 29, 2003	Same As
M-3	Efficacy and safety information in which alendronate was used concomitantly with estrogen alone or with estrogen plus progestin	Nov 24, 2002	Same As

NS	Introduction of 35 mg and 70 mg strengths	Oct. 20, 2003	Same As
D-61	Once weekly dosing for the treatment of postmenopausal osteoporosis	Oct. 20, 2003	Same AS
D-62	Once weekly dosing for prevention of postmenopausal osteoporosis	Oct. 20, 2003	Same As

* Blue print = 5, 10, 40 mg strengths; Brown print = 35 and 70 mg (once weekly). Created 10/12/01 amp.

Reference Listed Drug

RLD on the 356(h) form	Fosamax Tablets
NDA Number	20-560
RLD established name	Alendronate Sodium Tablets
Firm	Merck
Currently approved PI	S/024 and 025
AP Date	January 31, 2001

Note.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	

Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTE TO CHEMIST: I could not find exactly what the final card configuration for the 20 pak carton would be. Is it 2 cards with 10 tabs, or 5 cards with 4 tabs?

FOR THE RECORD:

1. MODEL LABELING:

   The labeling review was based on the labeling for the reference listed drug, FOSAMAX® (Merck; NDA#20-560/S-024 and 025; approved January 31, 2001).

2. PATENTS/EXCLUSIVITIES. Current submission of August 20, 2001 page 11 cites PIV for all patents. And the feb. 2, 28, 2001 exclusivities certifies that firm will not market the 70 and 35 mg strengths until after the expiration of the patients. Since this is a combined insert for the 5 mg, 10 mg , 40 mg strengths then, firm cannot go to market until 2003. See chart above.

3. MANUFACTURING FACILITY (Vol. 1.14, page 6047)

   TEVA Pharmaceuticals USA
   650 Cathill Road
   Sellersville, PA, 18960

4. SCORING/PRODUCT DESCRIPTION

   NDA: 5 mg - white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other.

   10 mg - white, round, uncoated tablets with a bone image and code MRK 936 on one side and a bone image and FOSAMAX on the other.

   40 mg - white, triangular-shaped, uncoated tablets with code MRK 212 on one side and FOSAMAX on the other.

70 mg - white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other.
35 mg - white, oval, uncoated tablets with code 77 on one side and an outline of a bone image on the other.

ANDA: 5 mg - white to off-white, round flat-faced beveled-edge tablets debossed with "93" on one side and "5140" on the other side.

10 mg - white to off-white, round, convex tablets debossed with "93" on one side and "5141" on the other side.

40 mg - white to off-white, oval convex tablets debossed with "93" on one side and "5142" on the other side.

70 mg - white to off-white, pillow shaped, convex tablets debossed with "93" on one side and "5171" on the other side.

35 mg strength. white to off-white, pillow shaped, convex tablets debossed with "93" on one side and "5172" on the other side.

5. STORAGE RECOMMENDATIONS:

NDA: Store in a well-closed container at room temperature, 15-30°C (59-86°F).

ANDA: Store at [redacted] (b) (4)

USP: Not applicable

6. DISPENSING RECOMMENDATIONS:

NDA: None

ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

7. INACTIVE INGREDIENTS (Vol. 3.1, Section V, page 11A)

There is no discrepancy between the listing in the DESCRIPTION section of the insert labeling and the Components and Composition Statements for the 5 mg, 10 mg, and 40 mg products. However at the time this amendment was submitted, the 35 mg and 70 mg products were not on the market and were unavailable to Teva. Teva, therefore, compared its 70 mg product with the 10 mg product .

8. PRODUCT LINE:

RLD: 5 mg tablets - unit of use bottles of 30 and 100

10 mg tablets - unit of use bottles of 30 and 100; unit dose packages of 100; bottles of 1000; UNIBLISTER cards of 31 tablets for hospital use.

40 mg tablets - unit of use bottles of 30

70 mg tablets - unit of use blister package of 4 tablets; unit dose packages of 20

35 mg tablets - unit of use blister package of 4 tablets; unit dose packages of 20

ANDA: 5 mg tablets - bottles of 100

10 mg tablets - bottles of 100 and 1000

40 mg tablets - bottles of 100

70 mg tablets - unit-of-use blisters of 4s, unit dose package of 20s, bottles of 12 and 100
35 mg tablets - unit-of-use blisters of 4s, unit dose package of 20s, bottles of 12 and 100

The innovator will package its 70 mg and 35 mg product in unit dose blisters of 4 and 20. Product will not be packed in bottles. The decision to only package in unit dose blisters **was not** based on safety issues, according to the PM, Randy Hedin. We will allow bottles at this time. [redacted] (b) (4)

[redacted] (b) (4)

The applicant is proposing to package its product in bottles of 12 and 100.

9. Regulatory will determine if the inclusion of the 35 mg strength will hold up approval of the 5 mg, 10, 40 mg. As for now the insert models the reference listed drug is all respects based on the exclusivity expiration for the 35 mg once weekly strength. Regulatory has stated that the product can get a TA until April 2003 when the exclusivity expires for the once weekly dosing 35 mg and 70 mg strengths. Please note that in the event that Reg. permits approving the 5, 10 and 40 mg strengths separately the firm has submitted such labeling in the January 14, 2002 submission.

Date of Review: May 15, 2002 **Date of Submission: April 26, 2002**

cc: ANDA: 75-710
DUP/DIVISION FILE
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Review

5/16/2002
5/16/2002

Tentative APPROVAL SUMMARY (minor)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	75-710
Date of Submission	June 21, 2002
Applicant	Teva Pharmaceuticals
Drug Name	Alendronate Sodium Tablets,
Strength(s)	5 mg, 10 mg, 40 mg, 35 mg and 70 mg

Draft Approval Summary		
Container Labels		**Submitted**
5 mg, 10 mg, and 40 mg	100s	Jan 14, 2002 vol. 7.1, FPL
10 mg	1000s	Jan 14, 2002 vol. 7.1, FPL
35 mg and 70 mg	12s and 100s	Jun 21, 2002 vol. 10.1 draft
Unit-dose Blister labels		
35 mg and 70 mg	4s and 20s	Jun 21, 2002 vol. 10.1 draft
Blister Carton labeling		
35 mg and 70 mg	4s and 20s	Jun 21, 2002 vol. 10.1 draft
Package Insert Labeling	Rev. 6/2002	Jun 21, 2002 vol. 10.1 draft with 35 &70 mg included.
Patient Daily leaflet	#XXXXXRev.	Apr. 26, 2002 vol. 9.1, FPL in attach 5
Patient weekly leaflet	#XXXXRev.	Apr. 26, 2002 vol. 9.1 FPL in attach 5

BASIS OF APPROVAL: Patent Data – NDA 20-560*

No	Expiration	Use Code	Use	How file	Labeling Impact
4621077	Aug 06, 2007	U-114	Inhibiting bone resorption	MOU	Carved Out
5358941	Dec 02, 2012		Dry mix formulation with biphosphoric acids w/lactose	PIV	
5681590	Dec 02, 2012		Dry mix formulation w/biphosphoric acid	PIV	
5804570	Feb 17, 2015		Method of lessening risk of nonvertebral bone fractures	PIV	Same as
5849726	Jun 06, 2015		Salt formulation	PIV	
6008207	Jun 06, 2015	U-303	Method of treating osteoporosis, Paget's Disease prevention & treatment of glucocorticoid-induced osteopososis	MOU changed to PIV	Same as
6090410	Dec 02,2012		Dry mix formulation w/biphosphoric acid	PIV	
6194004	Dec 02,2012		Dry mix formulation w/biphosphoric acid	PIV	
5994329	Jun 17, 2018		Method of inhibiting bone resorption	PIV	Same as
6225294	Jul 17, 2018		Method of inhibiting bone resorption	PIV	Same as
6015801	Jun 17, 2018	U-353	Prevention and treatment of osteoporosis	PIV	Same as

*Black print =5,10,40,35 and 70 mg strengths; Blue print = 5, 10, 40 mg strengths, Brown print = 35 mg and 70 mg (once weekly) strengths.

Exclusivity Data– NDA 20-560*

Code	Reference	Expiration	Labeling impact
I-272	Treatment of glucocorticoid induced osteoporosis in men and women receiving daily doses of glucocorticoids ≥ 7.5 mg prednisone & who have low bone mineral density	June 16, 2002	Same As
I-309	Increase bone mass in men with osteoporosis	Sept. 29, 2003	Same As
M-3	Efficacy and safety information in which alendronate was used concomitantly	Nov 24, 2002	Same As

	with estrogen alone or with estrogen plus progestin		
NS	Introduction of 35 mg and 70 mg strengths	Oct. 20, 2003	Same As
D-61	Once weekly dosing for the treatment of postmenopausal osteoporosis	Oct. 20, 2003	Same AS
D-62	Once weekly dosing for prevention of postmenopausal osteoporosis	Oct. 20, 2003	Same As

* Blue print = 5, 10, 40 mg strengths; Brown print = 35 and 70 mg (once weekly). Created 10/12/01 amp.

Reference Listed Drug

RLD on the 356(h) form	Fosamax Tablets
NDA Number	20-560
RLD established name	Alendronate Sodium Tablets
Firm	Merck
Currently approved PI	S/024 and 025
AP Date	January 31, 2001

Note. Check on status of pending supplements.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	

Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING:

   The labeling review was based on the labeling for the reference listed drug, FOSAMAX® (Merck; NDA#20-560/S-024 and 025; approved January 31, 2001).

2. PATENTS/EXCLUSIVITIES. Current submission of August 20, 2001 page 11 cites PIV for all patents. And the feb. 2, 28, 2001 exclusivities certifies that firm will not market the 70 and 35 mg strengths until after the expiration of the patients. Since this is a combined insert for the 5 mg, 10 mg , 40 mg strengths then, firm cannot go to market until 2003. See chart above.

3. MANUFACTURING FACILITY (Vol. 1.14, page 6047)

   TEVA Pharmaceuticals USA
   650 Cathill Road
   Sellersville, PA, 18960

4. SCORING/PRODUCT DESCRIPTION

   NDA: 5 mg - white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other.

   10 mg - white, round, uncoated tablets with a bone image and code MRK 936 on one side and a bone image and FOSAMAX on the other.

   40 mg - white, triangular-shaped, uncoated tablets with code MRK 212 on one side and FOSAMAX on the other.

   70 mg - white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the

other.
35 mg - white, oval, uncoated tablets with code 77 on one side and an outline of a bone image on the other.

ANDA: 5 mg - white to off-white, round flat-faced beveled-edge tablets debossed with "93" on one side and "5140" on the other side.

10 mg - white to off-white, round, convex tablets debossed with "93" on one side and "5141" on the other side.

40 mg - white to off-white, oval convex tablets debossed with "93" on one side and "5142" on the other side.

70 mg - white to off-white, pillow shaped, convex tablets debossed with "93" on one side and "5171" on the other side.

35 mg strength. white to off-white, pillow shaped, convex tablets debossed with "93" on one side and "5172" on the other side.

5. STORAGE RECOMMENDATIONS:

NDA: Store in a well-closed container at room temperature, 15-30°C (59-86°F).

ANDA: Store at (b) (4)

USP: Not applicable

6. DISPENSING RECOMMENDATIONS:

NDA: None

ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

7. INACTIVE INGREDIENTS (Vol. 3.1, Section V, page 11A)

There is no discrepancy between the listing in the DESCRIPTION section of the insert labeling and the Components and Composition Statements for the 5 mg, 10 mg, and 40 mg products. However at the time this amendment was submitted, the 35 mg and 70 mg products were not on the market and were unavailable to Teva. Teva, therefore, compared its 70 mg product with the 10 mg product .

8. PRODUCT LINE:

RLD: 5 mg tablets - unit of use bottles of 30 and 100

10 mg tablets - unit of use bottles of 30 and 100; unit dose packages of 100; bottles of 1000; UNIBLISTER cards of 31 tablets for hospital use.

40 mg tablets - unit of use bottles of 30

70 mg tablets - unit of use blister package of 4 tablets; unit dose packages of 20

35 mg tablets - unit of use blister package of 4 tablets; unit dose packages of 20

ANDA: 5 mg tablets - bottles of 100

10 mg tablets - bottles of 100 and 1000

40 mg tablets - bottles of 100

70 mg tablets - unit-of-use blisters of 4s, unit dose package of 20s, bottles of 12 and 100
35 mg tablets - unit-of-use blisters of 4s, unit dose package of 20s, bottles of 12 and 100

The innovator will package its 70 mg and 35 mg product in unit dose blisters of 4 and 20. Product will not be packed in bottles. The decision to only package in unit dose blisters **was not** based on safety issues, according to the PM, Randy Hedin. We will allow bottles at this time. (b) (4)

(b) (4)

The applicant is proposing to package its product in bottles of 12 and 100.

9. Regulatory will determine if the inclusion of the 35 mg strength will hold up approval of the 5 mg, 10, 40 mg. As for now the insert models the reference listed drug is all respects based on the exclusivity expiration for the 35 mg once weekly strength. Regulatory has stated that the product can get a TA until April 2003 when the exclusivity expires for the once weekly dosing 35 mg and 70 mg strengths. Please note that in the event that Reg. permits approving the 5, 10 and 40 mg strengths separately the firm has submitted such labeling in the January 14, 2002 submission.

Date of Review: July 8, 2002 **Date of Submission: June 21, 2002**

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cc: ANDA: 75-710
DUP/DIVISION FILE
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Review

7/8/02
7/9/2002

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	75-710
Date of Submission	November 20, 2007 (amendment)
Applicant	Teva Pharmaceuticals USA
Drug Name	Alendronate Sodium Tablets, USP
Strength(s)	5 mg, 10 mg, and 40 mg daily & 35 mg and 70 mg once weekly

Labeling Deficiencies:

1. GENERAL COMMENT:
   70 mg: The contain label states "Each tablet contains 91.36 mg..." The carton labeling states "Each tablet contains 91.37 mg..." Please comment. Ensure that the "Each tablet contains" statement is consistent with the description section of the insert labeling and your composition statement.

2. CONTAINER LABELS for once-daily tablets (5 mg, 40 mg: 30s, 100s; 10 mg: 30s, 100s, 1000s)
   Satisfactory in final print as submitted in the November 20, 2007 e-amendment.

3. CONTAINER LABELS for once-weekly tablets (35 mg and 70 mg: 12s and 100s)
   a. 35 mg: Add "Once Weekly" above the established name.
   b. 70 mg:
      i. We encourage you to relocate "Once Weekly" to appear above the established name.
      ii. Bottle of 12s: The NDC number on the bar code does not match the NDC number on the principal display panel. Please comment.

4. UNIT-DOSE BLISTERS (35 mg and 70 mg: 5 x 2)
   Once Weekly
   ALENDRONATE SODIUM Tablet USP
   XX mg (base)

5. UNIT-OF-USE BLISTERS (35 mg and 70 mg: 4s)
   Once Weekly
   ALENDRONATE SODIUM Tablet USP
   XX mg (base)

6. UNIT-DOSE CARTON (35 mg and 70 mg: 2 x 10)
   a. We encourage you to relocate "Once Weekly" to appear above the established name.
   b. Revise "(b) (4) not intended for dispensing." to read "This container not intended for dispensing."

7. UNIT-OF-USE CARTON (35 mg and 70 mg: 1 x 4s)
   a. How to take section: revise "alendronate sodium tablets (Once Weekly)" to read "Once Weekly alendronate sodium tablets".
   b. We encourage you to relocate "Once Weekly" to appear above the established name.

8. PROFESSIONAL INSERT
   a. Merck received 3 years Waxman-Hatch marketing exclusivity for miscellaneous exclusivity (M-51 – information added to labeling regarding osteogenesis imperfecta study). The attached labeling is consistent with the recommendations of the BPCA consult. Please revise your insert labeling to be in accord with the attached labeling, regardless of which strength(s) of the tablet formulation you're seeking approval for. Ensure that you have addressed the patents and exclusivities in the orange book.
   b. You are reminded final printed labels must be true to color, size and clarity. The PDF file of the FPL should be text based (not image based). Please also provide a word document to facilitate our review.

9. PATIENT WEEKLY-DOSE LEAFLET:
   Please revise your once weekly patient information leaflet to be in accord with the attached labeling.

10. PATIENT DAILY-DOSE LEAFLET:
Please revise your once daily patient information leaflet to be in accord with the attached labeling.

Revise your labeling, as instructed above, and submit final printed labeling electronically. In addition, please review the guidance for industry titled Providing Regulatory Submissions in Electronic Format-Content of Labeling. Please provide the labeling in the Structured Product Labeling (SPL) format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the model labeling with all differences annotated and explained.

Attached: Model Labeling

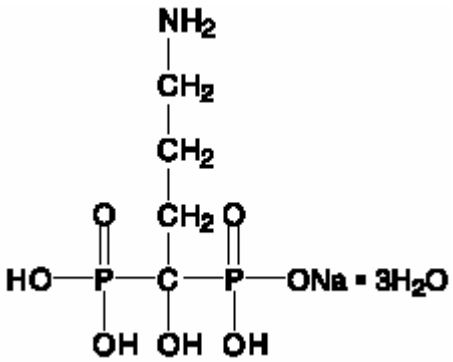
Model Labeling

Alendronate Sodium Tablets, USP

DESCRIPTION: Alendronate sodium is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxy-butylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is C4H12NNaO7P2•3H2O and its formula weight is 325.12. The structural formula is:



Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform. [Ensure that the description pertains to your drug substance]

Each tablet, for oral administration contains [include applicable strengths] of alendronate monosodium salt trihydrate, which is the molar equivalent of [include applicable strengths], respectively, of free acid, and the following inactive ingredients: [inactive ingredient list].

CLINICAL PHARMACOLOGY:

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.

Pharmacokinetics:

Absorption: Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution: Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism: *There* is no evidence that alendronate is metabolized in animals or humans.

Excretion: Following a single IV dose of [14C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with alendronate sodium (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations:

Pediatric: Alendronate is not indicated for use in children. Due to Merck's marketing exclusivity rights, this generic drug product is not approved with descriptive pharmacokinetic information in pediatric patients. Merck's alendronate sodium tablets and oral solution are approved with that descriptive pharmacokinetic information.

Gender: Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric: Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION).**

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: 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). **Alendronate sodium 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.**

Hepatic Insufficiency: 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. ***Drug Interactions*** (also see **PRECAUTIONS,** ***Drug Interactions)***

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

Pharmacodynamics: Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in postmenopausal women: Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5,20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with alendronate sodium 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received alendronate sodium 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with alendronate sodium. In osteoporosis treatment studies alendronate sodium 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau after 6 to 12 months. In osteoporosis prevention studies alendronate sodium 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with once weekly alendronate sodium 70 mg for the treatment of osteoporosis and once weekly alendronate sodium 35 mg for the prevention of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with alendronate sodium. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of alendronate sodium 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment; however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with alendronate sodium 5 mg/day. In one-year studies with once weekly alendronate sodium 35 and 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to alendronate sodium but also a decrease in renal phosphate reabsorption.

Osteoporosis in men: Treatment of men with osteoporosis with alendronate sodium 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly alendronate sodium 70 mg.

Glucocorticoid-induced Osteoporosis: Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone for-

mation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to two years' duration, alendronate sodium 5 and 10 mg/day reduced cross-linked N-telopeptides of type 1 collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition of bone resorption, alendronate sodium 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

Paget's disease of bone: Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

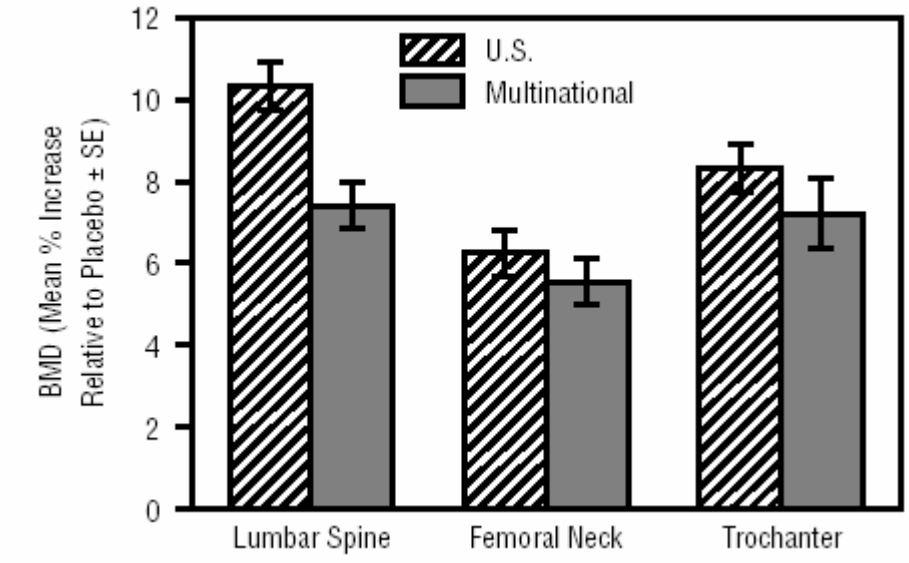
Alendronate sodium decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, alendronate sodium 40 mg once daily for six months produced significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, alendronate sodium induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

Clinical Studies:

Treatment of osteoporosis in postmenopausal women: Effect on bone mineral density: The efficacy of alendronate sodium 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multi-center studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving alendronate sodium 10 mg/day relative to placebo-treated patients at three years for each of these studies.

Osteoporosis Treatment Studies in Postmenopausal Women

Increase in BMD Alendronate Sodium 10 mg/day
at Three Years

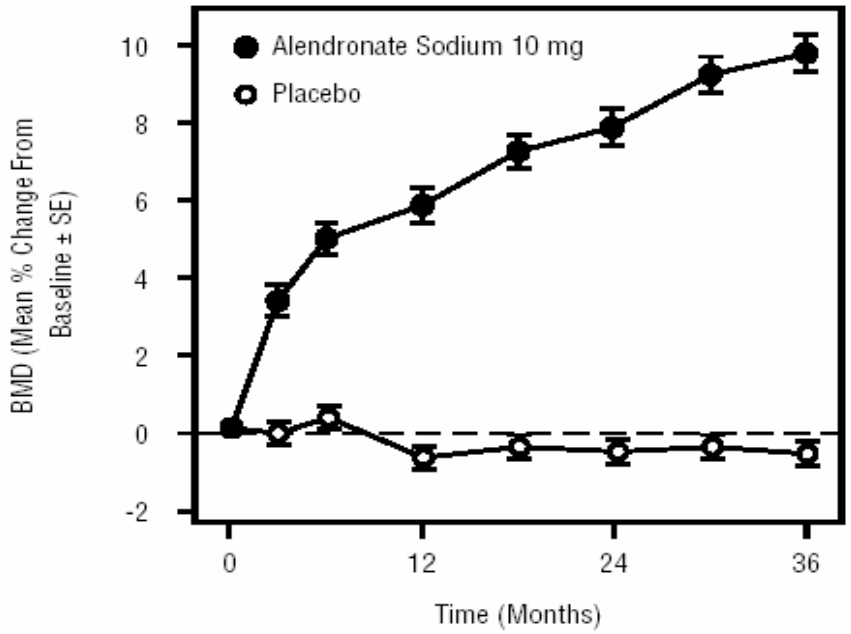


At three years significant increases in BMD, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received alendronate sodium 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the three years of treatment. (See figures below for lumbar spine results.) In the two-year extension of these studies, treatment of 147 patients with alendronate sodium 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. Alendronate sodium was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at least 2 standard deviations below the premenopausal mean). Thus, overall alendronate sodium reverses the loss of bone mineral density, a central factor in the progression of osteoporosis.

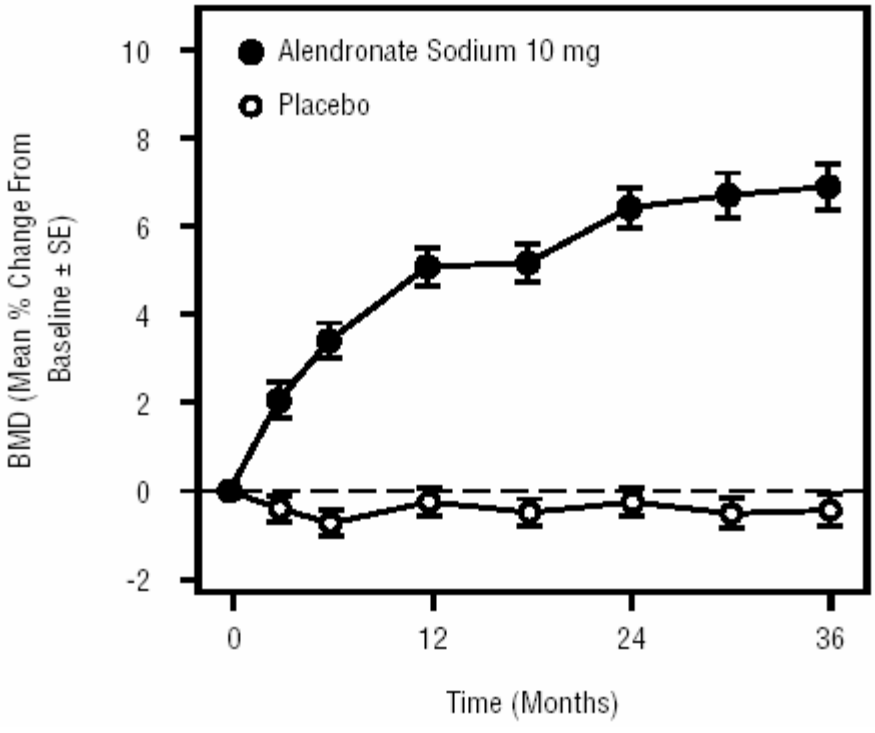
Osteoporosis Treatment Studies in Postmenopausal Women

Time Course of Effect of Alendronate Sodium 10 mg/day Versus Placebo: Lumber Spine BMD Percent Change From Baseline

U.S. Study



Multinational Study



In patients with postmenopausal osteoporosis treated with alendronate sodium 10 mg/day for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups. These data indicate that continued treatment with alendronate sodium is required to maintain the effect of the drug.

The therapeutic equivalence of once weekly alendronate sodium 70 mg (n=519) and alendronate sodium 10 mg daily (n=370) was demonstrated in a one-year, double-blind, multi-center study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8,5.4%; 95% CI) in the 70-mg once-weekly group (n=440) and 5.4% (5.0,5.8%; 95% CI) in the 10-mg daily group (n=330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Effect on fracture incidence: Data on the effects of alendronate sodium on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

To assess the effects of alendronate sodium on the incidence of vertebral fractures (detected by digitized radiography; approximately one-third of these were clinically symptomatic), the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of alendronate sodium (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients treated with alendronate sodium experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received alendronate sodium had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in post-menopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study); approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial:

Three-Year Study (patients with at least one baseline radiographic vertebral fracture): *This* randomized, double-blind, placebo-controlled, 2027-patient study (alendronate sodium, n=1022; placebo, n=1005) demonstrated that treatment with alendronate sodium resulted in statistically significant reductions in fracture incidence at three years as shown in the table below.

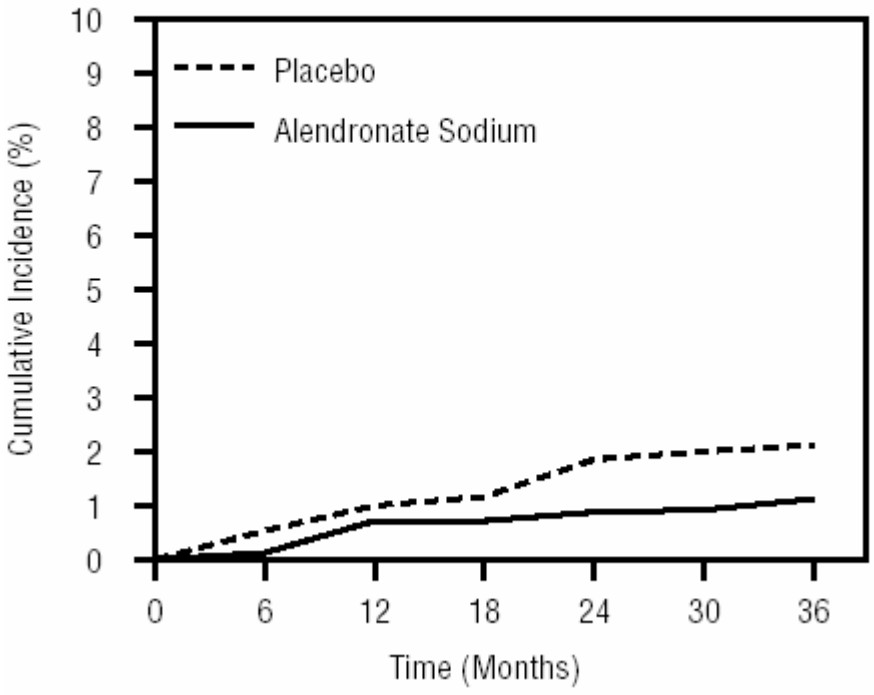
Effect of Alendronate Sodium on Fracture Incidence in the Three-Year Study of FIT (patients with vertebral fracture at baseline)				
	Percent of Patients			
	Alendronate Sodium (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)†				
≥1 new vertebral fracture	7.9	15.0	7.1	47***
≥2 new vertebral fractures	0.5	4.9	4.4	90***
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	26‡
≥1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54**
Hip fracture	1.1	2.2	1.1	51*
Wrist (forearm) fracture	2.2	4.1	1.9	48*

†Number evaluable for vertebral fractures: Alendronate sodium, n=984; placebo, n=966
*p<0.05, **p<0.01, ***p<0.001, ‡p=0.007

Furthermore, in this population of patients with baseline vertebral fracture, treatment with alendronate sodium significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on alendronate sodium, p=0.047. The figure below displays the cumulative incidence of hip fractures in this study.

Cumulative Incidence of Hip Fractures in the Three-Year Study of FIT
(patients with radiographic vertebral fracture at baseline)



Fracture Intervention Trial:
Four-Year Study (patients with low bone mass but without a baseline radiographic vertebral fracture): *This* randomized, double-blind, placebo-controlled, 4432-patient study (alendronate sodium, n=2214; placebo, n=2218) further investigated the reduction in fracture incidence due to alendronate sodium. The intent of the study was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

Effect of Alendronate Sodium on Fracture Incidence in Osteoporotic† Patients in the Four-Year Study of FIT (patients without vertebral fracture at baseline)

	Percent of Patients			
	Alendronate Sodium (n=1545)	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)††				
≥1 new vertebral fracture	2.5	4.8	2.3	48***
≥2 new vertebral fractures	0.1	0.6	0.5	78*
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22**
≥1 clinical (symptomatic) vertebral fracture	1.0	1.6	0.6	41 (NS)†††
Hip fracture	1.0	1.4	0.4	29 (NS)†††
Wrist (forearm) fracture	3.9	3.8	-0.1	NS†††

† Baseline femoral neck BMD at least 2 SD below the mean for young adult women

†† Number evaluable for vertebral fractures: Alendronate sodium, n=1426; placebo, n=1428

††† Not significant. This study was not powered to detect differences at these sites.

*p=0.035, **p=0.01, ***p<0.001

Fracture results across studies: In the Three-Year Study of FIT, alendronate sodium reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, p<0.001); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction, p=0.001);and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, p=0.034).

Alendronate sodium reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, p<0.001) in the combined U.S./Multinational studies and from 4.9% to 0.5% (90% relative risk reduction, p<0.001) in the Three-Year Study of FIT. In the Four-Year Study of FIT, alendronate sodium reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, p=0.035).

Thus, alendronate sodium reduced the incidence of radiographic vertebral fractures in osteoporotic women whether or not they had a previous radiographic vertebral fracture.

Alendronate sodium, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.

Bone histology: Bone histology in 270 postmenopausal patients with osteoporosis treated with alendronate sodium at doses ranging from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed during therapy with alendronate sodium is of normal quality.

Men: The efficacy of alendronate sodium in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.

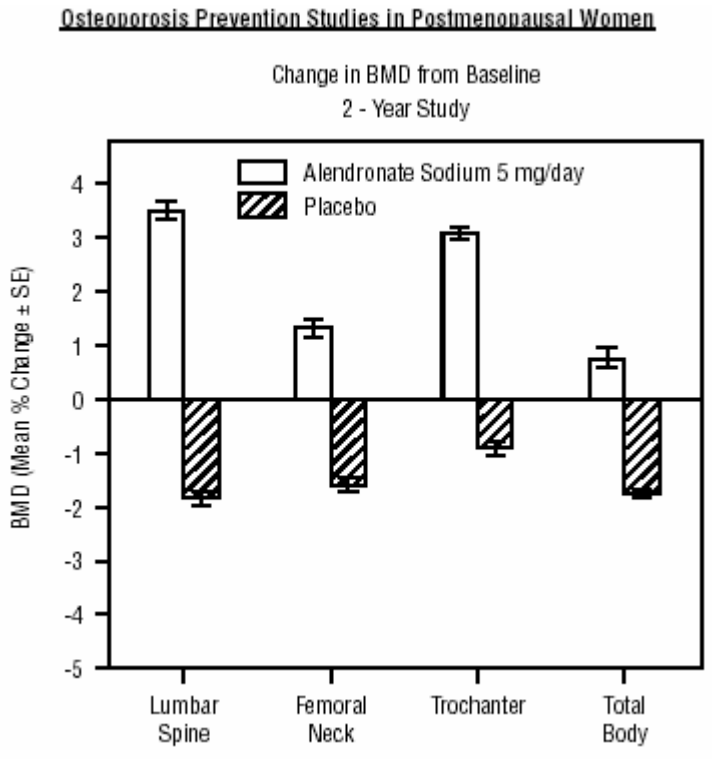
A two-year, double-blind, placebo-controlled, multi-center study of alendronate sodium 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving alendronate sodium 10 mg/day were significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with alendronate sodium also reduced height loss (alendronate sodium, -0.6 mm vs. placebo, -2.4 mm).

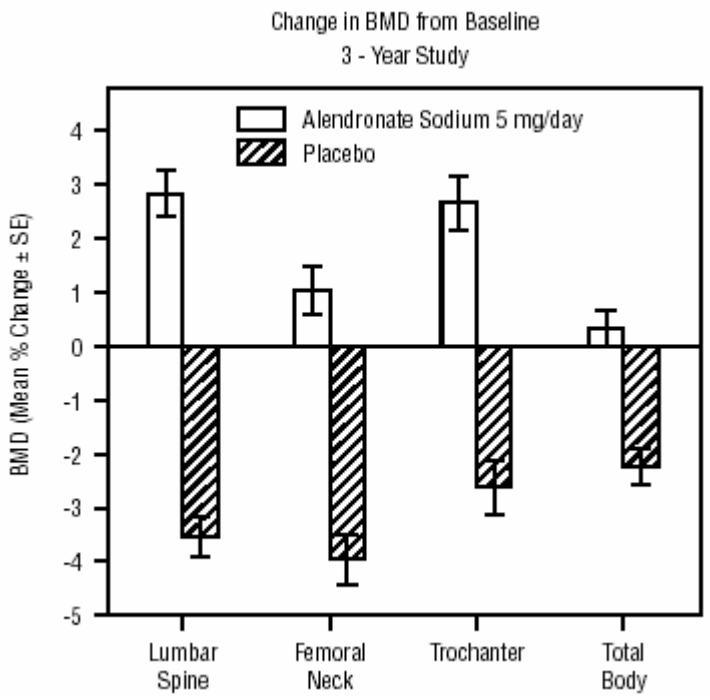
A one-year, double-blind, placebo-controlled, multi-center study of once weekly alendronate sodium 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, 2) a BMD T-score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving alendronate sodium 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

In both studies, BMD responses were similar regardless of age (≥65 years vs. <65 years), gonadal function (baseline testosterone <9 ng/dL vs. ≥9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤-2.5 vs. >-2.5).

Prevention of osteoporosis in postmenopausal women: Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40 to 60 years of age. One thousand six hundred nine patients (alendronate sodium 5 mg/day; n = 498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (alendronate sodium 5 mg/day; n = 88), who were between six months and three years postmenopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1 % per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, alendronate sodium 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). In addition, alendronate sodium 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo.

Alendronate sodium 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.





The therapeutic equivalence of once weekly alendronate sodium 35 mg (n=362) and alendronate sodium 5 mg daily (n=361) was demonstrated in a one-year, double-blind, multi-center study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35-mg once-weekly group (n=307) and 3.2% (2.9, 3.5%; 95% CI) in the 5-mg daily group (n=298). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Bone histology: Bone histology was normal in the 28 patients biopsied at the end of three years who received alendronate sodium at doses of up to 10 mg/day.

Concomitant use with estrogen/hormone replacement therapy (HRT): The effects on BMD of treatment with alendronate sodium 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or alendronate sodium alone (both 6.0%).

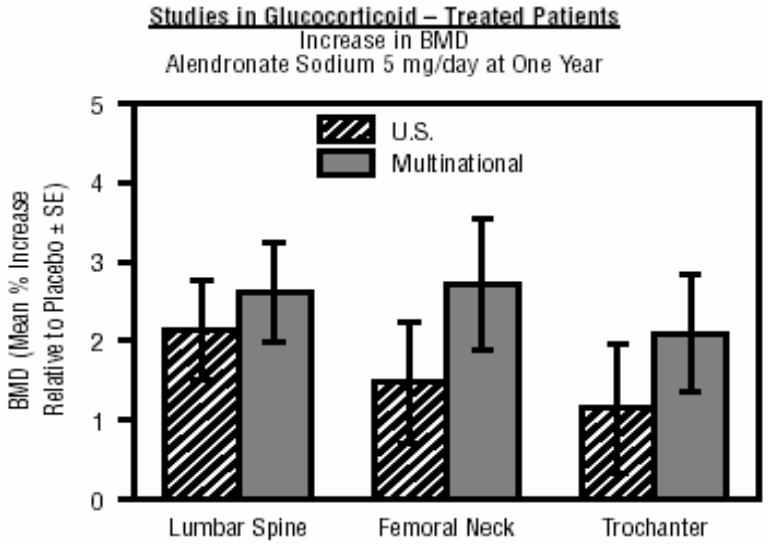
The effects on BMD when alendronate sodium was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of alendronate sodium 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1 %).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral

neck, and trochanter. No significant effect was seen for total body BMD.

Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with alendronate sodium and HRT, 94% on alendronate sodium alone, and 78% on HRT alone. The long-term effects of combined alendronate sodium and HRT on fracture occurrence and fracture healing have not been studied.

Glucocorticoid-inducedosteoporosis: *The* efficacy of alendronate sodium 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multi-center studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included alendronate sodium 2.5 mg/day]). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving alendronate sodium 5 mg/day for each study.



After one year, significant increases relative to placebo in BMD were seen in the combined studies at each of these sites in patients who received alendronate sodium 5 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller

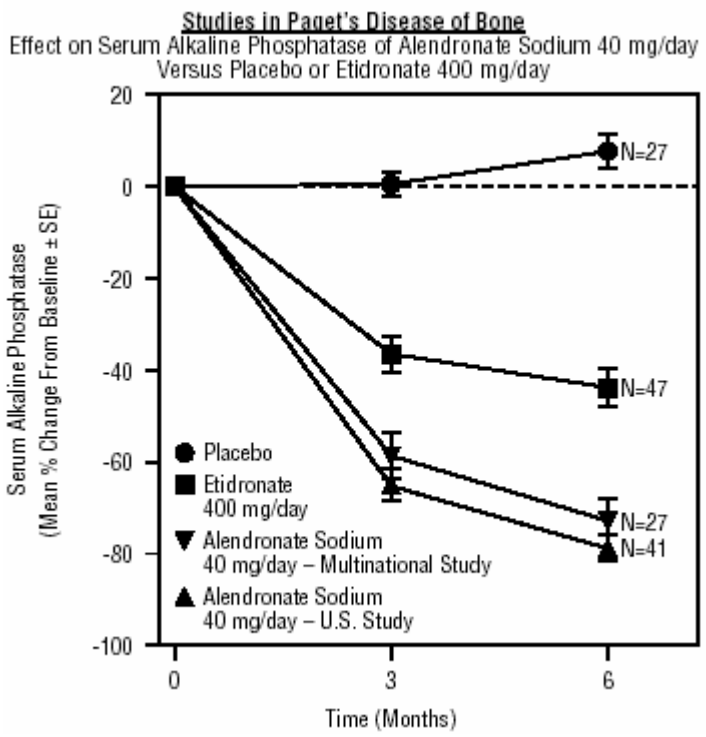
decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with alendronate sodium 5 mg/day. The increases in BMD with alendronate sodium 10 mg/day were similar to those with alendronate sodium 5 mg/day in all patients except for postmenopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with alendronate sodium 10 mg/day were greater than those with alendronate sodium 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. Alendronate sodium was effective regardless of dose or duration of glucocorticoid use. In addition, alendronate sodium was similarly effective regardless of age (<65 vs. ≥65 years), race (Caucasian vs. other races), gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone histology was normal in the 49 patients biopsied at the end of one year who received alendronate sodium at doses of up to 10 mg/day.

Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with alendronate sodium 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

After one year, 2.3% of patients treated with alendronate sodium 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with alendronate sodium (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (alendronate sodium 0.7% vs. placebo 6.8%).

Paget's disease of bone: The efficacy of alendronate sodium 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled, multinational study and a U.S. comparative study with etidronate disodium 400 mg/day. The following figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.



At six months the suppression in alkaline phosphatase in patients treated with alendronate sodium was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline ≥60%) occurred in approximately 85% of patients treated with alendronate sodium in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. Alendronate sodium was similarly effective regardless of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with alendronate sodium 40 mg/day for 6 months. As in patients treated for osteoporosis (see **Clinical Studies, *Treatment of osteoporosis in postmenopausal women, Bone histology),*** alendronate sodium did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with alendronate sodium, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with alendronate sodium is of normal quality.

ANIMAL PHARMACOLOGY: The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered

with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE: Alendronate sodium tablets are indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women
  - For the treatment of osteoporosis, alendronate sodium tablets increase bone mass and reduce the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture. (See **CLINICAL PHARMACOLOGY, *Pharmacodynamics.)***
  - For the prevention of osteoporosis, alendronate sodium tables may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture. Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of post-menopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of alendronate sodium for prevention of osteoporosis.
- Treatment to increase bone mass in men with osteoporosis.
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see **PRE CAUTIONS, *Glucocorticoid-induced osteoporosis).*** Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.
- Treatment of Paget's disease of bone in men and women
  - Treatment is indicated in patients with Paget's disease of bone hav ing alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complica tions from their disease.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Hypersensitivity to any component of this product
- Hypocalcemia (see **PRECAUTIONS, *General)***

WARNINGS: Alendronate sodium, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with alendronate sodium. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue alendronate sodium and seek medical atten-

tion if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking alendronate sodium and/or who fail to swallow it with the recommended amount of water, and/or who continue to take alendronate sodium after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see **DOSAGE AND ADMINISTRATION).** In patients who cannot comply with dosing instructions due to mental disability, therapy with alendronate sodium should be used under appropriate supervision.

Because of possible irritant effects of alendronate sodium on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when alendronate sodium is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

There have been post-marketing reports of gastric and duodenal ulcers, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS:

General: Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with alendronate sodium (see **CONTRAINDICATIONS).** Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with alendronate sodium.

Presumably due to the effects of alendronate sodium on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain: In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see **ADVERSE REACTIONS).** However, such reports have been infrequent. This category of drugs includes alendronate sodium. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of alendronate sodium, the percentages of patients with these symptoms were similar in the alendronate sodium and placebo groups.

Dental: Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radio-

therapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., pre-existing dental disease, anemia, coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Renal insufficiency: Alendronate sodium is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See **DOSAGE AND ADMINISTRATION.)**

Glucocorticoid-induced osteoporosis: The risk versus benefit of alendronate sodium for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see **INDICATIONS AND USAGE).** Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined alendronate sodium and glucocorticoid treatment.

The efficacy of alendronate sodium for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of alendronate sodium has been established in studies of two years' duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of alendronate sodium beyond two years has not been studied.

The efficacy of alendronate sodium in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients:

General: Physicians should instruct their patients to read the patient package insert before starting therapy with alendronate sodium and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions: Patients should be instructed that the expected benefits of alendronate sodium may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of alendronate sodium (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, *Absorption).***

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of alendronate sodium with a full glass of water (6 to 8 oz). Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of

a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take alendronate sodium at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking alendronate sodium and consult their physician.

Patients should be instructed that if they miss a dose of once weekly alendronate sodium, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Drug Interactions: (also see **CLINICAL PHARMACOLOGY, Pharmacokinetics, *Drug Interactions)***

Estrogen/hormone replacement therapy (HRT): Concomitant use of HRT (estrogen ± progestin) and alendronate sodium was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined alendronate sodium and HRT on fracture occurrence have not been studied (see **CLINICAL PHARMACOLOGY, Clinical Studies, Concomitant use with estrogen/hormone replacement therapy (HRT)** and **ADVERSE REACTIONS, Clinical Studies, Concomitant use with estrogen/hormone replacement therapy).**

Calcium Supplements/Antacids: It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of alendronate sodium. Therefore, patients must wait at least one-half hour after taking alendronate sodium 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 alendronate sodium greater than 10 mg and aspirin-containing products.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs): Alendronate sodium 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 alendronate sodium 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 alendronate sodium.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell muta-

genesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m2).

Pregnancy:

Pregnancy Category C: Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

There are no studies in pregnant women. Alendronate sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers: It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when alendronate sodium is administered to nursing women.

Pediatric Use: *The efficacy and safety of alendronate sodium 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 alendronate sodium daily (weight <40 kg) or 10 mg alendronate sodium daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine 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 alendronate sodium-treated patients and 0.1 in the placebo-treated patients. Treatment with alendronate sodium did not reduce the risk of fracture. Sixteen percent of the alendronate sodium 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 alendronate sodium -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 alendronate sodium and placebo groups in reduction of bone pain.

Alendronate sodium tablets are not indicated for use in children.

(For clinical adverse experiences in children, see ADVERSE REACTIONS, Clinical Studies, Osteogenesis Imperfecta.)

Geriatric Use: Of the patients receiving alendronate sodium 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 alendronate sodium in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see **CLINICAL PHARMACOLOGY, Clinical 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.

ADVERSE REACTIONS:

Clinical Studies: In clinical studies of up to five years in duration adverse experiences associated with alendronate sodium usually were mild, and generally did not require discontinuation of therapy.

Alendronate sodium has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of osteoporosis:

Postmenopausal women: In two identically designed, three-year, placebo-controlled, double-blind, multi-center studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with alendronate sodium 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with alendronate sodium 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: alendronate sodium, 3.2%; placebo, 2.7%. In these study populations, 49 to 54% had a history of gastrointestinal disorders at baseline and 54 to 89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either alendronate sodium or placebo are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients				
	United States/ Multinational Studies		Fracture Intervention Trial	
	Alendronate Sodium* % (n=196)	Placebo % (n=397)	Alendronate Sodium** % (n=3236)	Placebo % (n=3223)
Gastrointestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
Nervous System/Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

*10 mg/day for three years
**5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred.

One patient treated with alendronate sodium (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and alendronate sodium were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of alendronate sodium in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of alendronate sodium in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with alendronate sodium 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly alendronate sodium 70 mg and alendronate sodium 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	Once Weekly Alendronate Sodium 70 mg % (n=519)	Alendronate Sodium 10 mg/day % (n=370)
Gastrointestinal		
abdominal pain	3.7	3.0
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distension	1.0	1.4
constipation	0.8	1.6
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle, joint) pain	2.9	3.2
muscle cramp	0.2	1.1

Men: In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of alendronate sodium 10 mg/day and a one-year study of once weekly alendronate sodium 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for alendronate sodium 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly alendronate sodium 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either alendronate sodium or placebo are presented in the following table.

Osteoporosis Studies in Men
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients

	Two-year Study		One-year Study	
	Alendronate Sodium 10 mg/day % (n=146)	Placebo % (n=95)	Once Weekly Alendronate Sodium 70 mg % (n=109)	Placebo % (n=58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

Prevention of osteoporosis in postmenopausal women: The safety of alendronate sodium 5 mg/day in postmenopausal women 40 to 60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive alendronate sodium for either two or three years. In these studies the overall safety profiles of alendronate sodium 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with alendronate sodium 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multi-center study, the overall safety and tolerability profiles of once weekly alendronate sodium 35 mg and alendronate sodium 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either once weekly alendronate sodium 35 mg, alendronate sodium 5 mg/day or placebo are presented in the following table.

Osteoporosis Prevention Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	Two/ Three-Year Studies		One-Year Study	
	Alendronate Sodium 5 mg/day % (n=642)	Placebo % (n=648)	Alendronate Sodium 5 mg/day % (n=361)	Once Weekly Alendronate Sodium 35 mg % (n=362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Concomitant use with estrogen/hormone replacement therapy: In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with alendronate sodium 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis: In two, one-year, placebo-controlled, double-blind, multi-center studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of alendronate sodium 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either alendronate sodium 5 or 10 mg/day or placebo are presented in the following table:

One-Year Studies in Glucocorticoid-Treated Patients Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients			
	Alendronate Sodium 10 mg/day % (n=157)	Alendronate Sodium 5 mg/day % (n=161)	Placebo % (n=159)
Gastrointestinal			
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (alendronate sodium: n=147) was consistent with that observed in the first year.

Paget's disease of bone: In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking alendronate sodium 40 mg/day for 3 to 12 months were similar to those in post-menopausal women treated with alendronate sodium 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking alendronate sodium 40 mg/day (17.7% alendronate sodium vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with alendronate sodium 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with alendronate sodium 40 mg/day and 2.4% of patients treated with placebo.

Osteogenesis Imperfecta:

Alendronate sodium tablets are not indicated for use in children.

The overall safety profile of alendronate sodium in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with alendronate sodium. However, there was an increased occurrence of vomiting in OI patients treated with alendronate sodium compared to placebo. During the 24-month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with alendronate sodium and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of alendronate sodium 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates, including alendronate sodium. See ADVERSE REACTIONS, *Post-Marketing Experience*, *Body as a Whole*.

Laboratory Test Findings: In double-blind, multi-center, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%,

respectively, of patients taking alendronate sodium versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience: The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with alendronate sodium, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see **WARNINGS, PRECAUTIONS, *Information for Patients,*** and **DOSAGE AND ADMINISTRATION).**

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see **PRECAUTIONS, *Dental).***

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see **PRECAUTIONS, *Musculoskeletal Pain);*** *joint swelling.*

Nervous system*: dizziness and vertigo.*

Skin: *rash* (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE: Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m2) and 966 mg/kg (2898 mg/m2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m2).

No specific information is available on the treatment of overdosage with alendronate sodium. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION: Alendronate sodium tablets must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see **PRECAUTIONS, *Information for Patients).*** Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of alendronate sodium tablets (see **PRECAUTIONS, *Drug Interactions).*** Waiting less than 30 minutes, or taking alendronate sodium tablets with food, beverages (other than plain water) or other medications will lessen the effect of alendronate sodium tablets by decreasing its absorption into the body.

Alendronate sodium tablets should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, an alendronate sodium tablet should be swallowed with a full glass of water (6 to 8 oz). Patients should not lie down for at least 30 minutes and until after their first food of the day. Alendronate sodium tablets should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see **WARNINGS, PRECAUTIONS, *Information for Patients).***

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see **PRECAUTIONS, *General).***

No dosage adjustment is necessary for the elderly or for patients with mild-

to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). Alendronate sodium tablets are not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see **INDICATIONS AND USAGE)**

The recommended dosage is:

- one 70 mg tablet once weekly
  or
- one 10 mg tablet once daily

Treatment to increase bone mass in men with osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly
  or
- one 10 mg tablet once daily.

Prevention of osteoporosis in postmenopausal women (see **INDICATIONS AND USAGE)** The recommended dosage is:

- one 35 mg tablet once weekly
  or
- one 5 mg tablet once daily.

The safety of treatment and prevention of osteoporosis with alendronate sodium has been studied for up to 7 years.

Treatment of glucocorticoid-induced osteoporosis in men and women: The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's disease of bone in men and women:*The* recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease: In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with alendronate sodium tablets. Specific retreatment data are not available, although responses to alendronate sodium tablets were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with alendronate sodium tablets may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED: Alendronate sodium tablets, for oral administration, are available as: [add information]

Store between 20^0-25^0C (68^0-77^0F) [see USP controlled room temperature].
Dispense in a tight, light-resistant container.

Revision date

Manufactured by:

Patient Information
Once Daily
Alendronate Sodium Tablets, USP

Read this information before you start taking Alendronate Sodium Tablets. Also, read the leaflet each time you refill your prescription, just in case anything has changed. This leaflet does not take the place of discussions with your doctor. You and your doctor should discuss Alendronate Sodium Tablets when you start taking your medicine and at regular checkups.

What is the most important information I should know about Alendronate Sodium Tablets?

- **You must take Alendronate Sodium Tablets exactly as directed to help make sure it works and to help lower the chance of problems in your esophagus (the tube that connects your mouth and stomach). (See "How should I take Alendronate Sodium Tablets?").**

- **If you have chest pain, new or worsening heartburn, or have trouble or pain when you swallow, stop taking Alendronate Sodium Tablets and call your doctor. (See "What are the possible side effects of Alendronate Sodium Tablets?").**

What is Alendronate Sodium Tablets?

Alendronate Sodium Tablets are prescription medicines for:
- The treatment or prevention of osteoporosis (thinning of bone) in women after menopause. It reduces the chance of having a hip or spinal fracture (break).
- Treatment to increase bone mass in men with osteoporosis.
- The treatment of osteoporosis in either men or women who are taking corticosteroid medicines (for example, prednisone).

Improvement in bone density may be observed as early as 3 months after you start taking Alendronate Sodium Tablets even though you won't see or feel a difference. For Alendronate Sodium Tablets to continue to work, you need to keep taking it.

Alendronate Sodium Tablets are not hormones.

There is more information about osteoporosis at the end of this leaflet.

Who should not take Alendronate Sodium Tablets?

Do not take Alendronate Sodium Tablets if you:
- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in your blood
- Are allergic to Alendronate Sodium Tablets or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before using Alendronate Sodium Tablets?
Tell your doctor about all of your medical conditions, including if you:

- **have problems with swallowing**
- **have stomach or digestive problems**
- **have kidney problems**

- **are pregnant or planning to become pregnant.** It is not known if Alendronate Sodium Tablets can harm your unborn baby.
- **are breastfeeding.** It is not known if Alendronate Sodium Tablets pass into your milk and if it can harm your baby.

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take Alendronate Sodium Tablets?

- Take 1 Alendronate Sodium Tablet once a day, every day **after** you get up for the day and **before** taking your first food, drink, or other medicine.

- Take Alendronate Sodium Tablets while you are sitting or standing.

- Swallow your Alendronate Sodium Tablet with a full glass (6-8 oz) of plain water only.

  Do **not** take Alendronate Sodium Tablets with:

  Mineral water
  Coffee or tea
  Juice

  Alendronate Sodium Tablets work only if taken on an empty stomach.

  Do not chew or suck on a tablet of Alendronate Sodium.

  After swallowing your Alendronate Sodium Tablet, wait at least 30 minutes:
  - before you lie down. You may sit, stand or walk, and do normal activities like reading.
  - before you take your first food or drink except for plain water.
  - before you take other medicines, including antacids, calcium, and other supplements and vitamins.

  Do not lie down until after first food of the day.

- It is important that you keep taking Alendronate Sodium Tablets for as long as your doctor says to take it. For Alendronate Sodium Tablets to continue to work, you need to keep taking it.

What should I do if I miss a dose of Alendronate Sodium Tablets or if I take too many?

- If you miss a dose, do not take it later in the day. Continue your usual schedule of 1 tablet once a day the next morning.

- If you think you took more than the prescribed dose of Alendronate Sodium Tablets, drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

What should I avoid while taking Alendronate Sodium Tablets?

- Do not eat, drink, or take other medicines or supplements **before** taking Alendronate Sodium Tablets.

- Wait for at least 30 minutes **after** taking Alendronate Sodium Tablets to eat, drink, or take other medicines or supplements.

- Do not lie down for at least 30 minutes **after** taking Alendronate Sodium Tablets. Do not lie down until **after** your first food of the day.

What are the possible side effects of Alendronate Sodium Tablets?

Alendronate Sodium Tablets may cause problems in your esophagus (the tube that connects the mouth and stomach). (See "What is the most important information I should know about Alendronate Sodium Tablets?".) These problems include irritation, inflammation, or ulcers of the esophagus, which may sometimes bleed. This may occur especially if you do not drink a full glass of water with Alendronate Sodium Tablets or if you lie down in less than 30 minutes or before your first food of the day.

- **Stop taking Alendronate Sodium Tablets and call your doctor right away if you get any of these signs of possible serious problems of the esophagus:**

  - **Chest pain**
  - **New or worsening heartburn**
  - **Trouble or pain when swallowing**

- Esophagus problems may get worse if you continue to take Alendronate Sodium Tablets.

- Mouth sores (ulcers) may occur if the Alendronate Sodium Tablets are chewed or dissolved in the mouth.

- You may get flu-like symptoms typically at the start of treatment with Alendronate Sodium Tablets.

- You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.

- Alendronate Sodium Tablets may cause jaw-bone problems in some people. Jaw-bone problems may include infection, and delayed healing after teeth are pulled.

- The most common side effect is stomach area (abdominal) pain. Less common side effects are nausea, vomiting, a full or bloated feeling in the stomach, constipation, diarrhea, black or bloody stools (bowel movements), gas, eye pain, rash that may be made worse by sunlight, headache, dizziness, a changed sense of taste, joint swelling or swelling in the hands or legs, and bone, muscle, or joint pain.

- **Call your doctor if you develop severe bone, muscle, or joint pain.**

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects with Alendronate Sodium Tablets. Ask your doctor or pharmacist for more information.

How do I store Alendronate Sodium Tablets?

- Store Alendronate Sodium Tablets at room temperature, 68 to 77°F (20 to 25°C).
- Safely discard Alendronate Sodium Tablets that is out-of-date or no longer needed.
- **Keep Alendronate Sodium Tablets and all medicines out of the reach of children.**

General information about using Alendronate Sodium Tablets safely and effectively

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Alendronate Sodium Tablets for a condition for which it was not prescribed. Do not give Alendronate Sodium Tablets to other people, even if they have the same symptoms you have. It may harm them.

Alendronate Sodium Tablets are not indicated for use in children.

This leaflet is a summary of information about Alendronate Sodium Tablets. If you have any questions or concerns about Alendronate Sodium Tablets or osteoporosis, talk to your doctor, pharmacist, or other health care provider. You can ask your doctor or pharmacist for information about Alendronate Sodium Tablets written for health care providers. For more information, call [provide contact information].

What are the ingredients in Alendronate Sodium Tablets?

Alendronate Sodium Tablets contain alendronate sodium as the active ingredient and the following inactive ingredients: [provide contact information].

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.

At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, your spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who:
- Are going through or who are past menopause

Men who:
- Are elderly

People who:
- Are white (Caucasian) or oriental (Asian)
- Are thin
- Have family member with osteoporosis
- Do not get enough calcium or vitamin D

- Do not exercise
- Smoke
- Drink alcohol often
- Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help prevent or treat osteoporosis?

In addition to Alendronate Sodium Tablets, your doctor may suggest one or more of the following lifestyle changes:

- **Stop smoking.** Smoking may increase your chance of getting osteoporosis.
- **Reduce the use of alcohol.** Too much alcohol may increase the risk of osteoporosis and injuries that can cause fractures.
- **Exercise regularly.** Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.
- **Eat a balanced diet.** Having enough calcium in your diet is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements, such as calcium or vitamin D.

Rx only

Manufactured by:

Revision date:

Patient Information
Once Weekly
Alendronate Sodium Tablets, USP

Read this information before you start taking Alendronate Sodium Tablets. Also, read the leaflet each time you refill your prescription, just in case anything has changed. This leaflet does not take the place of discussions with your doctor. You and your doctor should discuss Alendronate Sodium Tablets when you start taking your medicine and at regular checkups.

What is the most important information I should know about once weekly Alendronate Sodium Tablets?

- **You must take once weekly Alendronate Sodium Tablets exactly as directed to help make sure it works and to help lower the chance of problems in your esophagus (the tube that connects your mouth and stomach). (See "How should I take once weekly Alendronate Sodium Tablets?").**

- **If you have chest pain, new or worsening heartburn, or have trouble or pain when you swallow, stop taking Alendronate Sodium Tablets and call your doctor. (See "What are the possible side effects of Alendronate Sodium Tablets?").**

What is Alendronate Sodium Tablets?

Alendronate Sodium Tablets are prescription medicines for:
- The treatment or prevention of osteoporosis (thinning of bone) in women after menopause. It reduces the chance of having a hip or spinal fracture (break).
- Treatment to increase bone mass in men with osteoporosis.

- Alendronate Sodium Tablets are for treatment and prevention of osteoporosis.

Improvement in bone density may be observed as early as 3 months after you start taking Alendronate Sodium Tablets even though you won't see or feel a difference. For Alendronate Sodium Tablets to continue to work, you need to keep taking it.

Alendronate Sodium Tablets are not hormones.

There is more information about osteoporosis at the end of this leaflet.

Who should not take Alendronate Sodium Tablets?

Do not take Alendronate Sodium Tablets if you:
- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in your blood
- Are allergic to Alendronate Sodium Tablets or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before using Alendronate Sodium Tablets?

Tell your doctor about all of your medical conditions, including if you:

- **have problems with swallowing**
- **have stomach or digestive problems**
- **have kidney problems**

- **are pregnant or planning to become pregnant.** It is not known if Alendronate Sodium Tablets can harm your unborn baby.
- **are breastfeeding.** It is not known if Alendronate Sodium Tablets passes into your milk and if it can harm your baby.

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take once weekly Alendronate Sodium Tablets?

- Choose the day of the week that best fits your schedule.

- Take 1 dose of Alendronate Sodium Tablets every week on your chosen day **after** you get up for the day and **before** taking your first food, drink, or other medicine

- Take Alendronate Sodium Tablets while you are sitting or standing.

- Take your Alendronate Sodium Tablets with plain water only as follows:

  - Swallow one tablet with a full glass (6-8 oz) of plain water.

  Do **not** take Alendronate Sodium Tablets with:

  Mineral water
  Coffee or tea
  Juice

  Alendronate Sodium Tablets works only if it is taken on an empty stomach.

  Do not chew or suck on a tablet of Alendronate Sodium Tablets.

  After taking your Alendronate Sodium Tablets, wait at least 30 minutes:
  - before you lie down. You may sit, stand or walk, and do normal activities like reading.
  - before you take your first food or drink except for plain water.
  - before you take other medicines, including antacids, calcium, and other supplements and vitamins.

  Do not lie down until after your first food of the day.

- It is important that you keep taking Alendronate Sodium Tablets for as long as your doctor says to take it. For Alendronate Sodium Tablets to continue to work, you need to keep taking it.

What should I do if I miss a dose of Alendronate Sodium Tablets or if I take too many?

- If you miss a dose, take only 1 dose of Alendronate Sodium Tablets on the morning after you remember. Do not take 2 doses on the same day. Continue your usual schedule of 1 dose once a week on your chosen day.

- If you think you took more than the prescribed dose of Alendronate Sodium Tablets, drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

What should I avoid while taking Alendronate Sodium Tablets?

- Do not eat, drink, or take other medicines or supplements **before** taking Alendronate Sodium Tablets.

- Wait for at least 30 minutes **after** taking Alendronate Sodium Tablets to eat, drink, or take other medicines or supplements.

- Do not lie down for at least 30 minutes **after** taking Alendronate Sodium Tablets. Do not lie down until **after** your first food of the day.

What are the possible side effects of Alendronate Sodium Tablets?

Alendronate Sodium Tablets may cause problems in your esophagus (the tube that connects the mouth and stomach). (See "What is the most important information I should know about once weekly Alendronate Sodium Tablets?".) These problems include irritation, inflammation, or ulcers of the esophagus, which may sometimes bleed. This may occur especially if you do not drink a full glass of water with Alendronate Sodium Tablets or if you lie down in less than 30 minutes or before your first food of the day.

- **Stop taking Alendronate Sodium Tablets and call your doctor right away if you get any of these signs of possible serious problems of the esophagus:**

    - **Chest pain**
    - **New or worsening heartburn**
    - **Trouble or pain when swallowing**

- Esophagus problems may get worse if you continue to take Alendronate Sodium Tablets.

- Mouth sores (ulcers) may occur if the Alendronate Sodium Tablet is chewed or dissolved in the mouth.

- You may get flu-like symptoms, typically at the start of treatment with Alendronate Sodium Tablets.

- You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.

- Alendronate Sodium Tablets may cause jaw-bone problems in some people. Jaw-bone problems may include infection, and delayed healing after teeth are pulled.

- The most common side effect is stomach area (abdominal) pain. Less common side effects are nausea, vomiting, a full or bloated feeling in the stomach, constipation, diarrhea, black or bloody stools (bowel movements), gas, eye pain, rash that may be made worse by sunlight, headache, dizziness, a changed sense of taste, joint swelling or swelling in the hands or legs, and bone, muscle, or joint pain.

- **Call your doctor if you develop severe bone, muscle, or joint pain.**

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects with Alendronate Sodium Tablets. Ask your doctor or pharmacist for more information.

How do I store Alendronate Sodium Tablets?

- Store at room temperature, 68 to 77°F (20 to 25°C).
- Safely discard Alendronate Sodium Tablets that is out-of-date or no longer needed.
- **Keep Alendronate Sodium Tablets and all medicines out of the reach of children.**

General information about using Alendronate Sodium Tablets safely and effectively

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Alendronate Sodium Tablets for a condition for which it was not prescribed. Do not give Alendronate Sodium Tablets to other people, even if they have the same symptoms you have. It may harm them.

Alendronate Sodium Tablets are not indicated for use in children.

This leaflet is a summary of information about Alendronate Sodium Tablets. If you have any questions or concerns about Alendronate Sodium Tablets or osteoporosis, talk to your doctor, pharmacist, or other health care provider. You can ask your doctor or pharmacist for information about Alendronate Sodium Tablets written for health care providers. For more information, call [provide contact information].

What are the ingredients in Alendronate Sodium Tablets?

Alendronate Sodium Tablets contain alendronate sodium as the active ingredient and the following inactive ingredients: [provide inactive ingredient list].

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.

At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, your spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who:
- Are going through or who are past menopause

Men who:
- Are elderly

People who:

- Are white (Caucasian) or oriental (Asian)
- Are thin
- Have family member with osteoporosis
- Do not get enough calcium or vitamin D
- Do not exercise
- Smoke
- Drink alcohol often
- Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help prevent or treat osteoporosis?

In addition to Alendronate Sodium Tablets, your doctor may suggest one or more of the following lifestyle changes:

- **Stop smoking**. Smoking may increase your chance of getting osteoporosis.
- **Reduce the use of alcohol.** Too much alcohol may increase the risk of osteoporosis and injuries that can cause fractures.
- **Exercise regularly**. Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.
- **Eat a balanced diet**. Having enough calcium in your diet is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements, such as calcium or vitamin D.

Rx only

Manufactured by:

Revision Date:

NOTE TO CHEMIST:

FOR THE RECORD:

****Note: Angela Payne was the primary reviewer and performed the AP summary 7/8/02****

1. MODEL LABELING:

   The labeling review was based on the labeling for the reference listed drug FOSAMAX® (Merck; NDA 20-560/S-047 & 048 approved Dec 28, 2006). Fosamax has a combined insert with the tablet formulation (NDA 20-560) and the oral solution formulation (NDA 21-575). Information pertaining to the oral solution has been carved out. There is currently a SLR pending for Fosamax Tablets.

   BPCA Consult for FOSAMAX:

   The following statement in Clinical Pharmacology needs to be carve-out of the labeling: "The oral bioavailability in children was similar to that observed in adults, however, FOSAMAX, is not indicated for use in children (see PRECAUTIONS, Pediatric use)."

   We will use the following disclaimer for ANDA products:
   Alendronate is not indicated for use in children. Due to Merck's marketing exclusivity rights, this generic drug product is not approved with descriptive pharmacokinetic information in pediatric patients. Merck's alendronate sodium tablets and oral solution are approved with that descriptive pharmacokinetic information.

   The rest of the information can stay in the labeling without any the disclaimer -- as proposed.

2. USP:
   Alendronic Acid Tablets
   (Title for this new monograph—to become official May 1, 2008)
   Packaging and storage— Preserve in tight containers. Store between 15 and 30.
   Labeling— The labeling indicates weekly dosing where appropriate.

   Based on email from Yana Mille, USP will revert back to Alendronate Sodium Tablets. Therefore, firms should continue to use "Alendronate Sodium Tablets USP".

   -----Original Message-----
   From: Mille, Yana R
   Sent: Friday, November 23, 2007 1:17 PM
   To: Wu, Ruby (Chi-Ann)
   Subject: RE: Alendronate
   Ruby,

   Based on correspondence I received from USP almost exactly a month ago, USP is in the process of drafting an interim revision announcement (IRA) that will tell the world that the official title is Alendronate Sodium Tablets. Thus, at this point in time, I think it is safe to tell the firms that they can use this title either with or without the initials "USP." I would expect the IRA to publish at any time. You E-mail has motivated me to check with USP and find out where things stand. If I hear anything, I will let you know.

   Yana

   From: Mille, Yana R
   Sent: Thursday, October 04, 2007 9:21 AM
   To: Golson, Lillie D
   Subject: Alendronate Sodium Tablets

   Lillie,

   Have any of the generic firms started using the title "Alendronic Acid Tablets?"

   As you may recall, USP is going to revert back to using the title "Alendronate Sodium Tablets." Before doing so, they need to know if there are any generics using
   'Alendronic Acid Tablets." If there are, the USP will make certain the monograph gives the firms 18

months to change their titles. However, if no one is using "Alendronic Acid Tablets," then it won't be necessary to allow for an 18 month transition period.

3. PATENTS/EXCLUSIVITIES. Current submission of August 20, 2001 page 11 cites PIV for all patents. And the feb. 2, 28, 2001 exclusivities certifies that firm will not market the 70 and 35 mg strengths until after the expiration of the patients. Since this is a combined insert for the 5 mg, 10 mg , 40 mg strengths then, firm cannot go to market until 2003. See chart above.

Patent Data – NDA 20-560

Strengths	No	Expiration	Use Code	Use	How file	Labeling Impact
5 mg, 10 mg, 35 mg, 40 mg, 70 mg	4621077	Aug 06, 2007 PED Feb 6, 2008	U-114	Inhibiting bone resorption	PIV	Same As
5 mg, 10 mg, 35 mg, 40 mg, 70 mg	5358941	Dec 02, 2012 PED jun 02, 2013		Dry mix formulation with biphosphoric acids w/lactose	PIV	Same as
5 mg, 10 mg, 35 mg, 40 mg, 70 mg	5681590	Dec 02, 2012 PED Jun 02, 2013		Dry mix formulation w/biphosphoric acid	PIV	Same as
5 mg, 10 mg, 35 mg, 40 mg, 70 mg	5849726	Jun 06, 2015 PED dec 6, 2015		Salt formulation	PIV	Same as
5 mg, 10 mg, 35 mg, 40 mg, 70 mg	6008207	Jun 06, 2015 PED dec 6, 2015	U-303	Method of treating osteoporosis, Paget's Disease prevention & treatment of glucocorticoid-induced osteopososis	PIV	Same as
5 mg, 10 mg, 35 mg, 40 mg, 70 mg	6090410	Dec 02,2012 PED jun 2, 2013		Dry mix formulation w/biphosphoric acid	PIV	Same as
10 mg	6194004	Dec 02,2012		Dry mix formulation w/biphosphoric acid	PIV	Same as
35 mg, 70 mg	*5994329*	*Jun 17, 2018 PED Jan 17, 2019*		*Method of inhibiting bone resorption*	*PIV*	*Same as*
35 mg, 70 mg	*6225294*	*Jul 17, 2018, PED Jan 17, 2019*		*Method of inhibiting bone resorption*	*PIV*	*Same as*
35 mg, 70 mg	*6015801*	*Jun 17, 2018 PED Jan 17, 2019*	*U-353*	*Prevention and treatment of osteoporosis*	*PIV*	*Same as*

Exclusivity Data– NDA 20-560

Strengths	Code	Reference	Expiration	Labeling impact
70 mg (ANDA 79-049)	*D-87*	*ADDITION OF ONCE-WEEKLY DOSING FOR THE TREATMENT TO INCREASE BONE MASS IN MEN WITH OSTEOPOROSIS*	*April 16, 2007 EXPIRED*	*None*
5 mg, 10 mg, 35 mg, 40 mg, 70 mg	M-51/SE1-38	INFORMATION ADDED TO LABELING REGARDING OSTEOGENESIS IMPERFECTA STUDY (Precautions Pediatric Use , and Adverse reactions, clinical studies, Osteogenesis Imperfecta)	Dec 21, 2008/PED JUN 21, 2009	**BPCA Carve-out**

M-51: A Pediatric Written Request was issued on October 27, 2000. On January 31, 2003, Merck submitted the 12-month data from Protocol 135, a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of oral alendronate sodium in pediatric patients with severe osteogenesis imperfecta. With that submission the company was seeking pediatric exclusivity and an indication for alendronate in the treatment of osteogenesis imperfecta in children. Although the indication was ultimately not approved, pediatric exclusivity was granted and Merck received 3 years Waxman-Hatch marketing exclusivity for miscellaneous exclusivity (M-51 – information added to labeling regarding osteogenesis imperfecta study) which expires on December 21, 2008. In addition, Merck was awarded pediatric exclusivity for the alendronate moiety, resulting in six additional months protection for every alendronate product marketed by Merck with patent protection or exclusivity.

3. MANUFACTURING FACILITY (Vol. 1.14, page 6047)

TEVA Pharmaceuticals USA
650 Cathill Road
Sellersville, PA, 18960

4. SCORING/PRODUCT DESCRIPTION

NDA: 5 mg - white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other.

10 mg - white, round, uncoated tablets with a bone image and code MRK 936 on one side and a bone image and FOSAMAX on the other.

40 mg - white, triangular-shaped, uncoated tablets with code MRK 212 on one side and FOSAMAX on the other.

70 mg - white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other.
35 mg - white, oval, uncoated tablets with code 77 on one side and an outline of a bone image on the other.

ANDA: 5 mg - white to off-white, round flat-faced beveled-edge tablets debossed with "93" on one side and "5140" on the other side.

10 mg - white to off-white, round, convex tablets debossed with "93" on one side and "5141" on the other side.

40 mg - white to off-white, oval convex tablets debossed with "93" on one side and "5142" on the other side.

70 mg - white to off-white, pillow shaped, convex tablets debossed with "93" on one side and "5171" on the other side.

35 mg strength. white to off-white, pillow shaped, convex tablets debossed with "93" on one side and "5172" on the other side.

5. STORAGE RECOMMENDATIONS:

NDA: Store in a well-closed container at room temperature, 15-30°C (59-86°F).

ANDA: Store at (b) (4)

USP: Not applicable

6. DISPENSING RECOMMENDATIONS:

NDA: None

ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

7. INACTIVE INGREDIENTS (Vol. 3.1, Section V, page 11A)

There is no discrepancy between the listing in the DESCRIPTION section of the insert labeling and the Components and Composition Statements for the 5 mg, 10 mg, and 40 mg products. However at the time this amendment was submitted, the 35 mg and 70 mg products were not on the market and were unavailable to Teva. Teva, therefore, compared its 70 mg product with the 10 mg product .

8. PRODUCT LINE:

RLD: 5 mg tablets - unit of use bottles of 30 and 100

10 mg tablets - unit of use bottles of 30 and 100; unit dose packages of 100; bottles of 1000; UNIBLISTER cards of 31 tablets for hospital use.

40 mg tablets - unit of use bottles of 30

70 mg tablets - unit of use blister package of 4 tablets; unit dose packages of 20

35 mg tablets - unit of use blister package of 4 tablets; unit dose packages of 20

ANDA: 5 mg tablets - bottles of 30, 100

10 mg tablets - bottles of 30, 100 and 1000

40 mg tablets - bottles of 30, 100

70 mg tablets - unit-of-use blisters of 4s, unit dose package of 20s, bottles of 12 and 100
35 mg tablets - unit-of-use blisters of 4s, unit dose package of 20s, bottles of 12 and 100

Bottles of 12s, 30s, and 100s are CRC. Unit-of use of 4s have (b) (4)

The innovator will package its 70 mg and 35 mg product in unit dose blisters of 4 and 20. Product will not be

packed in bottles. The decision to only package in unit dose blisters **was not** based on safety issues, according to the PM, Randy Hedin. We will allow bottles at this time. (b) (4)

(b) (4)

Date of Review: December 21, 2007 Date of Submission: November 20, 2007 (amendment)

Primary Reviewer: Ruby Wu

Team Leader: John Grace

ANDA: 75-710
V:\FIRMSNZ\TEVA\LTRS&REV\75710.na7.Ldoc.doc
Review

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

/s/

Ruby Wu
12/21/2007 02:05:56 PM
LABELING REVIEWER

John Grace
12/26/2007 12:42:29 PM
LABELING REVIEWER

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	75-710
Date of Submission	December 28, 2007 (amendment)
Applicant	Teva Pharmaceuticals USA
Drug Name	Alendronate Sodium Tablets, USP
Strength(s)	5 mg, 10 mg, and 40 mg daily & 35 mg and 70 mg once weekly

APPROVAL SUMMARY

Do you have Final Printed Labels and Labeling? Yes.

1. CONTAINER LABELS for once-daily tablets (5 mg, 40 mg: 30s, 100s; 10 mg: 30s, 100s, 1000s)
   Satisfactory in final print as submitted in the November 20, 2007 e-amendment.

2. CONTAINER LABELS for once-weekly tablets (35 mg and 70 mg: 12s and 100s)
   Satisfactory in final print as submitted in the December 28, 2007 amendment.

3. UNIT-DOSE BLISTERS (35 mg and 70 mg: 5 x 2)
   Satisfactory in final print as submitted in the December 28, 2007 amendment.
   According to (b) (6) of Teva on January 9, 2008, the circular overlay does not appear on hard-copies of the FPL.

4. UNIT-OF-USE BLISTERS (35 mg and 70 mg: 4s)
   Satisfactory in final print as submitted in the December 28, 2007 amendment.

5. UNIT-DOSE CARTON (35 mg and 70 mg: 2 x 10)
   Satisfactory in final print as submitted in the December 28, 2007 amendment.

6. UNIT-OF-USE CARTON (35 mg and 70 mg: 1 x 4s)
   Satisfactory in final print as submitted in the December 28, 2007 amendment.

8. PROFESSIONAL INSERT with PATIENT WEEKLY-DOSE LEAFLET
   Satisfactory in final print as submitted in the December 28, 2007 amendment.

9. PROFESSIONAL INSERT with PATIENT DAILY-DOSE LEAFLET:
   Satisfactory in final print as submitted in the December 28, 2007 amendment.

Revisions needed post-approval: Yes. On January 9, 2008, I communicated to Virginia Hogan of Teva that the PRECAUTIONS, Pediatric Use section of the insert should not be italicized. Virginia agreed to make this revision post approval and submit revised labeling in the annual report.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: FOSAMAX® Tablets

NDA Number: NDA 20-560

NDA Drug Name: Alendronate Sodium Tablets, USP

NDA Firm: Merck

Date of Approval of NDA Insert and supplement: NDA 20-560/S-047 & 048 approved Dec 28, 2006

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

FOR THE RECORD:

****Note: Angela Payne was the primary reviewer and performed the AP summary 7/8/02****

1. MODEL LABELING:

   The labeling review was based on the labeling for the reference listed drug FOSAMAX® (Merck; NDA 20-560/S-047 & 048 approved Dec 28, 2006). Fosamax has a combined insert with the tablet formulation (NDA 20-560) and the oral solution formulation (NDA 21-575). Information pertaining to the oral solution has been carved out. There is currently a SLR pending for Fosamax Tablets.

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   Alendronic Acid Tablets
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   Labeling— The labeling indicates weekly dosing where appropriate.

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   Yana

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   To: Golson, Lillie D
   Subject: Alendronate Sodium Tablets

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35 mg, 70 mg	*5994329*	*Jun 17, 2018 PED Jan 17, 2019*		*Method of inhibiting bone resorption*	*PIV*	*Same as*
35 mg, 70 mg	*6225294*	*Jul 17, 2018, PED Jan 17, 2019*		*Method of inhibiting bone resorption*	*PIV*	*Same as*
35 mg, 70 mg	*6015801*	*Jun 17, 2018 PED Jan 17, 2019*	*U-353*	*Prevention and treatment of osteoporosis*	*PIV*	*Same as*

Exclusivity Data– NDA 20-560

Strengths	Code	Reference	Expiration	Labeling impact
70 mg (ANDA 79-049)	*D-87*	*ADDITION OF ONCE-WEEKLY DOSING FOR THE TREATMENT TO INCREASE BONE MASS IN MEN WITH OSTEOPOROSIS*	*April 16, 2007 EXPIRED*	*None*
5 mg, 10 mg, 35 mg, 40 mg, 70 mg	M-51/SE1-38	INFORMATION ADDED TO LABELING REGARDING OSTEOGENESIS IMPERFECTA STUDY (Precautions Pediatric Use , and Adverse reactions, clinical studies, Osteogenesis Imperfecta)	Dec 21, 2008/PED JUN 21, 2009	**BPCA Carve-out**

M-51: A Pediatric Written Request was issued on October 27, 2000. On January 31, 2003, Merck submitted the 12-month data from Protocol 135, a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of oral alendronate sodium in pediatric patients with severe osteogenesis imperfecta. With that submission the company was seeking pediatric exclusivity and an indication for alendronate in the treatment of osteogenesis imperfecta in children. Although the indication was ultimately not approved, pediatric exclusivity was granted and Merck received 3 years Waxman-Hatch marketing exclusivity for miscellaneous exclusivity (M-51 – information added to labeling regarding osteogenesis imperfecta study) which expires on December 21, 2008. In addition, Merck was awarded pediatric exclusivity for the alendronate moiety, resulting in six additional months protection for every alendronate product marketed by Merck with patent protection or exclusivity.

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TEVA Pharmaceuticals USA
650 Cathill Road
Sellersville, PA, 18960

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40 mg - white, triangular-shaped, uncoated tablets with code MRK 212 on one side and FOSAMAX on the other.

70 mg - white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other.
35 mg - white, oval, uncoated tablets with code 77 on one side and an outline of a bone image on the other.

ANDA: 5 mg - white to off-white, round flat-faced beveled-edge tablets debossed with "93" on one side and "5140" on the other side.

10 mg - white to off-white, round, convex tablets debossed with "93" on one side and "5141" on the other side.

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35 mg strength. white to off-white, pillow shaped, convex tablets debossed with "93" on one side and "5172" on the other side.

6. STORAGE RECOMMENDATIONS:

NDA: Store in a well-closed container at room temperature, 15-30°C (59-86°F).

ANDA: Store at (b) (4)

USP: Not applicable

7. DISPENSING RECOMMENDATIONS:

NDA: None

ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. INACTIVE INGREDIENTS (Vol. 3.1, Section V, page 11A)

There is no discrepancy between the listing in the DESCRIPTION section of the insert labeling and the Components and Composition Statements for the 5 mg, 10 mg, and 40 mg products.

9. PRODUCT LINE:

RLD: 5 mg tablets - unit of use bottles of 30 and 100

10 mg tablets - unit of use bottles of 30 and 100; unit dose packages of 100; bottles of 1000; UNIBLISTER cards of 31 tablets for hospital use.

40 mg tablets - unit of use bottles of 30

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35 mg tablets - unit of use blister package of 4 tablets; unit dose packages of 20

ANDA: 5 mg tablets - bottles of 30, 100

10 mg tablets - bottles of 30, 100 and 1000

40 mg tablets - bottles of 30, 100

70 mg tablets - unit-of-use blisters of 4s, unit dose package of 20s, bottles of 12 and 100
35 mg tablets - unit-of-use blisters of 4s, unit dose package of 20s, bottles of 12 and 100

Bottles of 12s, 30s, and 100s are CRC. Unit-of use of 4s have Safety Pak.

The innovator will package its 70 mg and 35 mg product in unit dose blisters of 4 and 20. Product will not be packed in bottles. The decision to only package in unit dose blisters **was not** based on safety issues, according to the PM, Randy Hedin. We will allow bottles at this time.

Date of Review: January 9, 2008 Date of Submission: December 28, 2007 (amendment)

Primary Reviewer: Ruby Wu

Team Leader: John Grace

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

/s/

Ruby Wu
1/9/2008 11:57:54 AM
LABELING REVIEWER

John Grace
1/10/2008 11:20:28 AM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-710

CHEMISTRY REVIEWS

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER
1

2. ANDA NUMBER
75-710

3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
Kulpsville, PA 19443

4. LEGAL BASIS for ANDA SUBMISSION
The basis of Teva's proposed ANDA for Alendronate Sodium Tablets, 5 mg, 10 mg, and 40 mg, is the reference listed drug, Fosamax®, 5 mg, 10 mg, and 40 mg (NDA 20-560) manufactured by Merck & Co.. According to information published in the list of Approved Drug Products 19th Ed., Fosamax®, 5 mg, 10 mg, and 40 mg is covered by the following patents:

U.S. Patent No.	Expiration Date
4,621,077	August 6, 2007
5,358,941	December 2, 2012
5,681,590	December 2, 2012
5,804,570	February 17, 2015
5,849,726	June 6, 2015
6,008,207	June 6, 2015

The applicant is also aware of the existence of U.S. Patent No. 5,882,656 that issued on March 16, 1999 and is in the same family as U.S. Patent No. 5,358,941 and 5,681,590. The applicant stated that the above patents are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted. There are four exclusivities for the reference drug product currently:

Exclusivity	Expiration Date
I-185	April 25, 2000
I-187	April 25, 2000
I-272	June 16, 2002
New Chemical Entity (NCE)	September 29, 2000

5. SUPPLEMENT(s)
None

6. NAME OF DRUG
Alendronate Sodium Tablets

7. NONPROPRIETARY NAME

Alendronate Sodium Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR

None

9. AMENDMENTS AND OTHER DATES

9/29/1999	Original submission
11/22/1999	New corresponding (exclusivity)
12/2/1999	New corresponding (patent)
2/7/2000	New corresponding (patent)
2/14/2000	New corresponding (patent)

10. PHARMACOLOGICAL CATEGORY

Suppressant (bone resorption)

11. HOW DISPENSED

Prescription

12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
Alendronate Sodium Trihydrate (b) (4)	(b) (4)	(b) (4)	V1.2, p5980
			V1.3, p6298
			V1.3, p6299
			V1.3, p6304
			V1.3, p6307
			V1.3, p6349
			V1.3, p6315
			V1.3, p6358
			V1.3, p6355
			V1.3, p6366
			V1.3, p6367
			V1.3, p6370
			V1.3, p6380
			V1.3, p6381

13. DOSAGE FORM

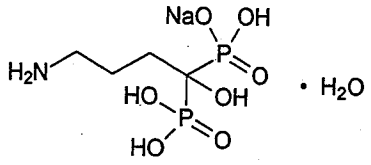
Tablet

14. POTENCY

5 mg, 10 mg, and 40 mg

15. CHEMICAL NAME AND STRUCTURE

Alendronate Sodium. Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate. $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$. 325.12. 121268-17-5.



16. RECORDS AND REPORTS

None

17. COMMENTS

The following sections are not satisfactory: DMF of Drug Substance, Raw Material Controls, Laboratory Controls, Stability, and Labeling. The method validation is pending.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable - Major.

19. REVIEWER AND DATE COMPLETED

Naiqi Ya/March 15, 2000

Following this page, 16 pages withheld in full (b)(4)-CCI/TS

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-710

APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Alendronate Sodium Tablets, 5 mg, 10 mg, and 40 mg

The deficiencies presented below represent **MAJOR** deficiencies.

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8. (b) (4)

9.

10.

11.

12.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Upon the resolution of the deficiencies of methodology and specifications indicated above, the analytical methods will need to be validated by an FDA laboratory.

2. Please provide the address of the (b) (4) site where future (b) (4) of the drug substance may be done.

2. A satisfactory compliance evaluation of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of the approval of the application.

Sincerely yours,

3/29/00

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-710
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-627/Naiqi Ya/3-17-00 3/22/2000
HFD-627/P.Schwartz/3-17-00 3/20/00
HFD-617/E. Hu, /3-20-00 3/21/00
V:\FIRMSNZ\TEVA\LTRS&REV\75710N00RV1.DOC
F/T by: bc/3-20-00

#2

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW NUMBER**
   2

2. **ANDA NUMBER**
   75-710

3. **NAME AND ADDRESS OF APPLICANT**
   TEVA Pharmaceuticals USA
   Attention: Deborah A. Jaskot
   1510 Delp Drive
   Kulpsville, PA 19443

4. **LEGAL BASIS for ANDA SUBMISSION**

   The basis of Teva's proposed ANDA for Alendronate Sodium Tablets, 5 mg, 10 mg, and 40 mg, is the reference listed drug, Fosamax®, 5 mg, 10 mg, and 40 mg (NDA 20-560) manufactured by Merck & Co.

   The list of related patents and exclusivities are summarized in the following tables (See CR#1 for more detail):

U.S. Patent No.	Expiration Date
4,621,077	August 6, 2007
5,358,941	December 2, 2012
5,681,590	December 2, 2012
5,804,570	February 17, 2015
5,849,726	June 6, 2015
6,008,207	June 6, 2015
6,015,801	**July 17, 2018***
5,994,329	**July 17, 2018***
6,090,410	**December 2, 2012***

Exclusivity	Expiration Date
I-185	April 25, 2000
I-187	April 25, 2000
I-272	June 16, 2002
New Chemical Entity	September 29, 2000
M-3	**November 24, 2002****

5. **SUPPLEMENT(s)**
None

6. **NAME OF DRUG**
Alendronate Sodium Tablets

7. **NONPROPRIETARY NAME**
Alendronate Sodium Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
None

9. **AMENDMENTS AND OTHER DATES**

Firm:

09/29/99	Original submission
11/22/99	New corresponding (Additional exclusivity)
12/02/99	New corresponding (Patent certification notice)
12/28/99	Tel Amendment, re Bioequvalence
02/09/00	New corresponding (receipt: Pat. Cert. Notice)
02/14/00	New corresponding (Additional patent)
03/23/00	New corresponding (Patent certification notice)
04/18/00	New corresponding (Additional patent)
04/24/00	New corresponding (Additional patent)
05/12/00 (2)	New corresponding (Patent certification notice)
*06/08/00	Major Amendment (CMC)
09/19/00	New corresponding (Additional patent)
10/17/00	New corresponding (Patent certification notice)

*Subject of this review.

FDA:

11/15/99	Accept for filing (1st generic)
11/19/99	Request: re patent/exclusivity
12/30/99	Bio review (1st): Acceptable
06/02/00	Labeling review (1st): Deficient
07/11/00	Bio (2nd): Update dissolution requirement

10. **PHARMACOLOGICAL CATEGORY**
Suppressant (bone resorption)

11. **HOW DISPENSED**
Prescription

12. **RELATED IND/NDA/DMF(s)**

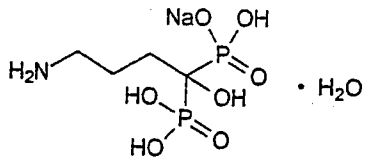
NDA 20-560, Fosamax® 5 mg, 10 mg, and 40 mg

Product	Holder	DMF No.	LOA
Alendronate Sodium Trihydrate	(b) (4)	(b) (4)	V1.2,p5980
Other related DMFs	See CR#1		

13. **DOSAGE FORM**
Tablet

14. **POTENCY**
5 mg, 10 mg, and 40 mg

15. **CHEMICAL NAME AND STRUCTURE**
Alendronate Sodium. Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate. $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$. 325.12. *121268-17-5*.



16. **RECORDS AND REPORTS**
None

17. **COMMENTS**

- EER: Found AC per 01/03/00.
- Labeling last reviewed on 06/02/00: Pending
- Bio-review: Acceptable w/Dissolution Comment (07/11/00).
- Micro: N/A.
- DMF: Satisfactory per this review.
- MV: will be issued later.
- FAX CMC deficiencies could be found in item 38.

18. **CONCLUSIONS AND RECOMMENDATIONS**
The application is not Approvable - NA/FAX

19. **REVIEWER AND DATE COMPLETED**
Bing Cai, Ph.D. Nov. 15, 2000

Following this page, 11 pages withheld in full (b)(4)- CCI/TS

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-710

APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Alendronate Sodium Tablets, 5 mg, 10 mg, and 40 mg

The deficiencies presented below represent **FAX** deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Upon the resolution of the issue of methodology indicated above, the analytical methods will need to be validated by an FDA laboratory. Please provide a commitment to expeditiously resolve any deficiencies that may be identified in the Methods Validation study if the ANDA is approved before the study is completed.

2. Please provide any additional stability data that is available.

Sincerely yours,

11/30/06

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-710
Division File
Field Copy

Endorsements:

HFD-625/Bing Cai/11/17/00
HFD-625/Mike Smela/11/21/00
HFD-617/MDillahunt/11/21/00
V:\FIRMSNZ\TEVA\LTRS&REV\75710CR2.DOC
F/T by: gp/11/22/00

#3

Chemistry Closed

JAN 5 1999

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER

3

2. ANDA NUMBER

75-710

3. NAME AND ADDRESS OF APPLICANT

TEVA Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
Kulpsville, PA 19443

4. LEGAL BASIS for ANDA SUBMISSION

The basis of Teva's proposed ANDA for Alendronate Sodium Tablets, 5 mg, 10 mg, 40 mg and 70 mg, is the reference listed drug, Fosamax®, 5 mg, 10 mg, 40, and 70 mg (NDA 20-560) manufactured by Merck & Co.

The list of related patents and exclusivities:
see previous review.

5. SUPPLEMENT(s)

None

6. NAME OF DRUG

Alendronate Sodium Tablets

7. NONPROPRIETARY NAME

Alendronate Sodium Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR

None

9. AMENDMENTS AND OTHER DATES

Firm:

09/29/99	Original submission
11/22/99	New corresponding (Additional exclusivity)
12/02/99	New corresponding (Patent certification notice)
12/28/99	Tel Amendment, re Bioequvalence
02/09/00	New corresponding (receipt: Pat. Cert. Notice)
02/14/00	New corresponding (Additional patent)
03/23/00	New corresponding (Patent certification notice)

04/18/00		New corresponding (Additional patent)
04/24/00		New corresponding (Additional patent)
05/12/00	(2)	New corresponding (Patent certification notice)
06/08/00		Major Amendment (CMC)
09/19/00		New corresponding (Additional patent)
10/17/00		New corresponding (Patent certification notice)
10/23/00*		**Added new strength (70 mg)**
12/14/00		New corresponding (Patent clarification)
12/20/00		New corresponding (Patent clarification)
12/27/00*		**Fax amendment (re NA letter dated 11/27/00)**

*Subject of this review.

FDA:

11/15/99	Accept for filing (1st generic)
11/19/99	Request: re patent/exclusivity
12/30/99	Bio review (1st): Acceptable
06/02/00	Labeling review (1st): Deficient
07/11/00	Bio (2nd): Update dissolution requirement
11/27/00	CMC review/letter: NA FAX

10. PHARMACOLOGICAL CATEGORY

Suppressant (bone resorption)

11. HOW DISPENSED

Prescription

12. RELATED IND/NDA/DMF(s)

NDA 20-560, Fosamax® 5 mg, 10 mg, 40 mg and 70 mg

Product	Holder	DMF No.	LOA
Alendronate Sodium Trihydrate	(b) (4)	(b) (4)	V1.2,p5980
Other related DMFs	See CR#1		

13. DOSAGE FORM

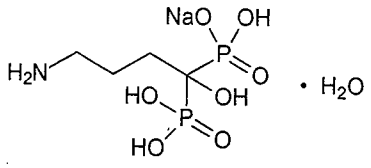
Tablet

14. POTENCY

5 mg, 10 mg, and 40 mg **and <u>70 mg (new strength added)</u>**

15. CHEMICAL NAME AND STRUCTURE

Alendronate Sodium. Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate. $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$. 325.12. *121268-17-5*.



16. RECORDS AND REPORTS

None

17. COMMENTS

On 10/23/00, the firm has provided an Unsolicated amendment to include a new strength (70 mg tablets) into this ANDA. The submission contains a full report of in vivo bio study. The firm claimed that the innovator strength of 70 mg was not commercially available, that the delay in marketing of 70 mg tablets is not the result of a safety or efficacy problem.

- EER: Found AC per 01/03/00.
- Labeling last reviewed on 06/02/00: Pending for 70 mg
- Bio last reviewed on 07/11/00: Pending for 70 mg.
- Micro: N/A.
- DMF (b) (4): Satisfactory per this review.
- MV: will be issued at this time.
- CMC Closed.

18. CONCLUSIONS AND RECOMMENDATIONS

CMC closed, pending for Bio and Labeling review (re the new strength, 70 mg tablets).

19. REVIEWER AND DATE COMPLETED

Bing Cai, Ph.D. January 2, 2001
(Revised 01/05/01)

Following this page, 11 pages withheld in full (b)(4)- CCI/TS

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-710

APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Alendronate Sodium Tablets, 5 mg, 10 mg, and 40 mg

The deficiencies presented below represent **FAX** deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Upon the resolution of the issue of methodology indicated above, the analytical methods will need to be validated by an FDA laboratory. Please provide a commitment to expeditiously resolve any deficiencies that may be identified in the Methods Validation study if the ANDA is approved before the study is completed.

2. Please provide any additional stability data that is available.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-710
Division File
Field Copy

Endorsements:

HFD-625/Bing Cai/01/02/00/01/05/00
HFD-625/Mike Smela/
~~HFD-617/MDillahunt/~~
V:\FIRMSNZ\TEVA\LTRS&REV\75710CR3.DOC

F/T by:

M Smela
1/5/01

1/5/01 Revised

Addendum to Chemistry Review #3

ANDA Number: 75-710
Drug: Alendronate Sodium Tablets, 5 mg, 10 mg, 40 mg and 70 mg
Firm: TEVA Pharmaceuticals USA

This ANDA was last reviewed in January 2001. It was Chemistry Closed, pending for bio and labeling review. The MV request was issued on 01/09/01 to Philadelphia and it is in progress. Labeling comments were faxed to the firm on 1/18/01.

The Bio review for 70 mg tablet has completed (signed on 1/29/01) and it is found NOT Acceptable. The review comments were faxed to the firm on 1/31/01.

The ANDA is not approvable. An NA (Major) letter will be issued.

2/1/01

Bing Cai/01/30/01
Review Chemist

M Smela 2/1/01

Mike Smela
Team Leader

Chemistry Comments to be Provided to the Applicant:

ANDA: 75-710
APPLICANT: TEVA Pharmaceuticals USA
DRUG PRODUCT: Alendronate Sodium Tablets, 5 mg, 10 mg, 40 mg and 70 mg

The deficiency presented below represents a Major deficiency.

Bioequivalence for the 70 mg tablet has not been established. Please refer to the comments faxed to you on January 31, 2001 by the Division of Bioequivalence. If a new batch is manufactured to address the bioequivalence deficiencies, CMC information for the new batch must also be included in your amendment.

In addition to responding to the deficiency presented above, please note and acknowledge the following comments in your response:

1. You must also address the labeling deficiencies in your response which were faxed to you on January 18, 2001.

2. The method validation is pending. Please provide samples promptly when contacted.

3. Please provide any additional stability data that is available.

Sincerely yours,

Paul Lowenz on 2/1/01

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

cc:ANDA #75-710
DUP File
Division File
Field Copy

Endorsements:

HFD-625/BCai/01/30/01 01/31/01
HFD-625/MSmela/01/31/01

Project Manager:
HFD-625/M.Dillahunt, PM/02/01/01

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F/T: gp/02/01/01

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER
4

2. ANDA NUMBER
75-710

3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
Kulpsville, PA 19443

4. LEGAL BASIS for ANDA SUBMISSION
See previous review.

5. SUPPLEMENT(s)
None

6. NAME OF DRUG
Alendronate Sodium Tablets

7. NONPROPRIETARY NAME
Alendronate Sodium Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR
None

9. AMENDMENTS AND OTHER DATES (Original submission: 09/29/99)

New information since last review:

02/13/01	New corresponding (Patent certification)
02/28/01	New corresponding (Exclusivity statement)
03/09/01*	**Major amendment (CMC info. for new bio batch)**
03/21/01	New corresponding (Patent certification)
04/10/01	New corresponding (bio/70 mg tablets)
04/24/01	New corresponding (labeling changes)
05/23/01	New corresponding (Patent certification)

*Subject of this review.

FDA:

01/05/01	Chemistry Closed (pending for bio on 70 mg tabs)
01/05/01	MVP issued (Philadelphia)
01/18/01	Labeling: FAX/Deficiency on 70 mg tablets
01/29/01	Bio Not Acceptable/70 mg tablets
02/02/01	NA Major, required a new bio batch for 70 mg tabs

04/27/01 Bio review: Acceptable/70 mg, with dissolution requirement for release and stability testing

10. PHARMACOLOGICAL CATEGORY

Suppressant (bone resorption)

11. HOW DISPENSED

Prescription

12. RELATED IND/NDA/DMF(s)

NDA 20-560, Fosamax® 5 mg, 10 mg, 40 mg and 70 mg

Product	Holder	DMF No.	LOA
Alendronate Sodium Trihydrate	(b) (4)	(b) (4)	V1.2,p5980
Other related DMFs	See item 38		

13. DOSAGE FORM

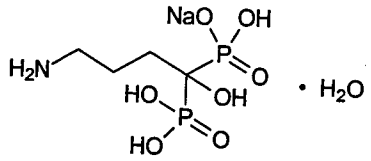
Tablet

14. POTENCY

5 mg, 10 mg, and 40 mg and 70 mg

15. CHEMICAL NAME AND STRUCTURE

Alendronate Sodium. Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate. $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$. 325.12. *121268-17-5*.



16. RECORDS AND REPORTS

None

17. COMMENTS

- EER: Found AC per 01/03/00.
- Labeling: Pending
- Bio last reviewed on 04/27/01 (70 mg): Acceptable.
- Micro: N/A.
- DMF (b) (4): Remains Satisfactory (07/25/01)
- MV: Pending (was put in Fast Track, see attached e-mail).
- Chemistry Closed.

18. **CONCLUSIONS AND RECOMMENDATIONS**

Chemistry Closed.
Labeling review is Pending.

19. **REVIEWER AND DATE COMPLETED**

Bing Cai, Ph.D. July 25, 2001

Following this page, 6 pages withheld in full (b)(4)-CCI/TS

cc: ANDA 75-710
Division File
Field Copy

Endorsements:

HFD-625/Bing Cai/07/26/01/07/31/01
HFD-625/MShaikh for Mike Smela/8/1/01
HFD-617/MDillahunt/8/7/01
V:\FIRMSNZ\TEVA\LTRS&REV\75710CR4.DOC
F/T by: gp/8/7/01

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW NUMBER**
   4 (Addendum)

2. **ANDA NUMBER**
   75-710

3. **NAME AND ADDRESS OF APPLICANT**
   TEVA Pharmaceuticals USA
   Attention: Deborah A. Jaskot
   1510 Delp Drive
   Kulpsville, PA 19443

4. **LEGAL BASIS for ANDA SUBMISSION**
   505 (j)

5. **SUPPLEMENT(s)**
   None

6. **NAME OF DRUG**
   Alendronate Sodium Tablets

7. **NONPROPRIETARY NAME**
   Alendronate Sodium Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
   None

9. **AMENDMENTS AND OTHER DATES** (Original submission: 09/29/99)
   New information since last review:

08/08/01	New correspondence (Patent Information)
08/20/01*	**Unsolicited Amendment (CMC for new batch/35 mg)**
08/27/01	New correspondence (Patent Information)
10/19/01	New correspondence (Patent Information)
10/23/01	New correspondence (Patent Information)

   *Subject of this review.

   FDA:

08/07/01	Chemistry Closed for 5/10/40/70 mg

10. **PHARMACOLOGICAL CATEGORY**
    Suppressant (bone resorption)

11. **HOW DISPENSED**
    Prescription

12. **RELATED IND/NDA/DMF(s)**

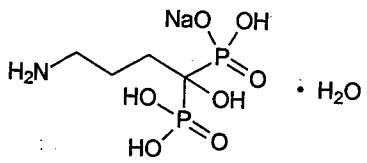
NDA 20-560, Fosamax® 5 mg, 10 mg, *35 mg*, 40 mg and 70 mg

Product	Holder	DMF No:	LOA
Alendronate Sodium Trihydrate	(b) (4)	(b) (4)	V1.2,p5980
Other related DMFs	See item 38		

13. **DOSAGE FORM**
Tablet

14. **POTENCY**
5 mg, 10 mg, *35 mg*, 40 mg and 70 mg (35 mg is newly added)

15. **CHEMICAL NAME AND STRUCTURE**
Alendronate Sodium. Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate. $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$. 325.12. *121268-17-5*.



16. **RECORDS AND REPORTS**
None

17. **COMMENTS**

This ANDA was last reviewed in July 2001. It was Chemistry Closed (August 7, 2001), pending for the labeling review (for 5 mg, 10 mg, 40 mg and 70 mg tablets). On 08/20/01, the firm provided an "Unsolicited Amendment" to add a new strength, 35 mg tablets to this ANDA. This information was not reviewed until this time due to the pending patent issues (the subject jacket was not available until the week of 11/12/2001). In the subject amendment, the firm has provided CMC documentation relevant to the 35 mg strength and updated CMC documentation applicable to the 5 mg, 10 mg, 40 mg and 70 mg tablets. A request of bio waiver for 35 mg tablets is included.

In addition, the MV has been completed by Philadelphia District Laboratory at this cycle. The completed report was received on 11/27/01. Few deficiencies/comments were cited.

Here is a summary of review for this "Special Amendment":

- EER: Found AC per 12/12/00, **Need update.**
- Labeling: Pending
- Bio waiver on 35 mg: Acceptable per 10/30/01.
- Micro: N/A.
- DMF (b) (4): Found Satisfactory per 11/21/01.
- **MV: Completed with few deficiencies/comments.**
- NA/Minor for all strengths (5 mg, 10 mg, **35 mg**, 40 mg and 70 mg).

18. CONCLUSIONS AND RECOMMENDATIONS

NA, Minor
EER needs to be update.
Labeling review is Pending.

19. REVIEWER AND DATE COMPLETED

Bing Cai, Ph.D. Nov. 14, 2001, Revised Nov. 27, 2001

Following this page, 8 pages withheld in full (b)(4)- CCI/TS

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-710

APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Alendronate Sodium Tablets, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg

The deficiencies presented below represent **Minor** deficiencies.

A. Deficiencies:

The methods validation has been completed by the Philadelphia Laboratory. Please address the following comments and provide copies of revised methods as appropriate:

- (b) (4)
-

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. Please provide any additional stability data that is available.

2. Your labeling information is pending review.

3. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

Paul Schwartz for 12/4/01

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-710
Division File
Field Copy

Endorsements:

HFD-625/Bing Cai/11/14/01/11/27/01
HFD-625/Mike Smela/11/27/01
HFD-617/MDillahunt/11/27/01 MDillahunt 11/28/01
V:\FIRMSNZ\TEVA\LTRS&REV\75710CR4ADD.DOC
F/T by: gp/11/28/01

M Smela 11/28/01

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW NUMBER**
   5

2. **ANDA NUMBER**
   75-710

3. **NAME AND ADDRESS OF APPLICANT**
   TEVA Pharmaceuticals USA
   Attention: Deborah A. Jaskot
   1510 Delp Drive
   Kulpsville, PA 19443

4. **LEGAL BASIS for ANDA SUBMISSION**
   505 (j)

5. **SUPPLEMENT(s)**
   None

6. **NAME OF DRUG**
   Alendronate Sodium Tablets

7. **NONPROPRIETARY NAME**
   Alendronate Sodium Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
   None

9. **AMENDMENTS AND OTHER DATES** (Original submission: 09/29/99)
   Most recent information:

12/4, 12/5, 12/6/01	Patent Amendments
01/14, 1/25/02	Labeling Amendments
02/28/02*	Minor Amendment

*Subject of this review.

FDA:

08/07/01	Chemistry Closed for 5/10/40/70 mg
12/05/01	NA (MINOR), issues of MVP, labeling and etc.

10. **PHARMACOLOGICAL CATEGORY**
    Suppressant (bone resorption)

11. **HOW DISPENSED**
Prescription

12. **RELATED IND/NDA/DMF(s)**

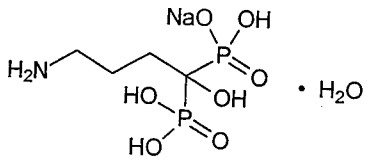
NDA 20-560, Fosamax® 5 mg, 10 mg, *35 mg*, 40 mg and 70 mg

Product	Holder	DMF No.	LOA
Alendronate Sodium Trihydrate	(b) (4)	(b) (4)	V1.2,p5980
Other related DMFs	See item 38		

13. **DOSAGE FORM** Tablet

14. **POTENCY**
5 mg, 10 mg, 35 mg, 40 mg and 70 mg

15. **CHEMICAL NAME AND STRUCTURE**
Alendronate Sodium. Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate. $C_4H_{12}NNaO_7P_2 \bullet 3H_2O$. 325.12. *121268-17-5*.



16. **RECORDS AND REPORTS**
None

17. **COMMENTS**

- **EER/Revised: Found AC per 11/28/01.**
- **Labeling: Pending**
- **Bio waiver on 35 mg: Acceptable per 10/30/01.**
- **Micro: N/A.**
- **DMF (b) (4): Remains Satisfactory per 11/21/01.**
- **MV: Completed/issues resolved per this review.**
- **Chemistry: Satisfactory**

18. **CONCLUSIONS AND RECOMMENDATIONS**
Chemistry Closed, Pending for Labeling review.

19. **REVIEWER AND DATE COMPLETED**
Bing Cai, Ph.D. March 15, 2002

Following this page, 7 pages withheld in full (b)(4)-CCI/TS

cc: ANDA 75-710
Division File
Field Copy

Endorsements:

HFD-625/Bing Cai/03/15/02
HFD-625/Mike Smela/
~~HFD-617/MDillahunt/~~
V:\FIRMSNZ\TEVA\LTRS&REV\75710CR5.DOC

M Smela 3/18/02

F/T by:

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW NUMBER** Addendum to CR#5

2. **ANDA NUMBER** 75-710

3. **NAME AND ADDRESS OF APPLICANT**
   TEVA Pharmaceuticals USA
   Attention: Philip Erickson, R.Ph.
   1090 Horsham Road, P.O. Box 1090
   North Wales, PA 19454

4. **LEGAL BASIS for ANDA SUBMISSION** 505 (j)

5. **SUPPLEMENT(s)** None

6. **NAME OF DRUG** Alendronate Sodium Tablets

7. **NONPROPRIETARY NAME** Alendronate Sodium Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR** None

9. **AMENDMENTS AND OTHER DATES** Original submission: 09/29/99

   Most recent submission:

   TEVA:

01/14, 01/25/02	Labeling Amendments
02/28/02	Minor Amendment (see CR#5)
04/26/02*	**Unsolicited Amendment(new batches)**
04/30/02*	**Unsolicited Amendment**
04/26/02 & 06/21/02	Labeling Amendments
05/02 to 06/02	Various patent amendments (see list below)

   *Subject for this review.

   Patent Amendments (05/02 to 06/02)/Paragraph IV: 05/16, 05/20, 05/16, 05/17, 05/21, 05/22, 05/23, 05/24, 05/28, 05/29, 05/30, 05/31, 06/04, 06/05, 06/06(2), 06/07(2), 06/10(3), 06/11(2), 06/12(2), 06/13(2), 06/14, 06/17, 06/18, 06/19(2), 06/20(2), 06/21(2).

   FDA:

08/07/01	Chemistry Closed for 5/10/40/70 mg
12/05/01	NA (MINOR), issues of MVP, labeling and etc.
03/18/02	Chemistry Closed(35 mg), Pending Labeling review.
07/09/02	Labeling: Acceptable

10. **PHARMACOLOGICAL CATEGORY** Suppressant (bone resorption)

11. **HOW DISPENSED** Prescription

12. **RELATED IND/NDA/DMF(s)**

NDA 20-560, Fosamax® 5 mg, 10 mg, *35 mg*, 40 mg and 70 mg

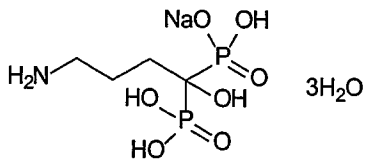
Product	Holder	DMF No.	LOA
Alendronate Sodium Trihydrate	(b) (4)	(b) (4)	V1.2,p5980
Other related DMFs	See item 38		

13. **DOSAGE FORM** Tablet

14. **POTENCY** 5 mg, 10 mg, 35 mg, 40 mg and 70 mg

15. **CHEMICAL NAME AND STRUCTURE**

Alendronate Sodium. Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate. $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$. 325.12. *121268-17-5*.



16. **RECORDS AND REPORTS** None

17. **COMMENTS**

- EER/Revised: Found AC per 07/12/02.
- Labeling: Acceptable per 07/09/02
- Last Bio on 35 mg: Acceptable per 10/30/01.
- Micro: N/A.
- DMF (b) (4): Remains Satisfactory per this cycle.
- MV: Sat. per CR#5
- Chemistry: Need additional stability data/70 mg tablets

18. **CONCLUSIONS AND RECOMMENDATIONS** NA/Minor Amendment.

19. **REVIEWER AND DATE COMPLETED** Bing Cai, Ph.D. July 17, 2002

Following this page, 9 pages withheld in full (b)(4)- CCI/TS

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-710

APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Alendronate Sodium Tablets, 5 mg, 10 mg, 35 mg, 40 mg, and 70 mg

The deficiencies presented below represent **Minor** deficiencies.

A. Deficiencies:

1. (b) (4)

2.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please provide accrued long term stability data.

Sincerely yours,

Paul Schwartz for 7/29/02

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-710
Division File
Field Copy

Endorsements:

HFD-625/Bing Cai/07/20/02
HFD-625/Shing Liu/07/22/02 S.H.Liu 7/26/02
HFD-617/PM/Peter Chen/ 7/24/02
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F/T by: gp/07/25/02

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW NUMBER** 6

2. **ANDA NUMBER** 75-710

3. **NAME AND ADDRESS OF APPLICANT**
   TEVA Pharmaceuticals USA
   Attention: Deborah A. Jaskot
   1090 Horsham Road
   North Wales, PA 19454

4. **LEGAL BASIS for ANDA SUBMISSION** 505 (j)

5. **SUPPLEMENT(s)** None

6. **NAME OF DRUG** Alendronate Sodium Tablets

7. **NONPROPRIETARY NAME** Alendronate Sodium Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR** None

9. **AMENDMENTS AND OTHER DATES**

   Original Submission: 09/29/99

   Most recent submission:
   TEVA:

04/16/02	Unsolicited Amendment(See CR#6)
04/30/02	Unsolicited Amendment(See CR#6)
04/26/02 & 06/21/02	Labeling Amendments
05/02 to 07/02	Various patent amendments (see list below)
07/31/02	***Minor Amendment/Chemistry**

   *Subject for this review.

   Additional Patent Amendments (Paragraph IV) Since CR#6/Jun & Jul, 2002): 06/24, 06/25(2), 06/26(2), 06/27(2), 06/28(2), 07/01(2), 07/02(2), 07/03, 07/05, 07/07, 08/07, 07/09, 07/10, 07/11, 07/12, 07/15, 07/16, 07/17, 07/18.

   FDA:

08/07/01	Chemistry Closed for 5/10/40/70 mg
12/05/01	NA (MINOR), issues of MVP, labeling and etc.
03/18/02	Chemistry Closed(35 mg), Pending Labeling review.
07/09/02	Labeling: Acceptable
07/30/02	CMC NA Minor

10. **PHARMACOLOGICAL CATEGORY** Suppressant (bone resorption)

11. **HOW DISPENSED** Prescription

12. **RELATED IND/NDA/DMF(s)**

NDA 20-560, Fosamax® 5 mg, 10 mg, *35 mg*, 40 mg and 70 mg

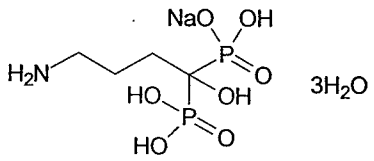
Product	Holder	DMF No.	LOA
Alendronate Sodium Trihydrate	(b) (4)	(b) (4)	V1.2,p5980
Other related DMFs	See item 38		

13. **DOSAGE FORM** Tablet

14. **POTENCY** 5 mg, 10 mg, 35 mg, 40 mg and 70 mg

15. **CHEMICAL NAME AND STRUCTURE**

Alendronate Sodium. Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate. $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$. 325.12. *121268-17-5*.



16. **RECORDS AND REPORTS** None

17. **COMMENTS**

X **EER/Revised: Found AC per 07/12/02.**
X **Labeling: Acceptable per 07/09/02**
X **Last Bio on 35 mg: Acceptable per 10/30/01.**
X **Micro: N/A.**
X **DMF (b) (4): Remains Satisfactory per this cycle.**
X **MV: Sat. per CR#5**
X **Chemistry: Acceptable**

18. **CONCLUSIONS AND RECOMMENDATIONS Approved**

19. **REVIEWER AND DATE COMPLETED** Bing Cai, Ph.D. Aug. 9, 2002

Following this page, 6 pages withheld in full (b)(4)-CCI/TS

cc: ANDA 75-710
Division File
Field Copy

Endorsements:

HFD-625/Bing Cai/08/09/02 12/04/02
HFD-625/Shing Liu/ 12/4/02
HFD-617/Wanda Pamphile/ 12/4/02
V:\FIRMSNZ\TEVA\LTRS&REV\75710CR7.BBC.DOC
F/T by:

CHEMISTRY REVIEW

ANDA 75-710

Alendronate Sodium Tablets, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg

TEVA Pharmaceuticals USA

Bing Cai, Ph.D.

Chemistry Division 1

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Chemistry Review Data Sheet

The end of chemistry review #6 references chemistry review #7 in the file name. However, it appears there was a numbering error. No chemistry review #7 was located.

1. ANDA: 75-710

2. REVIEW #: 8

3. REVIEW DATE: 8/20/07, 12/14/07, 1/31/08

4. REVIEWER: Bing Cai, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
TEVA:	
Original Submission	09/29/99
Minor Amendment/Chemistry	07/31/02
FDA:	
Chemistry Review #7/TA	07/31/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Various Patent Amendments (30-See COMIS for full list) .	2003-2007
Major amendment (New API source for 40 mg)	**Apr. 29, 2005**
Major amendment (New API source for 70 mg)	**Dec. 12, 2006**
Major amendment	**Oct. 19, 2007**
Major amendment	**Nov. 20, 2007**
Minor amendment	**Jan. 10, 2008**

7. NAME & ADDRESS OF APPLICANT:

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
North Wales, PA 19454

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Alendronate Sodium Tablets

9. LEGAL BASIS FOR SUBMISSION: 505 (j)

The basis of Teva's ANDA for Alendronate Sodium Tablets USP 5 mg, 10 mg, 35 mg, 40 mg and 70 mg is the approved reference listed drug, Fosamax®Tablets 5 mg, 10 mg, 35 mg, 40 mg and 70 mg (Alendronate Sodium Tablets), the subject of NDA 020-560, held by Merck & Co., Inc.

This ANDA is TAed on 7/31/2002 and it is pending for unexpired patents and exclusivities before the final approval.

10. PHARMACOL CATEGORY:

Inhibitor of osteodastmediated bone resorption. Prevention of osteoporosis in postmenopausal women

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 5 mg, 10 mg, 35 mg and 70 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

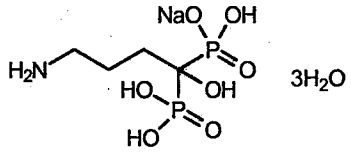
_____SPOTS product – Form Completed

__XX___Not a SPOTS product

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

Alendronate Sodium. Phosphonic acid, (4-amino-1-hydroxybutylidene) bis-, monosodium salt, trihydrate; $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$. 325.12. CAS: *121268-17-5.*

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF No.	DMF	Action Code	Result of Review	Date Review Completed
(b) (4)		7	See comment below*	
18327	II/Alendronate Sodium Trihydrate/TEVA	1	Adequate	11/26/07
	Comment: DMF is adequate.			
(b) (4)		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: (2) Type 1 DMF; (3) Reviewed previously and no relevant revision since last review; (4) Sufficient information in application; (5) Authority to reference not granted; (6) DMF not available; (7) Other (explain under "Comments").

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

*Comment: The DMF (b) (4) was found AC when the ANDA was TAed in 2002 (See Item 22 for more details)

B. Other Documents: N/A

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	AC	1/11/2008	S. Adams
Methods Validation	N/A		
Labeling	AC	1/11/2008	R. Wu
Bioequivalence	AC (previously TAed)		
EA	N/A		
Radiopharmaceutical	N/A		

**BPCA consult is pending*

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes _XX___ No If no, explain reason(s) below:

Following this page, 13 pages withheld in full (b)(4)- CCI/TS

31. **SAMPLES AND RESULTS**
Review status: No changes since TA'ed on 7/31/02.

32. **LABELING**
Review status: Satisfactory, 1/11/08, R Wu

33. **ESTABLISHMENT INSPECTION**
Satisfactory, 1/11/08 S. Ferguson

34. **BIOEQUIVALENCY STATUS**
Review status: No changes since TA'ed on 7/31/02.

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION**
Review status: Satisfactory per CR#1

36. **ORDER OF REVIEW**
The application submission(s) covered by this review was taken in the date order of receipt?

☐ Yes or ■ No. If no, explain reason(s) below:

TAed, Pending for exclusivity.

Special Product Online Tracking (SPOT)?

☐ Yes or ■ No. If yes, complete a SPOT form.

cc: ANDA 75-710
ANDA DUP
Division File
Field Copy

Endorsements:
HFD-620/BCai/ Dec. 14, 2007, Jan. 31, 2007
HFD-620/GBykadi/ Dec 26, 2007/ Feb 1, 2008
HFD-617/BDanso/
V:\Chemistry Division I\Team 5\PM Folder\75710CR8.doc

F/t by: Simon Eng 2/1/08

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

/s/

Bing Cai
2/4/2008 11:40:45 AM
CHEMIST

Gururaj Bykadi
2/5/2008 07:21:44 AM
CHEMIST

Benjamin Danso
2/6/2008 12:25:44 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-710

BIOEQUIVALENCE REVIEWS

Alendronate Sodium
5 mg, 10 mg and 40 mg Tablets
ANDA 75-710
Reviewer: James E. Chaney
V:\FIRMSNZ\TEVA\LTRS&REV\75710SDW.999

Teva Pharmaceuticals
Sellersville, PA
Submission Date:
September 29, 1999
December 28, 1999

Review of a Single Dose Bioequivalence Study Under Fasting Conditions, *in vitro* Dissolution Testing, Two Waiver Requests and an Amendment

I. INTRODUCTION

The original submission of September 29, 1999 included a single dose bioequivalence study under fasting conditions on the 40 mg tablet with *in vitro* dissolution testing on all three strengths and waiver requests on the 5 mg and 10 mg strengths. The application was found acceptable with the exception that frozen stability data on alendronate stored in frozen urine was not included. This stability determination was reported as ongoing. On 12/21/99 Ms. Jennifer Fan advised the firm *via* telephone that the stability data on alendronate in frozen urine should be submitted. On 12/29/99 the Agency received a fax and hard copy of the requested frozen stability data (12/28/99 amendment). The amended results are acceptable and are presented in the analytical methods section of this review.

II. BACKGROUND

RLD:
The RLD for this product is Fosamax®, 40 mg tablets (Merck & Co.).

Indication:
The drug is indicated for the treatment and prevention of osteoporosis in post-menopausal women.

Bioavailability:
The oral bioavailability of alendronate in women is 0.7% for doses ranging from 5-40 mg under fasting conditions. Bioavailability decreases by approximately 40% when a 10 mg tablet is administered 0.5-1 hour before the breakfast. The bioavailability of this product in the NDA was determined using urinary elimination of the parent drug.

Food-effect study requirement:
The drug product is administered at least 30 minutes before the first food of the day. No food study is required.

Distribution:
Alendronate distributes to soft tissues, but is then rapidly redistributed to bone or is excreted in the urine.

T1/2:
Following a single 10 mg I.V. dose, plasma concentration falls by more than 95% in 6 hours. Concentrations of drug in plasma following therapeutic oral doses are too low (<5 ng/mL) for analytical detection. However, terminal half-life in humans is estimated to exceed 10 years, reflecting release of alendronate from the bone.
DBE guidance: None.

III. FASTING IN-VIVO BIOEQUIVALENCE STUDY

A. STUDY OBJECTIVE

The objective of this study was to compare the bioavailability of TEVA Pharmaceuticals' 40 mg alendronate sodium tablets with Merck's Fosamax® under fasting conditions.

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY

Clinical Site: Phoenix Clinical Research Center in Montreal, Quebec, Canada
Principal Clinical Investigator: Samuel Serfaty, M.D.
Analytical Site: Phoenix International

C. INFORMED CONSENT AND IRB APPROVAL

Copies of the signed informed consent and IRB review forms were provided.

D. STUDY DESIGN

This study was an open-label, randomized, single-dose, 2-way crossover comparative bioavailability study performed on 130 healthy non-smoking adult male subjects. Subjects were dosed in four groups. Groups 1 and 3 consisted of 32 subjects each. Groups 2 and 4 consisted of 33 subjects each.

E. SUBJECT SELECTION CRITERIA

The complete list of exclusion and inclusion criteria can be found in the protocol (Volume 1.2, p150g-150i).

F. STUDY SCHEDULE

Subjects drank 200 mL of water every 30 minutes from 1 hour prior to dosing to 30 minutes after dosing (excluding water administered at dosing). Subjects were also administered 240 mL of water at 2 and 3 hours post-dose. Water was available at all other times.

In each period, subjects were housed from at least 12 hours before dosing until after their 36-hour urine collection. The periods were separated by a seven (7) day washout.

Urine samples were collected one hour prior to dosing for the time zero samples. The subjects were instructed not to void their bladder until the 0.25 hour post-dose collection time in order for them to have enough urine in their bladder at 0.25 hour. Urine samples were then collected at 1, 2, 3, and 4 hours post-dose and over the following collection intervals: 4-6, 6-8, 8-12, 12-24 and 24-36 hours post-dose.

Volumes and pH's were recorded and 2X5 mL samples were taken from each interval. The samples were stored frozen at -22°C until analysis.

G. DRUG TREATMENTS

Test Product (A): TEVA Pharmaceuticals, alendronate sodium tablets, 1X40 mg, Lot No. 1081-044; Manufacturing Date: 1/99; Assay: 95.6%, Content Uniformity: 97.6% (91.3-100.8), 2.3 %CV; Lot size, 99,200

Reference Product (B): Merck Co. Inc., (Fosamax®) 40 mg alendronate sodium tablets. Lot No. H1 Date: 2/00. Assay: 96,0%, Content Uniformity: 94.9% (91.2-100.6), 2.8 %CV

H. STUDY DATES:

Subject Nos. 1-32 (Group 1): June 5 and 12, 1999
Subject Nos. 33-65 (Group 2): June 7 and 14, 1999
Subject Nos. 66-97 (Group 3): June 12 and 19, 1999
Subject Nos. 98-130 (Group 4): June 14 and 21, 1999

Samples were analyzed during the period of 7/1/99 to 8/13/99. (The maximum storage time was 69 days.)

I. ANALYTICAL METHODS

The method developed for the analysis of alendronate in human urine was performed using high performance liquid chromatography with fluorescence detection.

A summary of the pre-study assay validation data is shown in Table 1. A summary of during study assay validation is shown in Table 2.

Table 1. Pre-Study Assay Validation For Alendronate Analyses

Parameter	Q. C. Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	10.0, 29.7, 297.3, and 693.7	10.0, 20.0, 50.0, 100.0, 199.9, 499.8, 750.1 and 999.6
Intra-day Precision (%CV)	3.7 to 10.1	
Intra-day Accuracy (%)	96.2 to 105.1	
Inter-day Precision (%CV)	2.7-14.5	0.4-5.0
Inter-day Accuracy (%)	90.8-97.5	93.8-105.8

% Recovery	Analyte at low, middle and high QC concentrations were 49.9, 60.2 and 51.4; Mean IS, 69.0
Linearity	$r^2 \geq 0.9996$
Linear Range	10 to 999.6 ng/mL
Sensitivity/LOQ	10 ng/mL
Stability in Urine a) Hr @ Room Temp. b) Freeze-Thaw c) Long-Term Frozen	a) Stable at room temperature 4 hours. b) Stable after 3 cycles c) Acceptable per amended data
d) Reconstituted Stability	d) Reconstituted extracts are stable 88.2 hrs at room temperature.
Specificity	No interference from endogenous components at the retention time of alendronate, or internal standard, (b) (4).

The data on alendronate stability in frozen urine was not included in the original submission of 9/29/99. The amended stability data submitted 12/28/99 are acceptable. The analysis was completed on June 8, 1999 after storage of the stability samples at -22°C for 96 days. The methodology is acceptable and the mean analyzed concentrations are within 6% of the nominal values for alendronate. The stability data demonstrates that alendronate is stable when stored in frozen urine corresponding to the temperature (-22°C) and exceeding the time (69 days) used for storage of the frozen urine samples in the bioequivalence study.

Table 2. During Study Analytical

Parameter	**Q.C. Samples**	**Std. Curve Samples**
QC or Std. Curve Conc. (ng/mL)	30.06, 300.63 and 701.46	Same as for pre-study validation
Interday Precision (%CV)	6.6 - 10.0	4.3 - 8.6
Interday Accuracy %	97.5-100.0	96.1-106.9
Sensitivity/LOQ (ng/mL)	10	

Representative calibration and study sample chromatograms were submitted for 20% of the subjects.

J. RESULTS OF FASTING BIOEQUIVALENCE STUDY

Pharmacokinetic Parameters Reported:

Ae: Amount of drug excreted during each collection interval, calculated by multiplying the drug concentration in urine by the volume of urine over this particular collection period.

TAe': Total amount of drug excreted unchanged in the urine over selected collection intervals. The collection intervals were selected to ensure that measurable or interpolated values were present over the same interval for both formulations. For example, following dosing with the test product subject 89 had measurable amounts of alendronate in all collection intervals included in the interval of 0-24 hours. However, following dosing with the reference product the subject had measurable amounts in the collection intervals within 0.25-6 hours only. Therefore, the intervals 0-0.25 hours and 6-24 hours were not used in calculating Tae' for this subject.

TAe(0-36): Total amount of drug excreted unchanged in the urine over the entire period of sample collection, obtained by adding the amounts excreted over each collection interval.

Re: Urinary rate of drug excretion, obtained by dividing the amount of drug excreted in each urine collection interval by the time over which it was collected.

Rmax: Maximum urinary excretion rate.

Tmax: Time of maximum excretion rate, defined as the midpoint of the collection interval during which Rmax occurred.

Tables of pertinent pharmacokinetic data reported by the firm follow (Tables 3-6). Plots of the mean rates of alendronate urinary excretion *vs* time and mean cumulative alendronate urinary excretion *vs* time are presented in attached Figures 1 and 2, respectively.

Table 3. Arithmetic Mean Urine Cumulative Amounts of Alendronate (ng) at Each Collection Interval

Interval (h)	Test			Reference			T/R
	N	Mean	CV%	N	Mean	CV%	
0-0.25	128	248	298	128	43	751	5.74
0.25-1	128	27846	86	128	27468	75	1.01
1-2	128	58772	84	128	57813	75	1.02
2-3	128	77613	84	128	76560	73	1.01
3-4	128	89049	86	128	87056	74	1.02
4-6	128	99836	88	128	96691	75	1.03
6-8	128	104642	89	128	100977	76	1.04
8-12	128	108954	91	128	105125	77	1.04
12-24	128	112873	93	128	108760	79	1.04
24-36	128	113906	94	128	109503	81	1.04

Table 4. Arithmetic Mean Rate of Alendronate Excretion (ng/h) During Each Urine Collection Interval

Interval (h)	Test			Reference			T/R
	N	Mean	CV%	N	Mean	CV%	
0-0.25	127	998	297	128	140	698	7.15
0.25-1	128	36835	86	128	36578	75	1.01
1-2	128	30987	91	126	30847	80	1.00
2-3	128	18804	92	128	18550	80	1.01
3-4	128	11537	123	128	10496	95	1.10
4-6	128	5397	114	127	4855	97	1.11
6-8	127	2418	127	127	2147	107	1.13
8-12	128	1075	145	128	1011	127	1.06
12-24	128	327	178	128	303	169	1.08
24-36	126	88	366	126	63	392	1.39

Table 5. Arithmetic Mean Alendronate Pharmacokinetic Parameters

Parameter	Test			Reference			T/R
	N	Mean	CV%	N	Mean	CV%	
Tae(0-36) (ng)	128	113906	95	128	109503	81	1.04
Tae' (ng)	128	107502	94	128	103922	82	1.03
Rmax (ng/h)	128	40211	85	128	39843	71	1.01
Tmax (h)	128	0.946	55	128	0.961	59	0.98
Ka (1/h)	128	10.92	16	128	11.22	17	0.97
F (%)	128	0.27784	81	128	0.27356	70	1.02

Table 6. LSMeans, Geometric Lsmeans, T/R Ratios and 90% Confidence Intervals (90% C.I.) for Alendronate Pharmacokinetic Parameters

Parameter	LSMeans		Ratio of LSMeans %	90% C.I.	Intra-Subject CV%
	Test	Ref			
Tae(0-36)(ng)	108531	107757	100.7	--	--
*LnTAe(0-36)(ng)	81228	85343	95.2	85.1-106.5	57
Tae' (ng)	102569	101882	100.7	--	--
*LnTAe' (ng)	76764	80160	95.8	86.9-105.5	48
Rmax	39093	39512	98.9	--	--
*LnRmax	30806	32721	94.1	85.2-104	49
Ka (1/h)	11.00	11.29	97.4	--	--
*Ln Ka (1/h)	10.81	11.06	97.8	95.3-100.3	12
F (%)	0.26706	0.26851	99.5	--	--
*LnF (%)	0.21797	0.22678	96.1	89.2-103.5	36

* Geometric LSMeans

There were non-zero pre-dose concentrations for which adjustment to the data set was considered necessary except for Subject No. 117 in Period 2 (Formulation B). Taking into account that most subjects had BLQ values by 36 hours post-dose in

Period 1 it is unlikely that after a 7 day washout period residual drug carryover was the cause for the reported non-zero pre-dose concentration. So, this value was set to zero (BLQ) for pharmacokinetic and statistical analyses.

K. STATISTICAL ANALYSIS

An ANOVA was performed to test if there was a significant formulation-by-group interaction. The ANOVA model included group, sequence, period nested within group, formulation and formulation-by-group interaction as fixed effects and subject nested within group-by-sequence as a random effect. The formulation-by-group interaction was not statistically significant at the 5% level and the interaction term was dropped from the model. The statistical analyses were done using the SAS GLM procedure.

L. CLINICAL NOTES

No serious medical events were reported during the study, except for Subject No. 6 in period 1 at 2.2 days post-dose (pneumothorax diagnosis). In Period 1 Subject No. 48 fell out of bed and hurt his right elbow. Subjects 6 and 48 were withdrawn from the study. Of the 130 healthy non-smoking adult male subjects who enrolled in this study, a total of 128 subjects completed the crossover.

IV. PRODUCT FORMULATION (NOT TO BE RELEASED UNDER FOI):

The formulation of the test product, as supplied by the manufacturer, is given in Table 7.

Table 7.

INGREDIENT	5 mg Strength		10 mg Strength		40 mg Strength	
	mg/ Tablet	%/ Tablet	mg/ Tablet	%/ Tablet	mg/ Tablet	%/ Tablet
Alendronate Sodium, Trihydrate	6.53	3.625	13.05	6.525	52.21	26.105
Microcrystalline Cellulose, NF	(b) (4)					
Croscarmellose Sodium, NF (b) (4)						
Magnesium Stearate, NF						
Total	200.0	100.0	200.0	100.0	200.0	100.0

The formulations of the 5 mg and 10 mg strengths of the test product are proportionally similar to that of the 40 mg strength, which underwent the bioequivalence studies.

The total weights of the tablets are equal. The decreases in the amount of drug substance in the lower strengths relative to the highest strength account for the increases in the microcrystalline cellulose content in the lower strengths. From the dissolution data it is seen that the dissolution is not affected by this variation in formulation.

V. DISSOLUTION

There is no USP dissolution method or specification for the drug product. The results of the dissolution testing and the method used are given in Table 8. The dissolution methodology used is the firm's own method and it was the same as that used in the NDA (20-560): 900 mL of water at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. Teva's specification was NLT 80% in 30 min and the innovator's specification was NLT (b) (4)% in 30 min. All three strengths of Teva's product meet the innovator's specification.

TABLE 8. *IN VITRO* DISSOLUTION TESTING

Drug (Generic Name): Alendronate Sodium Tablets
Dose Strength: 5 mg, 10 mg and 40 mg
ANDA No.: 75-710
Firm: Teva Pharmaceuticals
Submission Date: 9/29/99
File Name: 75710SDW.999

I. Conditions for Dissolution/Release Testing:

USP 23 Apparatus: Paddle RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Tolerance (Q): NLT 80% in 30 min
Reference Drug: Fosamax® Tablets (Merck & Co.)
Assay Method: HPLC, 266 nm

II. Results of In Vitro Dissolution/Release Testing:

Sampling Times (Min)	Test Product: Lot No.: 1081-044 Strength: 40 mg			Reference Product: Lot No.: H1531 Strength: 40 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	87	(b) (4)	5.3	80	(b) (4)	11.0
20	94		4.0	94		4.6
30	97		2.6	98		3.0
40	99		2.6	97		2.8

Sampling Times (Min)	Test Product: Lot No.: 1081-067 Strength: 10 mg			Reference Product: Lot No.: J3506 Strength: 10 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	98	(b) (4)	5.1	82	(b) (4)	9.3
20	100		3.7	94		5.9
30	100		3.2	99		5.9
40	98		4.7	98		5.4

Sampling Times (Min)	Test Product: Lot No.: 1081-065 Strength: 5 mg			Reference Product: Lot No.: J3858 Strength: 5 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	94	(b) (4)	3.2	94	(b) (4)	4.0
20	100		2.7	98		3.0
30	101		2.6	100		2.2
40	100		2.9	99		1.7

VI. COMMENTS:

1. The single-dose, fasting bioequivalence study conducted by Teva Pharmaceuticals on its test product, alendronate

tablet, 40 mg, lot # 1081-044, comparing it with the reference product, Fosamax®, 40 mg tablet manufactured by Merck has been found acceptable.

2. In future submissions the firm should submit the long-term frozen stability data on the analytes in the appropriate matrix such as urine as soon as the data is available. Otherwise, delays in the evaluation of the applications could result.
3. The FDA has relied on urinary excretion data as the basis for the pharmacokinetics section of Fosamax® labeling. Absolute bioavailability as well as food, gender and age effects detailed in the labeling were determined from urinary excretion studies. It is appropriate to use total urinary alendronate excretion amounts and excretion rates to evaluate bioequivalence of orally-administered alendronate. (Note: the parameter Tae(0-36) is the same as the cumulative amount excreted through the last measurable interval.)
4. The Tae' data from noncompatmental methods, and the availability (F) and rate of absorption data (Ka) from compartmental methods reported by the firm are not pivotal. The reviewer calculated individual F values (bioavailability) by dividing the Tae(0-36) values by the dosed amount (40 mg, 40,000,000 ng) and multiplying by 100. The reviewer calculated mean values for the test and reference products were 0.285% and 0.274%, respectively. These results agree very closely with the firm's estimated values (0.278% and 0.274% for test and reference products, respectively).
5. The *in vitro* dissolution data for the test and reference products of all strengths are acceptable. The Similarity Factors (f_2) were calculated by the reviewer, and the following values were obtained:

    65 for 40 mg test vs 10 mg test
    64 for 40 mg test vs 5 mg test
    68 for 40 mg test vs 40 mg reference
    57 for 10 mg test vs 10 mg reference
    90 for 5 mg test vs 5 mg reference

6. The analytical data is acceptable.
7. The formulations of the 5 mg and 10 mg strengths of the test product are proportionally similar to that of the 40 mg strength, which underwent bioequivalence testing.
8. The calculations of the noncompartmental pharmacokinetic parameters of cumulative excretion and excretion rates were checked by the reviewer using Microsoft Excel and the results agree with what the firm reported.

9. The assayed potency and the content uniformity of the test and reference products are satisfactory.
10. Due to excessive sampling during (b) (4) (b) (4), the final packaged yield (b) (4) was slightly lower than the required (b) (4) tablets. This degree of sampling is not typical of commercial production. Therefore, the batch size is acceptable.
11. The products used in the biostudies and dissolution studies were from the same batch.
12. After dosing with the test product the R_{max} (maximum urinary excretion rate) values for 72 out of 128 subjects were the first nonzero alendronate urinary excretion rates in the plots of excretion rates *vs* mid-times of urine collection intervals (70 observations in the 0-0.25 hour interval and two observations in the 0.25-1 hour interval). Similarly, upon dosing with the reference product the R_{max} values for 86 out of 128 subjects were the first nonzero alendronate urinary excretion rates (all 86 in the 0-0.25 hour interval).

VII. RECOMMENDATIONS

1. The single-dose, fasting bioequivalence study conducted by Teva Pharmaceuticals Inc. on its test product, alendronate tablet, 40 mg, lot # 1081-044, comparing it with the reference product, Fosamax®, 40 mg tablet manufactured by Merck, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Teva Pharmaceuticals' alendronate tablet, 40 mg, is bioequivalent to the reference product, Merck's Fosamax® 40 mg tablet under fasting.
2. The *in-vitro* dissolution testing conducted by Teva Pharmaceuticals Inc. on its alendronate tablets, 5 mg, 10 mg and 40 mg, has been found acceptable. The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following interim specifications:

   Not less than (b) (4)% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.
3. The firm has demonstrated that the formulations of its alendronate tablets, 5 mg and 10 mg, are proportionally similar to that of the 40 mg strength that underwent acceptable *in vivo* bioequivalence and dissolution testing. The request for waiver of *in vivo* bioequivalence study requirements for the 5 mg and 10 mg tablets may be granted.

The firm's alendronate tablets, 5 mg and 10 mg, are therefore deemed bioequivalent to Merck's Fosamax® tablets, 5 mg and 10 mg.

4. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.
5. The firm should be advised of comment 2 and the dissolution methodology and specifications in recommendation 2.

James E. Chaney

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang YCH Date 12/30/99

Concur: Dale P. Conner Date 12/30/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/122999
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T. Thomas

BIOEQUIVALENCY COMMENTS

ANDA: 75-710 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Alendronate Sodium Tablets 5 mg, 10 mg and 40 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following interim specifications:
>
> Not less than (b)(4)% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

In future bioequivalence study submissions you should submit long-term frozen stability data on the analytes in the appropriate matrix such as plasma or urine as soon as the data is available. Otherwise, delays in the evaluation of your applications could result.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-710
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney J. Chaney 12/30/99
HFD-652/ Y. Huang 1/3/2000
HFD-617/ J. Fan 1/3/2000
HFD-650/ D. Conner 12/30/99

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BIOEQUIVALENCY - ACCEPTABLE Submission dates: September 29, 1999
December 28, 1999

1. FASTING STUDY (STF) o/c Strengths: 40 mg
Outcome: **AC**

Clinical: Phoenix Clinical Research Center in Montreal, Quebec, Canada

Analytical: Phoenix International

3. DISSOLUTION WAIVER (DIW) o/c Strengths: 5 mg
Outcome: **AC**

3. DISSOLUTION WAIVER (DIW) o/c Strengths: 10 mg
Outcome: **AC**

5. STUDY AMENDMENT (STA) o/c Strengths: All
Outcome: **AC**

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:
The biostudy and dissolution data were found acceptable. Waivers on the 5 mg and 10 mg strengths are granted

Figure 1
Project No. 991323
Mean Rate of Alendronate Urinary Excretion at
Each Collection Interval
(Linear Plot)

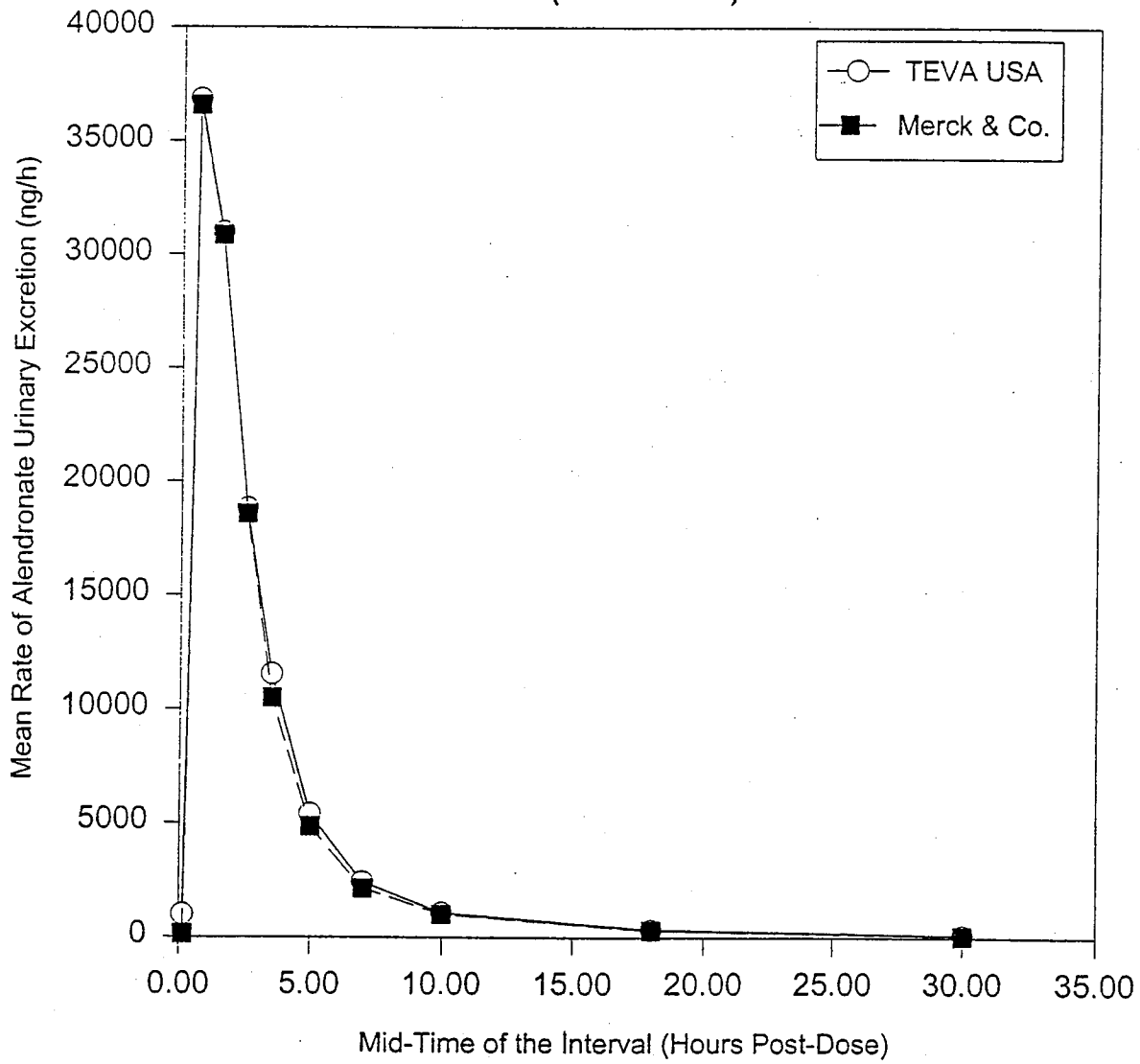
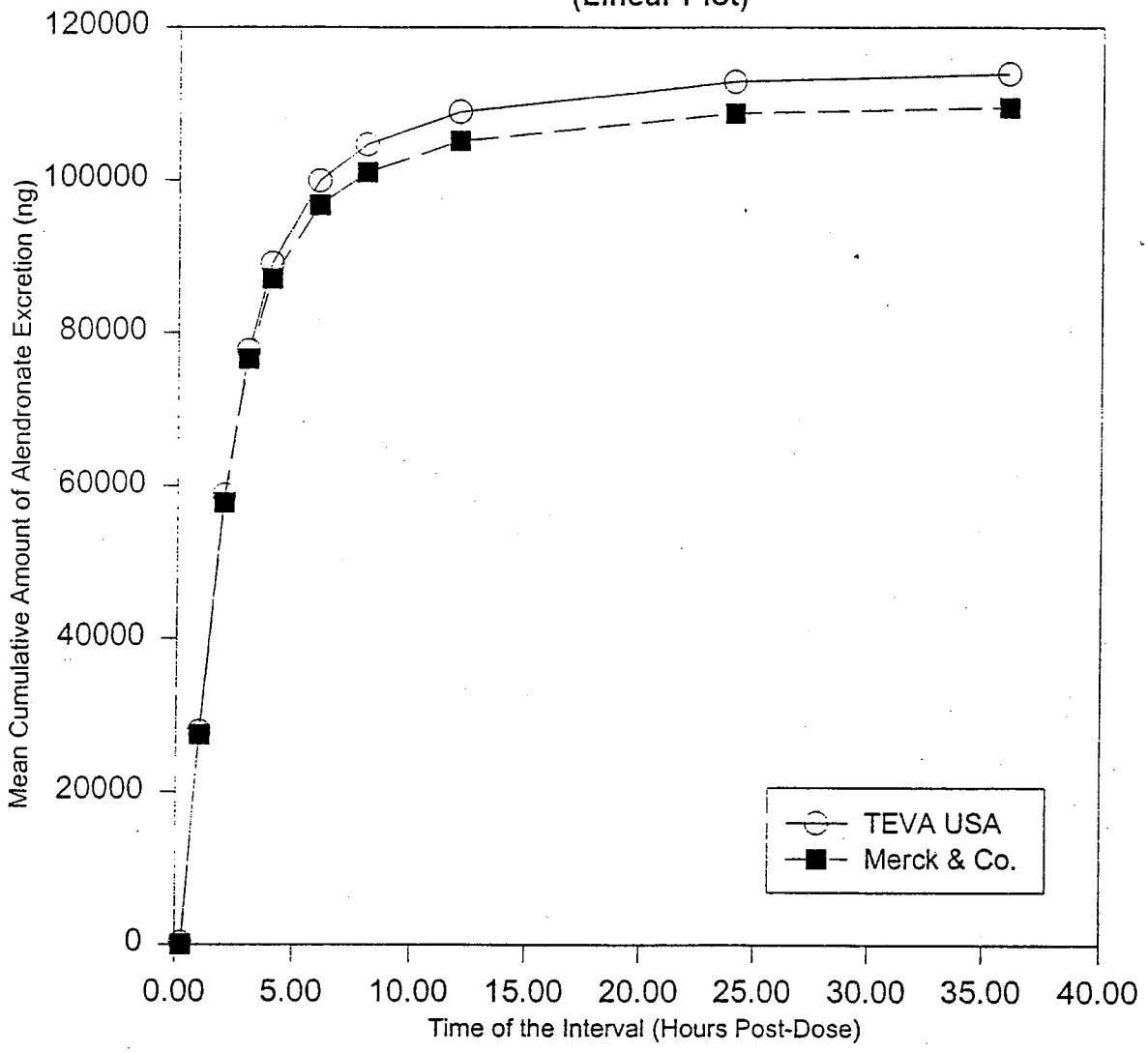


Figure 2

Project No. 991323

Mean Cumulative Amount of Alendronate Urinary Excretion at Each Collection Interval

(Linear Plot)



OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-710 SPONSOR : Teva Pharmaceuticals
DRUG AND DOSAGE FORM : Alendronate Tablets
STRENGTH(S): 5 mg, 10 mg & 40 mg
TYPES OF STUDIES: Fasting
CINICAL STUDY SITE: Phoenix Clinical Research Center in Montreal, Quebec, Canada
ANALYTICAL SITE: Phoenix International

STUDY SUMMARY: Acceptable

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

Inspection needed: ~~YES~~ NO	Inspection status:	Inspection results:
First Generic YES New facility_____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	No need to inspect Phoenix sites.

PRIMARY REVIEWER: James Chaney BRANCH: I
INITIAL: JEC DATE: 12/29/99

TEAM LEADER: Yih-Chain Huang BRANCH: I
INITIAL: [signature] DATE: 12/30/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.
INITIAL : [signature] DATE : 12/30/99

Alendronate Sodium
5 mg, 10 mg and 40 mg Tablets
ANDA 75-710
Reviewer: James E. Chaney
V:\FIRMSNZ\TEVA\LTRS&REV\75710a.600

Teva Pharmaceuticals
Sellersville, PA
Submission Date:
June 8, 2000

Review of an Amendment to the Firm's *in vitro* Dissolution Testing Specifications

Objective

The firm has requested a change in the Agency's recommended dissolution specification.

Background

On September 29, 1999 the firm submitted an acceptable bioequivalence study on its 40 mg strength. Waivers were granted for the 5 mg and 10 mg strengths based on proportional compositional similarity and acceptable comparative dissolution testing.

There was no USP dissolution method or specification for this drug product. The dissolution methodology used was the firm's own method which was the same as that used in the NDA (20-560): 900 mL of water at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. Teva's specification was NLT 80% in 30 min and the innovator's specification was NLT (b) (4)% dissolved in 30 min. All three strengths of Teva's product met the innovator's specification.

Current Amendment

The firm has presented dissolution testing data generated on its ANDA batches (p72). The firm claims that the use of the FDA proposed specification of NLT (b) (4)% dissolved in 30 minutes would require S2 level testing approximately 13% of the time. Also, the firm suggests that the innovator product would not consistently meet the proposed specification.

Also, the firm refers to the recent monograph on this product contained in Pharmacopeial Forum, Volume 26, Number 2, p398 (March-April, 2000) which includes a dissolution specification of NLT 80% is dissolved in 30 minutes.

Therefore, the firm proposes to use the dissolution specification of NLT 80% dissolved in 30 minutes as originally submitted in its application of September 29, 1999.

Recommendation

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXIV apparatus II (paddle) at 50 rpm. The test product should meet the following interim specifications:

> Not less than 80% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

James E. Chaney

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang

Date 6/23/2000

fw Concur: N Saluja

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date 7/11/2000

JEC/062300
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BIOEQUIVALENCY COMMENTS

ANDA: 75-710

APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Alendronate Sodium Tablets 5 mg, 10 mg and 40 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXIV apparatus II (paddle) at 50 rpm. The test product should meet the following interim specifications:
>
> Not less than 80% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-710
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HFD-652/ J. Chaney J. Chaney
HFD-652/ Y. Huang 6/23/00
HFD-617/ K. Scardina
HFD-650/ D. Conner for 7/11/2000

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BIOEQUIVALENCY - ACCEPTABLE Submission dates: June 8, 2000

5. STUDY AMENDMENT (STA)

Strengths: All
Outcome: AC

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:

The firm's requested to use the specification NLT 80% is dissolved in 30 minutes is granted.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-710 SPONSOR : Teva Pharmaceuticals
DRUG AND DOSAGE FORM : Alendronate Tablets
STRENGTH(S): 5 mg, 10 mg & 40 mg
TYPES OF STUDIES: Fasting
CINICAL STUDY SITE: Phoenix Clinical Research Center in Montreal, Quebec, Canada
ANALYTICAL SITE: Phoenix International

STUDY SUMMARY: Acceptable

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic YES New facility_____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: James Chaney BRANCH: I
INITIAL: JMC DATE: 7/11/00

TEAM LEADER: Yih-Chain Huang BRANCH: I
INITIAL: YH DATE: 7/12/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.
INITIAL : DPC DATE : 7/12/00

Alendronate Sodium Tablets
5 mg, 10 mg, 40 mg and 70 mg
ANDA 75-710
Reviewer: James E. Chaney
V:\FIRMSNZ\TEVA\LTRS&REV\75710a2.O00

Teva Pharmaceuticals
North Wales, PA
Submission Date:
October 23, 2000

Amendment Including a Bioequivalence Study and Dissolution Testing on a New Strength - 70 mg

I. BACKGROUND

Original Submission of September 29, 1999 (5 mg, 10 mg and 40 mg)
The original submission of September 29, 1999 included a single dose bioequivalence study under fasting conditions on the 40 mg tablet (measuring urinary elimination of the parent drug) with i*n vitro* dissolution testing on all three strengths and waiver requests on the 5 mg and 10 mg strengths. The RLD was Fosamax®, 40 mg tablets (Merck & Co.). Merck's 40 mg and 10 mg products were approved on 9/29/95 and its 5 mg product was approved on 4/25/97. The bioequivalence and dissolution studies were found acceptable and waivers were granted for the 5 mg and 10 mg strengths.

October 23, 2000 Amendment Including a New Strength: 70- mg
The firm submitted an amendment to its ANDA for addition of the 70-mg strength of alendronate sodium tablets. This submission contains a report of an *in vivo* bioequivalence study and dissolution testing. The study compared alendronate sodium tablets, 70-mg manufactured by TEVA Pharmaceuticals USA to Fosamax Tablets, 10 mg (7 x 10-mg tablets) under fasting conditions. At the time of dosing (beginning June 7, 2000) the innovator's 70-mg strength had not been approved. The innovator's 70-mg and 35-mg strengths were approved on October 20, 2000 at which time the 70-mg strength became the RLD. Hence, Teva conducted the study before approval of the innovator's 70-mg product (RLD) and submitted the study to the Agency three days after approval of the 70-mg strength.

October 2, 2000 Biopharmaceutics Review of NDA 20-560
The dosing regimen for the 70-mg tablet is weekly administration. The new dosing regimen was designed to increase patient compliance and decrease potential esophageal irritation. The oral bioavailability of alendronate is less than 1%. Alendronate plasma levels are too low to measure. For the 70-mg strength the innovator 1) evaluated the relative urinary excretion of alendronate following dosing of the tablet, and 2) estimated the oral bioavailability of alendronate from the tablet relative to a 250-µg intravenous dose using urinary elimination of the parent drug.

Oct 23, 2000 Citizen Petition
On the same day (Oct 23, 2000) that Teva submitted the amendment for its new strength and only three days following the approval of the innovator's 70 mg strength Lachman Consultant Services, Inc. submitted a citizen's petition to the Agency on behalf of Teva, requesting the FDA to provide a determination as to whether Fosamax (alendronate sodium) tablets 35 mg and 70 mg (NDA 20560, S-021 and S-022), manufactured by Merck & Co., Inc., had been voluntarily withdrawn or withheld from sale for safety or efficacy reasons in that the products were not commercially available. The petitioner claims that the FDA has previously determined "for

purposes of 21 CFR 314.161 and 314.162 that never marketing an approved product is equivalent to withdrawing the drug from sale". The regulations also provide that the Agency must make a determination as to whether a listed drug is withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved (21 CFR 314.161(a)(1)).

Formulations of Innovator and Generic Drug Products
The percent compositions for the innovator's Fosamax® 5 mg, 10 mg, 40 mg and 70 mg tablets differ only in the content of lactose and active ingredient (Table1). The amounts of lactose in the 5 mg, 10 mg, 40 mg and 70 mg strengths are altered to account for the corresponding differing amounts of alendronate sodium. Therefore, these strengths are considered as not similar by definition 1 described in "Guidance for Industry: BA and BE Studies for Orally Administered Drug Products - General Considerations (September 2000)" which says: "All active and inactive ingredients are in exactly the same proportion between different strengths".

The innovator's 10 mg strength (200 mg tablet weight) and its 70 mg strength (350 mg tablet weight) clearly are not proportionally similar in composition based on definition 2 which requires that the total weight of the dosage form remain nearly the same for all strengths, the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredient and one or more of the inactive ingredients.

The method of manufacture of the 70 mg Fosamax® tablets is essentially the same as that for the currently approved strengths (5 mg, 10 mg and 40 mg).

The formulations of Teva's 5 mg, 10 mg, 40 mg and 70 mg strengths are shown in Table 2. The tablet weights of all strengths are equal. The percent compositions differ only in the content of microcrystalline cellulose and active ingredient. The amounts of in the 5 mg, 10 mg, 40 mg and 70 mg test strengths are altered to account for the corresponding differing amounts of alendronate sodium.

Dissolution Testing for Generic Drug Products
The comparative dissolution data is shown in Table 3. Both the test and reference products dissolve rapidly with 94% or greater dissolved at 20 minutes.

Dissolution Testing Innovator Drug Products
For the 70 mg strength the innovator's proposed specifications for all tests except for dissolution testing were the same as those approved for the 5 mg, 10 mg and 40 mg strengths. The NDA applicant proposed revision of the dissolution specifications for its 70 mg product from Q=(b) (4)% in 15 minutes to Q=75% in 15 minutes due to a slower dissolution profile observed for the 70 mg tablets. The slower dissolution at 15 minutes was attributed to the greater tablet mass (350 mg) relative to the above lower strength tablets (200 mg).

After the NDA chemist reviewed the dissolution data for the stability lots the proposed change of the dissolution specification was found unjustifiable and the requirement remained that the 70 mg tablets should meet the specification of Q=(b) (4)% at 15 minutes in the stability testing. (The applicant explained that 40% of the lots would fail the stage 1 test and would have to go through the stage 2 tests for dissolution.)

II. RECOMMENDATION

From the bioequivalence point of view, the firm has not met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing on the 70 mg strength and the application is unacceptable due to the fact that the study was conducted against the 10 mg strength of the reference product (7 X 10mg tablets). The study should be conducted on the current RLD, 70 mg strength.

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang Date 1/29/2001

Concur: Dale P. Conner Date 1/29/01
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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Table 1. Innovator Formulation								
INGREDIENT	**5 mg Strength**		**10 mg Strength**		**40 mg Strength**		**70 mg Strength**	
	mg/ Tablet	**%/ Tablet**	**mg/ Tablet**	**%/ Tablet**	**mg/ Tablet**	**%/ Tablet**	**Mg/ Tablet**	**%/ Tablet**
Alendronate Sodium, Trihydrate	[redacted] (b) (4)							
Microcrystalline Cellulose, NF								
Lactose Anhydrous, NF								
Croscarmellose Sodium, NF								
Magnesium Stearate, NF								
Carnauba Wax, NF	--	--	(b) (4)	-	--	--	--	--
Total	200	100.0	200	100.0	200	100.0	350.0	100.0

* Not included in total tablet weight.

Table 2. Generic Formulation								
INGREDIENT	**5 mg Strength**		**10 mg Strength**		**40 mg Strength**		**70 mg Strength**	
	mg/ Tablet	**%/ Tablet**	**mg/ Tablet**	**%/ Tablet**	**mg/ Tablet**	**%/ Tablet**	**mg/ Tablet**	**%/ Tablet**
Alendronate Sodium, Trihydrate	6.53	3.625	13.05	6.525	52.21	26.105	91.36	45.7
Microcrystalline Cellulose, NF	[redacted] (b) (4)							
Croscarmellose Sodium, NF								
(b) (4)								
Magnesium Stearate, NF								
Total	200.0	100.0	200.0	100.0	200.0	100.0	200.0	100.0

Table 3. Comparative *In Vitro* Dissolution Testing Conducted by Teva Pharmaceuticals

Drug (Generic Name): Alendronate Sodium Tablets
Dose Strength: 5 mg, 10 mg, 40 mg and 70 mg
ANDA No.: 75-710
Firm: Teva Pharmaceuticals
Submission Dates: September 29, 1999 for 5, 10 & 40 mg & October 23, 2000 for 70 mg
File Name: 75710a2.O00

I. Conditions for Dissolution/Release Testing:

USP 23 Apparatus: Paddle RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Tolerance (Q): NLT 80% in 30 min
Reference Drug: Fosamax® Tablets (Merck & Co.)
Assay Method: HPLC, 266 nm

II. Results of In Vitro Dissolution/Release Testing:

Sampling Times (Min)	Test Product: Alendronate Sodium Lot No.: 1081-102 Strength: 70 mg			Reference Product: Fosamax Lot No.: J3506 Strength: 10 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	92	(b) (4)	5.2	82	(b) (4)	9.3
20	99		3.5	94		5.9
30	102		4.1	99		5.9
40	103		2.7	98		5.4

Sampling Times (Min)	Test Product: Lot No.: 1081-065 Strength: 5 mg			Reference Product: Lot No.: J3858 Strength: 5 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	94	(b) (4)	3.2	94	(b) (4)	4.0
20	100		2.7	98		3.0
30	101		2.6	100		2.2
40	100		2.9	99		1.7

Sampling Times (Min)	Test Product: Lot No.: 1081-067 Strength: 10 mg			Reference Product: Lot No.: J3506 Strength: 10 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	98	(b) (4)	5.1	82	(b) (4)	9.3
20	100		3.7	94		5.9
30	100		3.2	99		5.9
40	98		4.7	98		5.4

Sampling Times (Min)	Test Product: Lot No.: 1081-044 Strength: 40 mg			Reference Product: Lot No.: H1531 Strength: 40 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	87	(b) (4)	5.3	80	(b) (4)	11.0
20	94		4.0	94		4.6
30	97		2.6	98		3.0
40	99		2.6	97		2.8

BIOEQUIVALENCY DEFICIENCY

ANDA: 75-710 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Alendronate Sodium Tablets, 5 mg, 10 mg, 40 mg and 70 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

You have not met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing on the 70 mg strength. The application is unacceptable due to the fact that the study was conducted against the 10 mg strength of the reference product (7 X 10 mg tablets). The study should be conducted on the 70 mg strength of the reference product.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney J. Chaney 1/26/2001
HFD-652/ Y. Huang 1/29/01
HFD-617/ K. Scardina 1/31/01
HFD-650/ D. Conner 1/29/01

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BIOEQUIVALENCY - UNACCEPTABLE

Submission date: October 23, 2000

5. ~~STUDY AMENDMENT (STA)~~ Study Fasting (STF)
Outcome: UN

Strengths: ~~All~~ 70mg

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Unacceptable

WINBIO COMMENTS:
The firm has not met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing on the 70 mg strength and the application is unacceptable due to the fact that the study was conducted against Merck's 10 mg strength (7 X 10 mg tablets). The study should be conducted on Merck's reference 70 mg strength.

Alendronate Sodium Tablets, 70 mg
ANDA 75-710
Reviewer: James Chaney
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Teva Pharmaceuticals
North Wales, PA
Submission Dates:
March 9, 2001
~~April 10, 2001~~ KS

Review of a Bioequivalence Study and Dissolution Data

I. Introduction

Original Submission of September 29, 1999 (5 mg, 10 mg and 40 mg)
The original submission of September 29, 1999 included a single dose bioequivalence study under fasting conditions on the 40 mg tablet (measuring urinary excretion of the parent drug) with *in vitro* dissolution testing on all three strengths and waiver requests on the 5 mg and 10 mg strengths. The RLD was Fosamax®, 40 mg tablets (Merck & Co.). Merck's 40 mg and 10 mg products were approved on 9/29/95 and its 5 mg product was approved on 4/25/97. The bioequivalence and dissolution studies were found acceptable by the Division of Bioequivalence (12/30/99).

October 23, 2000 Amendment Including a New Strength: 70- mg
The firm submitted an amendment to its ANDA for addition of the 70-mg strength of alendronate sodium tablets. This submission contains a report of an *in vivo* bioequivalence study and dissolution testing. The study compared alendronate sodium tablets, 70-mg manufactured by TEVA Pharmaceuticals USA to Fosamax Tablets, 10 mg (7 x 10-mg tablets) under fasting conditions. At the time of dosing (beginning June 7, 2000) the innovator's 70-mg strength had not been approved. The innovator's 70-mg and 35-mg strengths were approved on October 20, 2000 at which time the 70-mg strength became the RLD. Hence, Teva conducted the study before approval of the innovator's 70-mg product (RLD) and submitted the study to the Agency three days after approval of the 70-mg strength.

The Division of Bioequivalence advised the firm that it had not met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing on the 70 mg strength and that the application was unacceptable due to the fact that the study was conducted against the 10 mg strength of the reference product (7 X 10mg tablets). The study should have been conducted on the current RLD, 70 mg strength.

Current Submission
The firm submitted *in vivo* bioequivalency and *in vitro* dissolution testing on the 70 mg strength March 9, 2001. It submitted the requested data diskette on urine concentrations for alendronate and urine volumes on April 10, 2001.

II. BACKGROUND

RLD:
The RLD for this product is Fosamax®, 70 mg tablets (Merck & Co.).

Indication:
The drug is indicated for the treatment and prevention of osteoporosis in post-menopausal women.

II. Single-dose Fasting Bioequivalence Study

A. Study Information

Clinical Facility:	Anapharm Inc.
Medical Director:	(b) (6)
Scientific Director:	Eric Masson
Dosing Dates:	Subject Nos. 1-20 (Group 1): 11/25/2000 and 12/9/2000 Subject Nos. 21-60 (Group 2): 11/28/2000 and 12/12/2000 Subject Nos. 61-100 (Group 3): 12/6/2000 and 12/20/2000 Subject Nos. 101-140 (Group 4): 12/7/2000 and 12/21/20
Analytical Facility	Anapharm Inc.
Analytical Study Dates:	2/12/2001 to 2/26/2001
Storage Periods:	The maximum time samples were stored frozen from the first day of collection (11/25/2000) to the last day of analysis (2/26/2001) was 93 days.

TREATMENT INFORMATION

Treatment ID:	A		B
Test or Reference:	Test		Reference
Product Name:	Alendronate Sodium		Fosamax
Manufacturer:	Teva Pharmaceuticals		Merck
Manufacturer Date:	May 2000		--
Expiration Date:	TBD		June 2002
ANDA Batch Size:	(b) (4)		--
Full Batch Size:			--
Batch/Lot Number:	1081-102		K7381
Potency:	99.0%		102.1
Content Uniformity:	97.7%, 0.9%CV		101.0%; RSD, 1.2%; 98.9–102.5%
Strength:	70 mg		70 mg
Dosage Form:	Tablet		Tablet
Dose Administered:	1 Tablet		1 Tablet
Administration Route	Orally		Orally
Study Condition:	Fasting		Fasting
Length of Fasting:	10 hours pre-dose to 4 hours post-dose		10 hours pre-dose to 4 hours post-dose

No. of Sequences	2	**Crossover**	Yes
No. of Periods	2	**Replicate Design**	No
No. of Treatments	2	**Balanced**	Yes
No. of Groups (if appropriate)	4	**Washout Period**	14 days

Randomization Scheme	AB: 1*,3,4,8,9,11,13,14,16,21,22,24*,25,29,30,32,34, 36,37,39,41,44,45,48,50,51*,53,55,56,60,63,65, 66,69,70,71,73,75,78,79,80,81,85,86,87,92,93*, 94,98,101,102,103,104,107,111,112,113,117,119, 120,121,123,124,127,128*132,133,135,136,140 BA: 2*,5,6,7,10,12,15*,17,18,19,20,23,26,27*,28*,31, 33,35,38,40,42,43,46,47,49,52,54,57,58,59,61,62,64, 67,68,72,74,76,77,82,83,84,88,89,90,91,95,96,97*,99, 100,105,106,108,109,110,114,115,116,118,122,125, 126,129,130,131,134,137,138,139 Group 1, Subject Nos. 1-20 Group 2, Subject Nos. 21-60 Group 3, Subject Nos. 61-100 Group 4, Subject Nos. 101-140
Urine Sampling Times	*Subjects who did not complete the study. Urine samples were collected between 1.5 hours prior to dosing and 1.0 hours prior to dosing (the time zero samples). Post-dose samples were collected at 0.25 hour and over the following collection intervals: 0.25-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24 and 24-36 hours post-dose.
Urine Volume Collected	Volume from each collection interval was measured and recorded. Measured aliquots of each collection were saved.
Urine Sample Storage	-20° or lower.
IRB Approval	Y
Informed Consent	Y
No. Enrolled	140
No. Completing	130
No. With Samples Analyzed	130
No. of Dropouts	10
Sex(es) Included	19 Females & 121 Males were dosed
Healthy Subjects	Y
Restrictions	Standard inclusion/exclusion criteria were followed per protocol.

B. Study Results

1. Clinical

Adverse Events: No serious medical events were reported during the study. All post-dose adverse events are summarized in Tables C2 Vol. 4.2, pp 244-260.

Protocol Deviations: There were no protocol deviations resulting in the integrity of study being compromised.

2. **Analytical Method Validation**
NOT TO BE RELEASED UNDER FOI

Description of Analytical Method Validation

Analyte	Alendronate
Assay Method	HPLC with fluorescence detection
Matrix	Urine
Internal Standard	(b) (4)

Pre-Study Assay Validation

Parameter	Q. C. Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	*CS1=5.09, QC1=15.00 QC2=150.00, QC3=350.00 **CS8=508.50	5.09, 10.17, 50.85, 101.70, 203.40, 305.10, 406.80, 508.50
Intra day Precision (%CV)	CS1=15.2, QC1=9.0 QC2=4.6, QC3=5.5 CS8=1.7	
Intra day Accuracy (% nominal)	CS1=103.8, QC1=106.7 QC2=102.0, QC3=102.7 CS8=101.0	
Inter day Precision (%CV)	QC1=3.4 QC2=3.2 QC3=2.9	0.5-4.4
Inter day Accuracy (% nominal)	QC1=102.9 QC2=101.1 QC3=102.7	97.3-101.6
% Recovery	Analyte at low and high QC concentrations were 36.1 and 42.1; IS, 42.0	
Linearity	r2 ≥ 0.9938	
Linear Range	5.09 to 508.50 ng/mL	
Sensitivity/LOQ	5.09 ng/L	
Stability in Urine a) Hr @ Room Temp. b) Freeze-Thaw c) Long-Term Frozen	a) Stable at room temperature 24 hours. b) Stable after 5 cycles c) 136 days	
d) Reconstituted Stability	d) Reconstituted extracts are stable 96 hrs at room temperature.	
Specificity	Acceptable	

*CS1 is the 5.09 ng/mL calibration standard.
**CS8 is the 508.50 ng/mL calibration standard

During Study Assay Validation

Parameter	Q.C. Samples	Std. Curve Samples
QC or Std. Curve Conc. (ng/mL)	QC1=15.00 QC2=150.00 QC3=350.00	5.09, 10.17, 50.85, 101.70, 203.40, 305.10, 406.80, 508.50
Interday Precision (%CV)	QC1=5.7 QC2=7.1 QC3=4.1	1.9 - 4.7
Interday Accuracy %	QC1=99.3 QC2=103.7 QC3=104.4	94.7-102.8
Sensitivity/LOQ (ng/mL)	5.09 ng/L	

Representative calibration and study sample chromatograms were submitted for 20% of the subjects.

Conclusion: The analytical method is acceptable.

3. Pharmacokinetic/Statistical Analysis

Mean Excretion Amounts and Rates	Tables 1 and 2, Figures 1 and 2
Mean PK Parameters	Tables 3 and 4
90% Confidence Intervals	*LnTAe(0-36), 91.8-107.3; *LnRmax, 93.6-109.2
Test/Reference Ratios (Arithmetic Means)	TAe(0-36), 1.15 (0.21-4.73), N=130 Rmax, 1.16 (0.22-4.09), N=130
Root MSE	TAe(0-36), 0.356024 Rmax, 0.352835

* Geometric LSMeans

Pharmacokinetic Parameters Reported:
TAe(0-36): Total amount of drug excreted unchanged in the urine over the entire period of sample collection, obtained by adding the amounts excreted over each collection interval.
Rmax: Maximum urinary excretion rate obtained by determining the maximum of urinary excretion rates across all collection intervals. For each collection interval the urinary excretion rate was obtained by dividing the amount of drug excreted in the interval by the actual duration of time over the interval.
Tmax: Time of maximum excretion rate, defined as the midpoint of the collection interval during which Rmax occurred.

Comments:

- Nine post-dose samples were re-assayed due to anomalous pharmacokinetic values. Four of these values resulted in reported values which were different from the first assay values:
  subj 8, per 2, 12-24 hr, originally BLOQ changed upon re-assay to 5.65 ng/mL
  subj 73, per 2, 12-24 hr, originally BLOQ changed upon re-assay to 5.37 ng/mL
  subj 139, per 2, 12-24 hr, originally BLOQ changed upon re-assay to 37.67 ng/mL

subj 92, per 1, 12-24 hr, originally 5.93 ng/mL changed upon re-assay to BLOQ
The reviewer set these re-assayed concentrations back to the original values and recalculated the test and reference Ae0-36 values. The changes in the Ae0-36 values were less than 0.04% for test and reference. There was no change in the Rmax values.

- The firm reported estimated values for amounts excreted for the following subjects: 6, 13, 14, 16, 18, 30, 31, 32, 35, 40, 76, 77, 79, 82, 89, 100 and 119. DBE does not recommend interpolation or estimation of concentrations.
- The reviewer statistically reanalyzed the data involving the four first-assay concentration values (first comment above) and deleted the 27/130 subjects with estimated urine alendronate concentrations (second comment above) and found that the log-transformed 90% confidence intervals for Ae0-36 and Rmax remained within the range of 80-125%.
- There were four subgroups in the study. The firm reported that ANOVA showed that the group*treatment interaction term was insignificant for Ae0-36 and Rmax, demonstrating that the subjects of all subgroups behaved similarly with regard to the treatment effect.
- Pharmacokinetic parameters calculated by the reviewer agree with the firm's calculations.

Conclusion: The single-dose fasting bioequivalence study is acceptable.

III. Formulation

Formulation information is provided in Table 5.

IV. Dissolution

A. Dissolution Method Used by Firm

The dissolution method is in agreement with the recent monograph on this product contained in Pharmacopeial Forum, Volume 26, Number 2, p398 (March-April, 2000). This dissolution testing was recommended to Teva for the 40, 10, and 5 mg strengths.

No. Units Tested: 12 tablets
USP XXIV apparatus 2 (paddle), 50 rpm
Medium: Water
Temperature: 37°C
Volume: 900 mL
Sampling Times: 10, 20, 30 and 40 minutes
Tolerance: Not less than 80% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

B. **Results:** Dissolution data are presented in Table 6.

C. Comment:

The dissolution testing is acceptable.

VI. COMMENT:

The single-dose, fasting bioequivalence study conducted by Teva Pharmaceuticals on its test product, alendronate tablet, 70 mg, lot # 1081-102, comparing it with the reference product, Fosamax®, 70 mg tablet manufactured by Merck has been found acceptable.

V. RECOMMENDATIONS

1. The single-dose, fasting bioequivalence study conducted by Teva Pharmaceuticals Inc. on its test product, alendronate tablet, 70 mg, lot # 1081-102, comparing it with the reference product, Fosamax®, 70 mg tablet manufactured by Merck, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Teva Pharmaceuticals' alendronate tablet, 70 mg, is bioequivalent to the reference product, Merck's Fosamax® 70 mg tablet under fasting conditions.

2. The *in-vitro* dissolution testing conducted by Teva Pharmaceuticals Inc. on its alendronate tablets, 70 mg, has been found acceptable. The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following interim specifications:

   Not less than 80% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

3. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang

Date 4/26/2001

Concur:

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date 4/27/01

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Table 1. Arithmetic Mean Urine Cumulative Amounts of Alendronate (µg) at Each Collection Interval (N=130)

Interval (h)	Test		Reference		T/R
	Mean	CV%	Mean	CV%	
0-0.25	1.08	173	1.15	144	0.94
0.25-1	50.79	74	47.03	59	1.08
1-2	110.35	65	104.93	55	1.05
2-3	146.40	66	143.41	59	1.02
3-4	167.72	66	165.93	61	1.01
4-6	188.07	68	186.07	63	1.01
6-8	197.72	69	196.03	63	1.01
8-12	206.98	69	205.07	64	1.01
12-24	218.38	70	216.68	65	1.01
24-36	225.02	70	223.48	65	1.01

Table 2. Arithmetic Mean Rate of Alendronate Excretion (µg/h) During Each Urine Collection Interval (N=130)

Interval (h)	Test		Reference		T/R
	Mean	CV%	Mean	CV%	
0-0.25	4.74	172	5.15	130	0.92
0.25-1	71.19	72	64.69	58	1.10
1-2	59.03	67	58.52	63	1.01
2-3	36.54	84	38.06	83	0.96
3-4	21.41	85	22.63	83	0.95
4-6	9.92	100	10.14	91	0.98
6-8	4.82	97	5.00	85	0.96
8-12	2.31	133	2.27	91	1.02
12-24	0.96	83	0.98	78	0.98
24-36	0.59	107	0.59	85	1.00

Table 3. Arithmetic Mean Alendronate Pharmacokinetic Parameters (N=130)

Parameter	Test		Reference		T/R
	Mean	CV%	Mean	CV%	
Tae(0-36) (µg)	225.02	70	223.48	65	1.01
Rmax (µg/h)	77.29	67	73.55	56	1.06
Tmax (h)	0.871	62	0.920	57	0.95

Table 4. LSMeans, Geometric Lsmeans, T/R Ratios and 90% Confidence Intervals (90% C.I.) for Alendronate Pharmacokinetic Parameters (N=130)

Parameter	LSMeans		Ratio of LSMeans %	90% C.I.	Intra-Subject CV%
	Test	Ref			
Tae(0-36) (µg)	225.02	223.48	1.15	--	--
*LnTAe(0-36) (µg)	181.13	182.46	0.99	91.8-107.3	36.8
Rmax (µg/h)	77.29	73.55	1.16	--	--
*LnRmax (µg/h)	63.89	63.18	1.0114	93.6-109.2	36.4

* Geometric LSMeans

Table 5. Formulation (mg/tablet) - NOT TO BE RELEASED UNDER FOI

INGREDIENTS	70 mg Strength*	
	mg/ Tablet	%/ Tablet
Alendronate Sodium, Trihydrate	91.36	45.7
Microcrystalline Cellulose, NF	(b) (4)	(b) (4)
Croscarmellose Sodium, NF		
Magnesium Stearate, NF		
Total	200.0	100.0

*The percent compositions of the 5 mg, 10 mg, 40 mg and 70 mg strengths differ only in the content of microcrystalline cellulose and active ingredient. The amounts of microcrystalline cellulose are altered to account for the corresponding differing amounts of alendronate sodium.

Table 6. Comparative *In Vitro* Dissolution Testing Conducted by Teva Pharmaceuticals

Sampling Times (Min)	Test Product: Alendronate Sodium Lot No.: 1081-102 Strength: 70 mg			Reference Product: Fosamax Lot No.: K7381 Strength: 70 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	92	(b) (4)	6	90	(b) (4)	4
20	99		4	96		3
30	102		3	98		3
40	103		3	98		2

BIOEQUIVALENCY COMMENTS

ANDA: 75-710 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Alendronate Sodium Tablets, 70 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXIV apparatus II (paddle) at 50 rpm. The test product should meet the following interim specifications:
>
> Not less than 80% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-710
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney
HFD-652/ Y. Huang
HFD-617/ K.Scardina
HFD-650/ D. Conner

V:\FIRMSNZ\TEVA\LTRS&REV\75710sdw.301

BIOEQUIVALENCY - ACCEPTABLE

Submission dates: March 9, 2001

1. FASTING STUDY (STF)

Strength: 70 mg
Outcome: AC

CLNICAL STUDY SITE: Anapharm Inc.
Québec, Canada,

ANALYTICAL SITES: Anapharm Inc.
Québec, Canada

Outcome: AC

~~2. STUDY AMENDMENT (STA)~~ ~~Strength: 70 mg~~ (168) This was changed to a New Correspondence
(Data diskette submitted 4/10/01 on urine alendronate concentrations and urine volumes)

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:
The biostudy and dissolution data were found acceptable.

#2

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-710
DRUG AND DOSAGE FORM : Alendronate Sodium Tablets
STRENGTH(S): 70 mg
TYPES OF STUDIES: Fasting
CLINICAL STUDY SITE: Anapharm
ANALYTICAL SITE: Anapharm
STUDY SUMMARY: Acceptable

SPONSOR : Teva Pharmaceuticals

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic YES New facility_____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: James Chaney BRANCH: I

INITIAL: JC DATE: 4/26/01

TEAM LEADER: Yih-Chain Huang BRANCH: I

INITIAL: YHH DATE: 4/26/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

INITIAL : DPC DATE : 4/27/01

Alendronate Sodium Tablets, 35 mg
ANDA 75-710
Reviewer: James E. Chaney
V:\FIRMSNZ\TEVA\LTRS&REV\75710dw.801

Teva Pharmaceuticals
North Wales, PA
Submission Dates:
August 20, 2001

Review of Dissolution Data and a Waiver Request

I. SUBMISSION HISTORY

The bioequivalence study and comparative dissolution testing on Teva's 70-mg formulation submitted March 9, 2001 was found acceptable April 27, 2001 (reviewed by J. Chaney).

The firm was advised that the dissolution testing should be conducted in 900 mL of water at 37°C using USP apparatus II (paddle) at 50 rpm and that he test product should meet the following specifications:

> Not less than 80% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Teva's formulation for its proposed 35-mg strength is proportionally identical to the its 70-mg strength.

II. OBJECTIVE OF CURRENT SUBMISSION

Teva Pharmaceuticals has submitted comparative dissolution data and comparative formulation data on its drug product, alendronate sodium tablet, 35-mg comparing it to the reference Fosamax® tablet, 35-mg marketed by Merck in support of its request for waiver of *in vivo* bioequivalence study requirements. The formulations of Teva's alendronate sodium, 35-mg and 70-mg tablets are shown in Table 1. The dissolution methods used and data obtained at Teva Pharmaceuticals are shown in Table 2.

III. COMMENTS

1. Teva's formulation for its proposed 35-mg strength is proportionally identical to the its 70-mg strength per the general BA/BE guidance, definition 1.

2. The comparative *in-vitro* dissolution testing conducted by Teva Pharmaceuticals Inc. on its alendronate tablets 35-mg has been found acceptable.

   In the current submission the firm did not submit dissolution testing on the 70-mg product. In addition to the comparative dissolution data on the current 35-mg strength, Table 2 includes the dissolution testing on the test and reference 70-mg products that was previously submitted with the acceptable bioequivalence study on the 70-mg product. The dissolution profiles for the 35-mg and 70-mg strengths are similar. Because by 20 minutes the lowest mean percent dissolved for the test and reference products of the 35-mg and 70-mg strengths was 89% or greater, it was not necessary to calculate f_2.

3. The waiver of bioequivalence studies may be granted under CFR 320.22(d)(2).

IV. RECOMMENDATIONS:

1. The dissolution testing reported by Teva Pharmaceuticals on its alendronate sodium, 35-mg tablet, lot number 1081-120, is acceptable. The firm has previously conducted an acceptable *in vivo* bioequivalence study comparing its 70-mg tablet of the test product with the 70-mg tablet of the reference product Fosamax® manufactured by Merck. The formulation of the 35-mg strength is proportionally identical to the 70-mg strength that underwent acceptable bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for the 35-mg tablet may be granted. The Division of Bioequivalence deems alendronate sodium tablets, 35-mg manufactured by Teva Pharmaceuticals to be bioequivalent to Merck's Fosamax® Tablets, 35-mg.

2. The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than 80% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the recommendations.

James E. Chaney

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang _____ Date 10/30/2001

Concur: _____ Date 10/30/01
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/102901
V:\FIRMSNZ\TEVA\LTRS&REV\75710dw.801

Table 1. Formulation (mg/tablet) – NOT TO BE RELEASED UNDER FOI				
INGREDIENTS	35-mg Strength*		70-mg Strength	
	mg/ Tablet	%/ Tablet	mg/ Tablet	%/ Tablet
Alendronate Sodium, Trihydrate	45.68	45.68	91.36	45.68
Microcrystalline Cellulose, NF	(b) (4)			
Croscarmellose Sodium, NF				
Magnesium Stearate, NF				
Total	100	100	200.0	100

*Equivalent to 35 mg of anhydrous alendronate sodium
** Equivalent to 70 mg of anhydrous alendronate sodium

Table 2. Comparative *In Vitro* Dissolution Testing Conducted by Teva Pharmaceuticals						
Conditions for Dissolution/Release Testing:						
USP Apparatus: Paddle RPM: 50 No. Units Tested: 12 Medium: Water Volume: 900 mL Tolerance (Q): NLT 80% in 30 min Reference Drug: Fosamax® Tablets (Merck & Co.) Assay Method: HPLC, 266 nm						
Results of In Vitro Dissolution/Release Testing:						
Sampling Times (Min)	Test Product Lot No.: 1081-120 Strength: 35-mg			Reference Product Lot No.: L4321 Strength: 35-mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	85	(b) (4)	10	81	(b) (4)	4
20	95		6	89		3
30	98		7	93		3
40	101		4	94		4
Sampling Times (Min)	Test Product: Alendronate Sodium Lot No.: 1081-102 Strength: 70-mg			Reference Product: Fosamax® Lot No.: K7381 Strength: 70-mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	92	(b) (4)	6	90	(b) (4)	4
20	99		4	96		3
30	102		3	98		3
40	103		3	98		2

BIOEQUIVALENCY COMMENTS

ANDA: 75-710 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Alendronate Sodium Tablets, 35 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXIV apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than 80% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-710
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney J. Chaney (10/30/2001)
HFD-652/ Y. Huang
HFD-617/ K.Scardina
HFD-650/ D. Conner 10/30/01

V:\FIRMSNZ\TEVA\LTRS&REV\75710dw.801

BIOEQUIVALENCY - ACCEPTABLE

Submission dates: August 20, 2001

DISSOLUTION WAIVER (DIW) n/a

Strengths: 35 mg
Outcome: AC

NOTE:
AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:
The biostudy and dissolution data were found acceptable.

#2

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-710 SPONSOR : Teva Pharmaceuticals
DRUG AND DOSAGE FORM : Alendronate Sodium Tablets
STRENGTH(S): 35 mg
TYPES OF STUDIES: Dissolution waivers per BE on 70 mg strength.
CLINICAL STUDY SITE: NA
ANALYTICAL SITE: NA
STUDY SUMMARY: Acceptable

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic YES New facility_____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: James Chaney BRANCH: I

INITIAL: JC DATE: 10/30/2001

TEAM LEADER: Yih-Chain Huang BRANCH: I

INITIAL: YCH DATE: 10/30/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

INITIAL : DPC DATE : 10/30/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-710

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Click for filing
S. Middleton
10/22/99

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

September 29, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg and 40 mg

Dear Mr. Sporn:

We submit herewith an abbreviated new drug application for the drug product Alendronate Sodium Tablets, 5 mg, 10 mg and 40 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of **31** volumes; **15** for the archival copy and **16** for the review copy.

The application contains a full report of one *in vivo* bioequivalence study. This study compared Alendronate Sodium Tablets, 40 mg, manufactured by TEVA Pharmaceuticals USA, to the reference listed drug, Fosamax® 40 mg under fasting conditions.

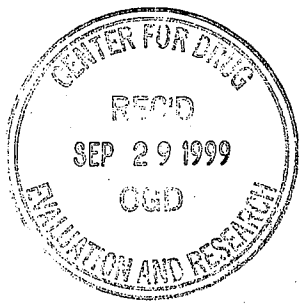
Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 256-8400, ext. 5249, or by facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures



ANDA 75-710

TEVA Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
Kulpsville PA 19443

NOV 15 1999

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Alendronate Sodium Tablets, 5 mg (base) and 10 mg (base)

DATE OF APPLICATION: September 29, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 29, 1999

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Nasser Mahmud, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-710
DUP/Jacket
Division File
Field Copy
HFD-330
HFD-92
HFD-600/Reading File
HFD-610/R.West
HFD-610/P.Rickman
HFD-615/M.Bennett

Endorsements: HFD-615/NMahmud, Chief, RSB date 11/10/99
HFD-615/SMiddleton, CSO date 10/29/99
HFD-625/MSmela, Sup. Chemistry, date
Word Document
V:\FIRMSNZ\TEVA\LTRS&REV\75710.ACK
F/T by mjl/10/28/99
ANDA Acknowledgment Letter!

1.1

ANDA 75-710

TEVA Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
Kulpsville PA 19443

NOV 19 1999

Dear Madam:

This letter is a correction to our November 15, 1999 acknowledgment letter. The dosage form of the drug product has been corrected from 5 mg (base) and 10 mg (base), to 5 mg (base), 10 mg (base) and 40 mg (base), in our records.

NAME OF DRUG: Alendronate Sodium Tablets, 5 mg (base), 10 mg (base) and 40 mg (base)

DATE OF APPLICATION: September 29, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 29, 1999

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Nasser Mahmud, Chief, Regulatory Support Branch, at (301) 827-5862.

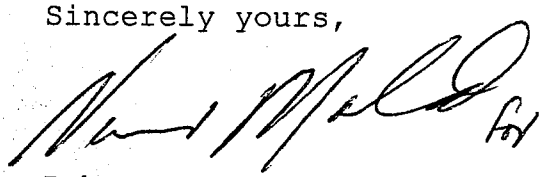
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,



Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-710
DUP/Jacket
Division File
Field Copy
HFD-330
HFD-92
HFD-600/Reading File
HFD-610/R.West
HFD-610/P.Rickman
HFD-615/M.Bennett

Endorsements: HFD-615/NMahmud, Chief, RSB date 11/19/99
HFD-615/SMiddleton, CSO S. Middleton date 11/19/99
HFD-625/MSmela, Sup. Chemistry, date
Word Document
V:\FIRMSNZ\TEVA\LTRS&REV\75710ACK.COR
F/T by
ANDA Acknowledgment Letter!

TERESA WATKINS.

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

November 22, 1999

NEW CORRESP
NC

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg and 40 mg
AMENDMENT-REVISED EXCLUSIVITY STATEMENT

Dear Mr. Sporn:

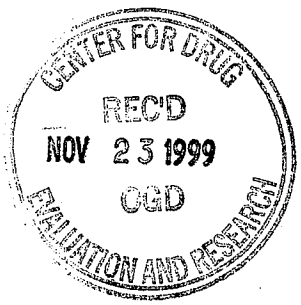
We submit herewith an amendment to the above referenced pending ANDA in accord with a comment by Teresa Watkins of your office earlier today. Specifically, Ms. Watkins requested that we provide an updated Exclusivity Statement which addresses the newly listed indication for the treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dose equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density. This exclusivity is set to expire on June 16, 2002. A revised Exclusivity Statement which now includes reference to I-272 is provided herein. This new statement is intended to replace page 12 of our original application and is paginated as such.

Should you have any further comments or questions please do not hesitate to contact me via telephone at (215) 256-8400 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/pe
Enclosures



TEVA

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

December 2, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg (base), 10 mg (base) and 40 mg (base)
NOTICE OF CERTIFICATION OF NON-INFRINGEMENT

Dear Mr. Sporn:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent No. 4,621,077; 5,358,941; 5,681,590; 5,882,656; 5,849,726; and 5,804,570 was provided to the holder of NDA 20-560, Merck & Co., for Fosamax® ,Alendronate Sodium Tablets, 5 mg (base), 10 mg (base) and 40 mg (base), and owners of the patents, Merck & Co. and Instituto Gentili S.p.A., in accord with 314.95(b). The notice dated November 29, 1999 contains the information as required under 314.95(c). A copy of the notice is provided herein.

If there are any further questions, please do not hesitate to contact me at (215)256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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TEVA PHARMACEUTICALS USA
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December 28, 1999

NDA ORIG AMENDMENT
N/Ab

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT
BIOEQUIVALENCE

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg (base), 10 mg (base) and 40 mg (base)
TELEPHONE AMENDMENT BIOEQUIVALENCE - RESPONSE TO 12/21/99 TELEPHONE REQUEST

Dear Mr. Sporn:

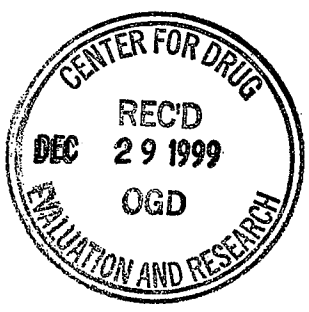
In response to a telephone communication on December 21, 1999 between Philip Erickson, Associate Director of Regulatory Affairs and Jennifer Fan of the Division of Bioequivalence, please find enclosed all available long- term frozen stability data for Alendronate in human urine as provided to us by Phoenix International Life Sciences, Inc. These stability data are representative of samples stored for ninety-six days, which is beyond the length of the longest storage time of any of the samples obtained from our bioequivalence study.

If you should have any further questions regarding this submission, please do not hesitate to contact me at (215)256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot, RPE

DAJ/jbp
Enclosures



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Deborah A. Jaskot
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February 9, 2000

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION
NEW CORRESP
NC

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg (base), 10 mg (base) and 40 mg (base)
RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT & END OF 45 DAY CLOCK

Dear Mr. Sporn:

In accord with 21 CFR 314.95 (e), TEVA Pharmaceuticals USA is hereby providing documentation of the receipt of Notice of Certification for U.S. Patent No 4,621,077; 5,358,941; 5,681,590; 5,882,656; 5,849,726; and 5,804,570. The Notice, sent to the NDA and patent holder Merck & Co., was received on December 7, 1999. This date is evidenced by the attached copy of the return receipt. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is December 8, 1999, the first day after receipt of notice. The 45-day period therefore ended on January 21, 2000.

This correspondence further serves to notify the Agency that suit was filed by Merck and Co. on January 19, 2000 in Delaware District Court and was assigned Case No. 00-035. This suit was filed within the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act.

If there are any further questions, please do not hesitate to contact me at (215)256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot /PE

DAJ/rsv
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
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FEB 10 2000
OGD

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February 14, 2000

NEW CORRESP
NC

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg and 40 mg
AMENDMENT - PATENT CERTIFICATION WITH RESPECT TO U.S. PATENT 6,008,207

Dear Mr. Sporn:

We submit herewith an amendment to the above referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,008,207 which, on its face, has been assigned to Merck & Co., Inc. On information and belief that Merck has taken steps to list the aforementioned patent in the Orange Book, Teva wishes to provide the enclosed statement with regards to this patent.

Should you have any further comments or questions please do not hesitate to contact me via telephone at (215) 256-8400 or via facsimile at (215) 256-8105.

Sincerely,

Deborah J Askot/PE

DAJ/pe
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 14 2000
OGD

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March 23, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION
NEW CORRESP
NC

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg (base), 10 mg (base) and 40 mg (base)
RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT

Dear Mr. Buehler:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent No. 6,008,207 was provided to the holder of NDA 20-560 for Fosamax®, Alendronate Sodium Tablets, 5 mg (base), 10 mg (base) and 40 mg (base), and owner of the patent, Merck & Co., in accord with 314.95(b). The notice dated March 10, 2000 contains the information as required under 314.95(c). A copy of the notice is provided herein.

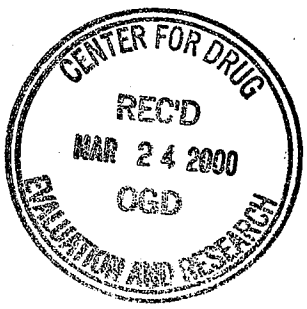
In accord with 21 CFR 314.95 (e), TEVA Pharmaceuticals USA is hereby providing documentation of the receipt of the above referenced Notice of Certification for U.S. Patent No 6,008,207. The Notice, sent to the NDA and patent holder, Merck & Co., was received on March 13, 2000. This date is evidenced by the attached copy of the return receipt. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is March 14, 2000, the first day after receipt of notice. Therefore, the 45-day period will end on April 27, 2000.

If there are any further questions, please do not hesitate to contact me at (215)256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures



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NAT 4/21/00

NEW CORRESP

NC

April 18, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

new patent certif. to include PTE for '329 & '207

OK! 4/21/00

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg and 40 mg
AMENDMENT - PATENT CERTIFICATION WITH RESPECT TO U.S. PATENT 5,994,329 and 6,008,207

Dear Mr. Buehler:

We submit herewith an amendment to the above referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 5,994,329 which, on its face, has been assigned to Merck & Co., Inc. On information and belief that the aforementioned patent has been listed in the Orange Book, Teva wishes to provide the enclosed statement with regards to this patent.

In addition, Teva had previously certified that U.S. Patent No. 6,008,207 was anticipated to become listed in the 'orange book". Our certification was conditional upon the actual listing of the patent. Since this submission, the patent has been deemed listed as evidenced by its appearance in the Patent Term Extension and New Patents - April 14, 2000 electronic docket, No. *95S-0117. The enclosed patent certification addresses both the 5,994,329 and the 6,008,207 patents.

Should you have any further comments or questions please do not hesitate to contact me via telephone at (215) 256-8400 or via facsimile at (215) 256-8105.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 18 2000
OGD

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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NEW CORRESP

April 24, 2000

PATENT AMENDMENT

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg and 40 mg
AMENDMENT - PATENT CERTIFICATION WITH RESPECT TO U.S. PATENT 6,015,801

Dear Mr. Buehler:

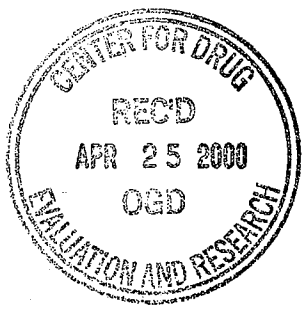
We submit herewith an amendment to the above referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,015,801 which, on its face, has been assigned to Merck & Co., Inc. On information and belief that the aforementioned patent is considered to be listed in the Orange Book, Teva wishes to provide the enclosed statement with regards to this patent.

Should you have any further comments or questions please do not hesitate to contact me via telephone at (215) 256-8400 ext.5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures



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May 12, 2000

NEW CORRESP

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

Merck has included '207 w/ pending litigation 00-035 w/in 45 days 9/25/00

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg (base), 10 mg (base) and 40 mg (base)
END OF 45 DAY CLOCK - U.S. PATENT No. 6,008,207

Dear Mr. Sporn:

In accord with 21 CFR 314.95 (e), TEVA Pharmaceuticals USA has provided documentation of the receipt of Notice of Certification for U.S. Patent No. 6,008,207. The Notice, sent to the NDA and patent holder Merck & Co., was received on March 13, 2000. Evidence of this date was provided in correspondence to this pending application dated March 23, 2000. In accord with 314.95(f), the first day of the 45 day period provided for in section 505(j)(4)(B)(iii) of the Act was March 14, 2000, the first day after receipt of notice. The 45 day period therefore ended on April 27, 2000.

This correspondence further serves to notify the Agency that Merck and Co. amended its original complaint, Case No. 00-035, on April 18, 2000. This amendment was filed within the 45 day period provided for in section 505(j)(4)(B)(iii) of the Act. Teva Pharmaceuticals USA hereby commits to provide notification of the outcome of this suit in an appropriate submission to this application.

If there are any further questions, please do not hesitate to contact me at (215)256-8400 ext. 5249 or via facsimile at (215) 256-8105.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 15 2000
OGD

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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May 12, 2000

NEW CORRESP

NTC

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

return receipt adequate for 1329

5/25/00

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg (base), 10 mg (base) and 40 mg (base)
RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT - US PATENT No. 5,994,329

Dear Mr. Buehler:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent No. 5,994,329 was provided to the holder of NDA 20-560 for Fosamax®, Alendronate Sodium Tablets, 5 mg (base), 10 mg (base) and 40 mg (base), and owner of the patent, Merck & Co., in accord with 314.95(b). The notice, dated May 3, 2000, contains the information as required under 314.95(c). A copy of the notice is provided herein.

In accord with 21 CFR 314.95 (e), TEVA Pharmaceuticals USA is hereby providing documentation of the receipt of the above referenced Notice of Certification for U.S. Patent No 5,994,329 . The Notice, sent to the NDA and patent holder, Merck & Co., was received on May 5, 2000. This date is evidenced by the attached copy of the return receipt. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is May 6, 2000, the first day after receipt of notice. Therefore, the 45-day period will end on June 19, 2000.

If there are any further questions, please do not hesitate to contact me at (215)256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 15 2000
OGD

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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June 8, 2000

ORIG AMENDMENT

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg (base), 10 mg (base) and 40 mg (base)
MAJOR AMENDMENT - RESPONSE TO MARCH 29 AND JUNE 5, 2000 REVIEW LETTERS

Dear Mr. Sporn:

In response to review letters dated March 29, 2000 and June 5, 2000, Teva Pharmaceuticals USA submits herewith a major amendment to the above referenced pending abbreviated new drug application. The deficiencies are addressed in the order in which they were presented with the March 29, 2000 review letter responses appearing first, followed by the response to the June 5, 2000 review letter. For the ease of your review, copies of the of the March 29 and June 5, 2000 review letters are provided as **Attachment 1**.

A. Deficiencies (CMC):

1. (b) (4)

2. (b) (4)

(b) (4)

3.

4.

5. (b) (4)

6.

7.

8.

9.

(b) (4)

10.

11.

12.

B. Notes & Acknowledgments:

1. We acknowledge that the non-compendial methods will be forwarded to the district laboratory upon resolution of the sited deficiencies. At this time we would like to draw to your attention page 6509 of the original application. This page is a validation commitment which certifies that Teva Pharmaceuticals USA will work with the district laboratory towards the resolution of any method/validation concerns that may arise during their verification/validation testing.

2. The site of drug substance (b) (4) is the same as that provided for the drug substance synthesis. The address is as follows:

(b) (4)

3. We acknowledge that satisfactory compliance evaluations of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of the approval of the application.

C. Bioequivalency Comments:

1. We have reviewed the dissolution data generated on the ANDA batches. It is apparent from the data generated that the use of the specification which you propose would cause dissolution testing to require S2 level testing approximately 13% of the time. Furthermore, our evaluation indicates that even the innovator product would not consistently meet the proposed specification. Tabular representation of the dissolution data is provided as **Attachment 11** . Additionally, the monograph contained in Volume 26, Number 2 of the Pharmacopeial Forum includes a dissolution specification of "Not Less than 80% $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ is dissolved in 30 minutes". Based on this information and our belief that the bioequivalence study submitted in our original application supports the bioequivalence of our product to the reference listed product, we propose to maintain the dissolution specification of "Not Less than 80% $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ is dissolved in 30 minutes", as originally submitted in our application.

D. Labeling

In response to the June 5, 2000 review letter pertaining to the draft labeling submitted in our original ANDA, we provide the following response to your comments:

1. Container

   a. It is Teva Pharmaceuticals USA's standard practice to differentiate various strengths of a drug product by color on the container label. This practice is not apparent on draft labeling, but will be noticeable upon the submission of our final print versions.

   b. Teva's standard practice includes the requirement that the established name and strength be the most prominent information appearing on the label, however, in draft form this practice is not readily apparent. Upon submission of final print labeling, our compliance with this request will be apparent.

2. Insert

   The product insert has been revised as per your review comments with the exception of the inclusion of the "Rx only" statement. It has been Teva Pharmaceuticals USA's format and practice to not include this statement in our drug product insert labeling. Revised insert labeling is provided as **Attachment 12**. Also provided in this attachment is a comparison document detailing the revisions made between the insert labeling submitted in our original application and that which is provided herein.

3. Patient Information Leaflet

   The Patient Information Leaflet has been revised in accord with all the review comments presented. The revised leaflet is provided as **Attachment 13**. Also provided in this attachment is a comparison document detailing the revisions made between the leaflet submitted in our original application and that which is provided herein.

The information provided in this submission represents, in Teva Pharmaceuticals USA's opinion, full response to the review comments presented thus far. If you should have any further questions regarding this submission, please do not hesitate to contact me at (215)256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures

Deborah A. Jaskot
Executive Director, Regulatory Affairs

Corporate Headquarters:
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1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Received RTT cert. for 416 exp 12/2/12
9/25/00

September 19, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg and 40 mg
AMENDMENT - PATENT CERTIFICATION WITH RESPECT TO U.S. PATENT 6,090,410

Dear Mr. Buehler:

We submit herewith an amendment to the above referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No.6,090,410 which, on its face, has been assigned to Merck & Co., Inc. As a result of the listing of the aforementioned patent in the Orange Book, Teva wishes to provide the enclosed statement with regards to this patent.

Should you have any further comments or questions please do not hesitate to contact me via telephone at (215) 591-3142 or via facsimile at (215) 591-8812.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
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OGD

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Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

NAI
12/23/00

October 17, 2000

NEW CORRESP
NC

PATENT INFORMATION

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg (base), 10 mg (base) and 40 mg (base)
RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT

Dear Mr. Buehler:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent No. 6,090,410 was provided to the holder of NDA 20-560 for Fosamax®, Alendronate Sodium Tablets, 5 mg (base), 10 mg (base) and 40 mg (base), and owner of the patent, Merck & Co., in accord with 314.95(b). The notice dated October 5, 2000 contains the information as required under 314.95(c). A copy of the notice is provided herein.

In accord with 21 CFR 314.95 (e), TEVA Pharmaceuticals USA is hereby providing documentation of the receipt of the above referenced Notice of Certification for U.S. Patent No 6,090,410. The Notice, sent to the NDA and patent holder, Merck & Co., was received on October 10, 2000. This date is evidenced by the attached copy of the return receipt. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is October 11, 2000, the first day after receipt of notice. Therefore, the 45-day period will end on November 24, 2000.

If there are any further questions, please do not hesitate to contact me at (215)591-3142 or via facsimile at (215) 591-8812.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 18 2000
OGD

Deborah A. Jaskot
Executive Director, Regulatory Affairs

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Phone: (215) 591 3000
FAX: (215) 591 8600
October 23, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT:
INCLUSION OF NEW STRENGTH:
70mg

NDA ORIG AMENDMENT
N/Ac

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 70 mg
UNSOLICITED AMENDMENT - INCLUSION OF NEW STRENGTH: 70 mg

Dear Mr. Buehler:

We submit herewith an amendment to our above referenced pending ANDA for addition of the 70 mg strength of the drug product Alendronate Sodium Tablets to this file. Please note that this submission is presented in the basic format of an ANDA for ease of review.

This submission contains a full report of one *in vivo* bioequivalence study. This study compared Alendronate Sodium Tablets, 70 mg manufactured by TEVA Pharmaceuticals USA to Fosamax® Tablets, 10 mg (7 x 10 mg tablets) under fasting conditions. Please note that at the time of dosing of our bioequivalence study, the innovator strength of 70 mg was not commercially available. In addition, a Citizen's Petition is being submitted to the Dockets Management Branch of the Agency simultaneous to the submission of this amendment, to find that the delay in marketing of Fosamax® Tablets, 70 mg is not the result of a safety or efficacy problem. A copy of this Petition is provided herein following this cover letter.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3142 or by facsimile at (215) 591-8812.

Sincerely,

Deborah Jaskot

DAJ/jbp
Enclosures

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
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FAX: (215) 591 8600

Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

December 14, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT
PATENT CLARIFICATION

NEW CORRESP
NC

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 40 mg and 70 mg
UNSOLICITED AMENDMENT - PATENT CLARIFICATION

Dear Mr. Buehler:
This letter is with respect to Teva Pharmaceuticals USA's patent certification dated October 23, 2000 concerning alendronate sodium tablets, 70 mg. That certification was included with Teva's October 23, 2000 amendment to pending ANDA # 75-710 to add the 70 mg strength of alendronate tablets. This amendment was submitted immediately following approval of the corresponding strength of the reference listed drug, Fosamax® 70 mg tablets, but before any patents had been listed in *Approved Drug Products With Therapeutic Equivalence Evaluations* (the "Orange Book") in connection with that strength.

The 70 mg strength of Fosamax® has now been published in the Orange Book (20th ed., Cum. Supp. No. 9, Sept. 2000) together with the corresponding listed patents: U.S. Patents 6,015,801; 4,621,077; 5,358,941; 5,681,590; 5,804,570; 5,849,716; 5,994,329; and 6,008,207. All these patents were included in Teva's above-referenced patent certification. U.S. Patent 6,090,410 (the "'410 patent"), which was also mentioned in Teva's patent certification, has not been listed in the Orange Book in connection with Fosamax® 70 mg tablets. Should the "410 patent be listed in the Orange Book in the future, Teva's patent certification of October 23, 2000 will likewise apply to that patent.

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3142 or by facsimile at (215) 591-8812.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
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DEC 15 2000
OGD

Corporate Headquarters:
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Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

NDA-T. S. Middleton
12/13/00

December 20, 2000

NEW CORRESP
NC

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 20 mg, and 70 mg
NOTICE OF CERTIFICATION OF NON-INFRINGEMENT AND RECEIPT OF NOTICE UNDER SECTION 505(j)(2)(B)(I) AND 21 CFR 314.95 FOR ALENDRONATE SODIUM TABLETS, 70 mg

Dear Mr. Buehler:

Teva Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent Nos. 4,621,077; 6,090,410; 5,681,590; 5,358,941; 6,008,207; 5,849,726; 5,804,570; 5,994,329; and 6,015,801, was provided to Merck & Co. Inc., as the holder of NDA 20-560 for Fosamax® (alendronate sodium tablets) and owner of the patents in accord with 314.95(b). The notice dated December 13, 2000 contains the information as required under 314.95(c). A copy of the notice is provided herein.

Also provided, in accord with 21 CFR 314.95 (e), is documentation of the receipt of Notice of Certification for U.S. Patent Nos.4,621,077; 6,090,410; 5,681,590; 5,358,941; 6,008,207; 5,849,726; 5,804,570; 5,994,329; and 6,015,801. The Notices sent to the affected patent owner, application holder, or authorized representative had been received on December 15, 2000. This date is evidenced by the attached copies of the return receipt. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is December 16, 2000, the first day after receipt of notice. The 45-day period will therefore end on January 29, 2001.

Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3142 or by facsimile at (215) 591-8812.

Sincerely,

Deborah Jaskot

DAJ/brb
Enclosures

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NDA COPIES
NC to Fax

December 27, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 40 mg and 70 mg (base)
FAX AMENDMENT - RESPONSE TO NOVEMBER 27, 2000 FAX REVIEW LETTER

Dear Mr. Buehler:

In response to a fax review letter dated November 27, 2000, Teva Pharmaceuticals USA submits herewith a fax amendment to the above referenced pending abbreviated new drug application. The deficiencies are addressed in the order in which they were presented. For the ease of your review, a copy of the November 27, 2000 fax review letter is provided as **Attachment 1**.

A. Deficiencies (CMC):

1. (b) (4)

2.

3. (b) (4)

B. Notes & Acknowledgments:

1. We acknowledge that the non-compendial methods will be forwarded to the district laboratory upon resolution of the sited deficiencies. At this time we would like to draw to your attention page 6509 of the original application and page 8060 of the supplemental application for the addition of the 70 mg strength. These pages are the validation commitment which certifies that Teva Pharmaceuticals USA will work with the district laboratory towards the resolution of any method/validation concerns that may arise during their verification/validation testing. A copy of both pages is provided as **Attachment 4** for the ease of review.

2. Provided as **Attachment 5** are the updated stability data for all four strengths of drug product for the continued review and approval of this pending application. Please note, the revised assay specifications of (b) (4) % will be implemented at the time of the next test station.

The information provided in this submission represents, in Teva Pharmaceuticals USA's opinion, full response to the review comments presented thus far. If you should have any further questions regarding this submission, please do not hesitate to contact me at (215)591-3141or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/RS

PE/tdt
Enclosures

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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Phone: (215) 591 3000
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC

February 13, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT
PATENT CLARIFICATION

2/23/01

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EVALUATION AND RESEARCH

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 40 mg and 70 mg
UNSOLICITED AMENDMENT - PATENT CLARIFICATION

Dear Mr. Buehler:

This letter is submitted with respect to TEVA Pharmaceuticals USA's patent certification dated October 23, 2000 concerning Alendronate Sodium Tablets, 70 mg. That certification was included in TEVA's October 23, 2000 amendment to pending ANDA # 75-710 to add the 70 mg strength of Alendronate Sodium Tablets. Because that amendment was submitted immediately following approval of the reference listed drug, Fosamax® 70 mg tablets, but before any patents had been listed in *Approved Drug Products With Therapeutic Equivalence Evaluations* (the "Orange Book") in connection with that strength, we submitted an amendment on December 14, 2000 providing clarification that eight patents had listed in Supplement #9 to the 20th Edition of the Orange Book. Specifically, at that time the following U.S. Patents were listed for the 70 mg strength of Fosamax®: 6,015,801; 4,621,077; 5,358,941; 5,681,590; 5,804,570; 5,849,726; 5,994,329; and 6,008,207.

Subsequent to TEVA's December 14, 2000 amendment, U.S. Patent 6,090,410 (the "'410 patent") listed in the Patent Term Extension and New Patents Docket dated January 19, 2001 in connection with Fosamax® 70 mg Tablets. Please note that all the patents mentioned above, including the '410 patent, were included in TEVA's original patent certification dated October 23, 2000.

In addition, we hereby notify the Agency of legal action incurred as a result of TEVA's paragraph IV patent certification with respect to the nine patents noted above. As indicated in previous correspondence to this file, Notice of Non-Infringement was received by Merck & Co., Inc. on December 15, 2000. Merck & Co., Inc. subsequently filed suit against TEVA Pharmaceuticals USA

on January 25, 2001 in the U.S. District Court system, namely in the District Court of Delaware. TEVA Pharmaceuticals USA hereby commits to provide updates pertaining to this suit as information develops during litigation and ruling.

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

Corporate Headquarters:
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Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Forwarded to DFG. Signed for submission 3/9/01

February 28, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT-
EXCLUSIVITY STATEMENT

Emily Thomas
WAI
3/13/01

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 40 mg and 70 mg
UNSOLICITED AMENDMENT - EXCLUSIVITY STATEMENT UPDATE

Dear Mr. Buehler:

This letter is submitted with respect to TEVA Pharmaceuticals USA's exclusivity statement dated October 23, 2000 concerning Alendronate Sodium Tablets, 70 mg. That statement was included in TEVA's October 23, 2000 amendment to pending ANDA # 75-710 to add the 70 mg strength of Alendronate Sodium Tablets. Because that amendment was submitted immediately following approval of the reference listed drug, Fosamax® 70 mg tablets, but before any exclusivities had been listed in *Approved Drug Products With Therapeutic Equivalence Evaluations* (the "Orange Book") in connection with the 70 mg strength, we submit herewith a revised statement indicating exclusivities that listed in the 9th Supplement to the 2000 Orange Book for the 70 mg strength. We acknowledge that the New Strength exclusivity must expire prior to final approval of the 70 mg strength.

Please find enclosed an exclusivity statement updated to reflect the exclusivities listed in the Orange Book as well as pages from the most recent docket showing the exclusivities and pages from the most recent supplement and/or Orange Book showing their definitions.

We look forward to your continued review of ANDA #75-710. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/jbp
Enclosures

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MAR 0 1 2001
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3-5-01

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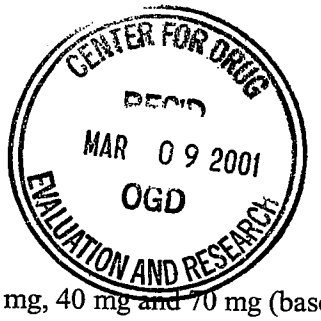
March 9, 2001

ORIG AMENDMENT
N/AC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT



ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 40 mg and 70 mg (base)
MAJOR AMENDMENT - RESPONSE TO FEBRUARY 2, 2001 REVIEW LETTER

Dear Mr. Buehler:

In response to a review letter dated February 2, 2001, Teva Pharmaceuticals USA submits herewith a major amendment to the above referenced pending abbreviated new drug application. The deficiencies are addressed in the order in which they were presented. For the ease of your review, copies of the February 2 as well as January 18 and 31, 2001 review letters are provided as **Attachment 1**.

Per your January 31 letter as well as your February 2 letter, please find enclosed a randomized, 2-way crossover, bioequivalence study of Teva Pharmaceuticals USA and Merck Sharp & Dohme (USA) (Fosamax®) Alendronate Sodium tablets administered as a 1 x 70 mg tablet in healthy adult males and/or females under fasting conditions in **Attachment 6**. Please note that a new batch was not manufactured to address the bioequivalence deficiencies therefore new CMC information will not be provided. Additionally, *in vitro* dissolution testing which contains the results of the dissolution profiles comparing: Fosamax® (Alendronate Sodium) Tablets, 70 mg, (lot# K7381) vs. Alendronate Sodium Tablets, 70 mg (lot# 1081-102) as well as a Certificate of Analysis from Teva Pharmaceuticals USA for the reference listed product, Fosamax® (Alendronate Sodium) Tablets, 70 mg may be found in **Attachment 4**. A certification for Financial Interests and Arrangements of Clinical Investigators is provided in **Attachment 5**.

1. In accord with your January 18, 2001 letter, all revisions have been made to all product labeling. TEVA USA practice differentiates product strengths by using different colors as does the reference listed drug. It is also Teva USA practice that the established name and strength are the most prominent information appearing on any container label. Four copies of Draft Insert

Labeling as well as four copies of the patient information leaflet for the once weekly dosing regimen are provided in **Attachment 2**. A Side-by-Side Comparison of our revised insert labeling vs. previously submitted labeling is also provided in **Attachment 2**.

2. Method validation samples have been submitted to the Agency on January 17,2001 in response to the District's written request of January 9, 2001.

3. **Attachment 3** contains updated stability data for the 70 mg strength of drug product packaged in bottles of 12s and 100s.

The information provided in this submission represents, in Teva Pharmaceuticals USA's opinion, a full response to the review comments presented thus far. If you should have any further questions regarding this submission, please do not hesitate to contact me at (215)591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

Corporate Headquarters:
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1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

March 21, 2001

NEW CORRESP

NC

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 40 mg and 70 mg
AMENDMENT - PATENT CERTIFICATION WITH RESPECT TO U.S. PATENT 6,194,004

Dear Mr. Buehler:

We submit herewith an amendment to the above referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No.6,194,004 which, on its face, has been assigned to Merck & Co., Inc. As a result of the listing of the aforementioned patent in the March 19, 2001 Docket, Teva wishes to provide the enclosed statement with regards to this patent. Also provided for the ease of your review, is a copy of the March 19, 2001 Docket document.

Should you have any further comments or questions please do not hesitate to contact me via telephone at (215) 591-3142 or via facsimile at (215) 591-8812.

Sincerely,

Deborah A. Jaskot, RAC

DAJ/sah
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
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MAR 21 2001
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Corporate Headquarters:
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FAX: (215) 591 8600

Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

faxed to Regulatory Desk 5/11/01

5/30/01 LT NFI

NEW CORRESP

April 24, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 40 mg and 70 mg
LABELING VARIATION REQUEST

Dear Mr. Buehler:

Merck & Co., Inc. has agreed to dismiss current litigation against TEVA Pharmaceuticals USA on U.S. Patent 5,804,570, listed in the "Orange Book," which relates to a method of use of alendronate sodium to reduce the risk of non-vertebral fractures. This agreement requires that TEVA Pharmaceuticals USA request from FDA that the INDICATIONS AND USAGE section of its insert be modified from:

> "For the treatment of osteoporosis, alendronate sodium increases bone mass and reduces the incidence of fractures, including those of the hip and spine...."

to:

> "For the treatment of osteoporosis, alendronate sodium increases bone mass and reduces the incidence of fractures, including those of the spine...."

By this letter, we are requesting FDA to allow TEVA Pharmaceuticals USA to make this change.

This information is submitted for your review and approval. If there are any further questions, please do not hesitate to contact me at (215) 591-3142 or via facsimile at (215) 591-8812.

Sincerely,

CENTER FOR DRUG EVALUATION AND RESEARCH
APR 25 2001
OGD

Deborah Jaskot

DAJ
Enclosures

5/11/01

Corporate Headquarters:
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Phone: (215) 591-3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 23, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT-ADDENDUM TO PATENT CERTIFICATION
NEW CORRESP
NC

Generic Pharmaceuticals
5/30/01
NDA I
Mbeckett
6/4/01

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 40 mg and 70 mg
PATENT AMENDMENT-ADDENDUM TO PATENT CERTIFICATION WITH RESPECT TO U.S. PATENT 6,225,294

Dear Mr. Buehler:

We submit herewith an amendment to the above referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,225,294 which, on its face, has been assigned to Merck & Co., Inc. As a result of the listing of the aforementioned patent in the May 18, 2001 Docket, Teva wishes to provide the enclosed statement with regards to this patent. Also provided for the ease of your review, is a copy of the May 18, 2001 Docket document.

Should you have any comments or questions please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Deborah Jaskot

CENTER FOR DRUG EVALUATION AND RESEARCH
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MAY 23 2001
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PE/jb
Enclosures

NC
5/31/01

Corporate Headquarters:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

August 8, 2001

NEW CORRESP

PATENT INFORMATION

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Adiministration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 40 mg and 70 mg
RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT/END OF 45-DAY CLOCK/LEGAL STATUS- US PATENT No. 6,194,004 B1

Dear Mr. Buehler:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent No. 6,194,004 B1 was provided to the holder of NDA 20-560 for Fosamax®, Alendronate Sodium Tablets, 5 mg, 10 mg, 40 mg, and 70 mg, and owner of the patent, Merck & Co., in accord with 314.95(c).

In accord with 21 CFR 314.95(e), TEVA Pharmaceuticals USA is hereby providing documentation of the receipt of the above referenced April 23, 2001 Notice of Certification for U.S. Patent No. 6,194,004 B1. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is April 26, 2001, the first day after correspondence of the receipt of Notice. Therefore, the 45-day period ended on June 9, 2001.

No action for infringement of the patent within the meaning of section 505(j)(5)(B)(iii) of the Act was brought against TEVA Pharmaceuticals USA within the required 45-day period.

Resultant from Merck & Co. failing to undertake legal action within the 45-day period, they have waived their right to pursue future legal endeavors under the scope of the Waxman-Hatch Act regarding this patent certification.

If there are any further questions, please do not hesitate to contact me at (215)591-3141 or via facsimile at (215)591-8812.

Sincerely,

PE/jb
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 0 9 2001
OGD

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

505(b)(2)(A)(d) ORIG AMENDMENT
25-OCT-2001

August 20, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT - ADDITION OF 35 mg STRENGTH

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 40 mg and 70 mg
UNSOLICITED AMENDMENT - ADDITION OF 35 mg STRENGTH

Dear Mr. Buehler:

We submit herewith an amendment to our above-referenced pending abbreviated new drug application for the addition of the 35 mg strength of the drug product Alendronate Sodium Tablets. Please note that this submission is presented in the basic format of an ANDA for ease of your review.

In support of this amendment, we have provided Chemistry, Manufacturing, and Controls (CMC) documentation relevant to the 35 mg strength and updated CMC documentation applicable to the 5 mg, 10 mg, 40 mg and 70 mg tablets. Please note that a waiver of *in-vivo* bioequivalence/bioavailability studies is requested pursuant to 21 CFR 320.22(d)(2) and is provided in Section VI.5.

Two separately bound copies of the finished product and bulk drug analytical methodology are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141, or by facsimile at (215) 591-8812

Sincerely,

PE/jb
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 20 2001
OGD

Administrative Offices:
TEVA PHARMACEUTICALS USA
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Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

August 27, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT ADDENDUM:
ADDENDUM TO 8/20/01
UNSOLICITED AMENDMENT
NEW CORRESP
NC

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
ADDENDUM TO AUGUST 20, 2001 UNSOLICITED AMENDMENT - CLARIFICATION OF PATENT CERTIFICATION

Dear Mr. Buehler:

We submit herewith an addendum to our August 20, 2001 unsolicited amendment which was submitted for the purpose of adding the 35 mg strength of Alendronate Sodium Tablets to ANDA #75-710. The purpose of this communication is to clarify the patent certification that was included in the August 20, 2001 amendment. Specifically, the patent certification noted eleven patents listed in the Orange Book for the reference listed product. However, in the second paragraph, one of the eleven patents (US Patent 6194004) was inadvertently omitted from the first sentence. Therefore, please find enclosed a patent certification which has been updated to reflect our intent with respect to US Patent 6194004. This certification is meant to replace the certification in the August 20, 2001 amendment. We apologize for any confusion or inconvenience this may have caused.

Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141, or by facsimile at (215) 591-8812

Sincerely,

Philip R. Erickson

PE/jbp
Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 2 8 2001
OGD

NAF/MMB 11/15/01

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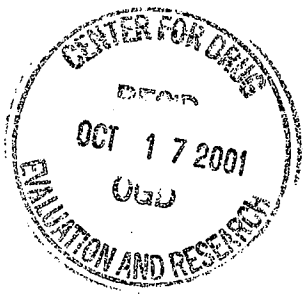
Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC

October 16, 2001

PATENT INFORMATION

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773



ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT/END OF 45-DAY CLOCK/LEGAL STATUS- US PATENT No. 6,225,294 B1

Dear Mr. Buehler:

Teva Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent No. 6,225,294 B1 (the '294 patent) for alendronate sodium tablets was provided to Merck & Co., Inc. as the holder of NDA 20-560 for Fosamax®Tablets and owner of the '294 patent in accord with 314.95(c).

In accord with 21 CFR 314.95(e), Teva Pharmaceuticals USA is hereby providing documentation of the receipt of the above-referenced August 23, 2001 Notice of Certification for the '294 patent **(Attachment 1)**. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is August 28, 2001, the first day after the receipt of Notice. Therefore, the 45-day period ended on October 11, 2001.

We hereby inform the Agency of a suit filed by Merck & Co., Inc. against Teva Pharmaceuticals USA concerning the '294 patent. The suit, Civil Action No. 01-675, was filed on October 4, 2001 in the United States District Court for the District of Delaware. The aforementioned suit was filed within the 45-day period. Teva Pharmaceuticals USA hereby commits to provide notification of the outcome of this suit in an appropriate submission to this application. A copy of the complaint is provided in **(Attachment 2)**.

If there are any further questions, please do not hesitate to contact me at (215)591-3141 or via facsimile at (215)591-8812.

Sincerely,

PE/jb
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESPONDENCE

October 19, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT
PATENT INFORMATION

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
TELEPHONE AMENDMENT- RESPONSE TO OCTOBER 10, 2001 REQUEST

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced ANDA in response to a telephone request made by Beth Fritch and Paras Patel of the Office of Generic Drugs in a discussion with Philip Erickson of TEVA on October 10, 2001. Specifically, Ms. Fritch and Mr. Patel requested that TEVA update our patent certification for the 35 mg strength of Alendronate Sodium Tablets to remove reference to U.S. Patents 6,194,004 and 5,882,656 as these two patents are not listed in the Orange Book for Fosamax® Tablets, 35 mg. They also requested revision of our exclusivity statement to indicate our marketing intentions with respect to the three exclusivities listed for Fosamax® Tablets, 35 mg.

With respect to our patent certification, please note that it has been TEVA's position to include patents for which we believe the innovator company may have taken steps to list in the Orange Book. As Merck may yet take such steps, or may have already taken such steps to list these patents, we are hesitant to remove these two patents from our certification. Furthermore, a detailed statement of the factual and legal basis for TEVA's opinion regarding Merck's Alendronate patents included these two patents and was already provided to them on September 25, 2001. We await word on whether or not Merck will assert any of the patents contained in the detailed statement, including the '004 and '656 patents, against us (the 45 day clock will expire on November 12, 2001).

We have taken steps through our Legal Counsel to ascertain Merck's intentions with respect to the '004 and '656 patents, however it is unlikely that Merck will be promptly forthcoming with this information. Therefore, we must rely on the Agency's instructions as indication that Merck has not and will not pursue listing of the '004 and '656 patents in the Orange Book for Fosamax® Tablets, 35 mg. In order to comply with the Agency's request that we remove these patents from our

certification, please find enclosed a patent certification revised as requested. Because we are taking these steps solely to conform with the Agency's instructions, it is our belief that if these patents list in the Orange Book in the future, the date on which TEVA was considered to have certified to these patents should be acknowledged as the date of our original certification. Further, it has been more than thirty days since these patents have issued, therefore if Merck pursues their listing they would be late-listed.

In addition, please find enclosed a revised exclusivity statement that notes TEVA will not market Alendronate Sodium Tablets, 35 mg prior to expiration of the NS, D-61 and D-62 exclusivities on October 20, 2003.

Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141, or by facsimile at (215) 591-8812

Sincerely,

PE/jbp
Enclosures

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 23, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
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Rockville, MD 20855-2773

TELEPHONE AMENDMENT
PATENT INFORMATION

NAE
25-OCT-2001

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
TELEPHONE AMENDMENT- RESPONSE TO OCTOBER 10, 2001 AND OCTOBER 23, 2001 REQUESTS

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced ANDA in response to a telephone request made by Beth Fritch and Paras Patel of the Office of Generic Drugs on October 10, 2001 and to a follow up call made by Greg Davis of OGD on October 23, 2001. Specifically, TEVA was asked in the October 10, 2001 call to revise our patent certification for the 35 mg strength of Alendronate Sodium Tablets to remove reference to U.S. Patents 6,194,004 and 5,882,656 as these two patents are not listed in the Orange Book for Fosamax® Tablets, 35 mg. A request was also made that we revise our exclusivity statement to indicate our marketing intentions with respect to the three exclusivities listed for Fosamax® Tablets, 35 mg. On October 23, 2001, Mr. Davis requested revision of the language in the cover letter that accompanied our October 19, 2001 amendment.

Please find enclosed copies of the revised patent certification and exclusivity statement that were provided on October 19, 2001 in response to the October 10, 2001 request. This letter reflects the revised language requested by Mr. Davis.

Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141, or by facsimile at (215) 591-8812

Sincerely,

Philip Erickson

PE/jbp
Enclosures

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

December 4, 2001

NEW CORRESP
PATENT INFORMATION

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT/END OF 45-DAY CLOCK/LEGAL STATUS-US PATENT Nos. 4,621,077; 5,358,941; 5,681,590; 5,849,726; 5,994,329; 6,008,207; 6,090,410; 6,015,801; 6,225,294 and 5,804,570

Dear Mr. Buehler:

Teva Pharmaceuticals USA hereby certifies that a Notice of Non-Infringement of US Patent Nos. 4,621,077; 5,358,941; 5,681,590; 5,849,726; 5,994,329; 6,008,207; 6,090,410; 6,015,801; 6,225,294 and 5,804,570 was provided to the holder of NDA 20-560 for Fosamax® (Alendronate Sodium) Tablets, 35 mg and owner of the patents, Merck & Co., in accord with 21 CFR 314.95(c).

In accord with 21 CFR 314.95(e), Teva Pharmaceuticals USA is hereby providing documentation of the receipt of the above-referenced September 24, 2001 Notice of Certification for US Patent Nos. 4,621,077; 5,358,941; 5,681,590; 5,849,726; 5,994,329; 6,008,207; 6,090,410; 6,015,801; 6,225,294 and 5,804,570 **(Attachment 1)**. In accord with 21 CFR 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is September 29, 2001, the first day after the receipt of Notice. Therefore, the 45-day period ended on November 12, 2001.

We hereby inform the Agency of a suit filed by Merck & Co., Inc. against Teva Pharmaceuticals USA concerning US Patent Nos. 4,621,077; 5,358,941; 5,681,590; 5,849,726; 5,994,329; 6,008,207; 6,090,410; 6,015,801 and 6,225,294. The suit, Civil Action No. 01-728, was filed on November 6, 2001 in the United States District Court for the District of Delaware. The aforementioned suit was filed within the 45-day period. Teva Pharmaceuticals USA hereby commits to provide notification of the outcome of this suit in an appropriate submission to this application. A copy of the complaint is provided in **Attachment 2**.

Further, no action for infringement of US Patent 5,804,570 within the meaning of section 505(j)(5)(B)(iii) of the Act was brought against Teva Pharmaceuticals USA within the required 45-day period. Resultant from Merck & Co. failing to undertake legal action within the 45-day period with respect to this patent, they have waived their right to pursue future legal endeavors under the scope of the Waxman-Hatch Act regarding this patent certification.

If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

ORIGINAL
N/AA

December 5, 2001

UNSOLICITED AMENDMENT

P.M.P
12/13/01

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
UNSOLICITED AMENDMENT-UPDATED EXCLUSIVITY STATEMENT

Dear Mr. Buehler:

Teva Pharmaceuticals USA herewith submits an updated Exclusivity Statement for Alendronate Sodium Tablets, 5 mg, 10 mg and 40 mg. This amendment is made in response to additional exclusivities listed for Fosamax® Tablets, 5 mg, 10 mg and 40 mg in the Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book) since our previous exclusivity statement dated November 22, 1999.

Specifically, we have updated our exclusivity statement to acknowledge the listing of M-3 and I-309. M-3 for the addition of efficacy and safety information in which Fosamax was used concomitantly with estrogen alone or with estrogen plus progestin is set to expire on November 24, 2002. I-309 for the increased bone mass in men with osteoporosis (10 mg strength only) is set to expire on September 29, 2003.

Please note that Teva Pharmaceuticals USA will not include these indications in our labeling until expiration of these exclusivities.

We look forward to your continued review of ANDA #75-710. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or via facsimile at (215) 591-8812.

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 06 2001
OGD

Sincerely,

PE/jb
Enclosures

Administrative Offices:
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FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

December 6, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

NEW CORRESP

ANDA # 75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
PATENT INFORMATION – WITHDRAWAL OF APRIL 24, 2000 PATENT AMENDMENT

Dear Mr. Buehler:

This letter is with respect to Teva Pharmaceuticals USA's patent amendment dated April 24, 2000 concerning US Patent No. 6,015,801 for Alendronate Sodium Tablets, 5 mg, 10 mg and 40 mg. We respectfully request withdrawal of the April 24, 2000 patent amendment from the above-referenced ANDA as the '801 patent never listed in the Orange Book for Fosamax® Tablets, 5 mg, 10 mg and 40 mg.

Please note that Notice of Certification for the '801 patent was not provided to Merck & Co. relative to the 5 mg, 10 mg and 40 mg strengths. Therefore no 45-day period was activated and no action for infringement of the '801 patent was brought against Teva Pharmaceuticals USA with regard to the 5 mg, 10 mg and 40 mg strengths.

We look forward to your continued review of ANDA #75-710. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 0 7 2001

Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

December 6, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

P.M.P 12/13/01 NEW CORRESP NC

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
END OF 45-DAY PERIOD/ LEGAL STATUS-U.S. PATENT Nos. 5,994,329 and 6,090,410

Dear Mr. Buehler:

The purpose of this communication to the above-referenced application is to provide the Agency follow-up regarding end of 45-day periods related to U.S. Patents 5,994,329 and 6,090,410 as well as the status of legal action related to these two patents with regard to the 5 mg, 10 mg and 40 mg strengths. Our review of the file history uncovered that this information was not previously provided to the Agency.

In accord with 21 CFR 314.95(a), Teva Pharmaceuticals USA provided documentation to Merck & Co. Notice of Certification for U.S. Patent No. 5,994,329 regarding Alendronate Sodium Tablets, 5 mg, 10 mg and 40 mg. The Notice was received by Merck & Co. on May 5, 2000. Evidence of this date was provided to the Agency in correspondence to this pending application dated May 12, 2000. In accord with 21 CFR 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act was May 6, 2000, the first day after receipt of notice. Therefore, the 45-day period ended on June 19, 2000.

In accord with 21 CFR 314.95(a), Teva Pharmaceuticals USA provided documentation to Merck & Co. Notice of Certification for U.S. Patent No. 6,090,410 regarding Alendronate Sodium Tablets, 5 mg, 10 mg and 40 mg. The Notice was received by Merck & Co. on October 10, 2000. Evidence of this date was provided in correspondence to this pending application dated October 17, 2000. In accord with 21 CFR 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act was October 11, 2000, the first day after receipt of notice. Therefore, the 45-day period ended on November 24, 2000.

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

January 14, 2002

ORIG AMENDMENT
N/A

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
LABELING AMENDMENT – FINAL PRINTED LABELING for 5 mg, 10 mg and 40 mg

Dear Mr. Buehler:

We submit herewith a labeling amendment to the above-referenced pending ANDA. Twelve final printed copies of patient package insert as well as a comparison to our previous revision are included in **Attachment 1**. Twelve final printed copies of package insert along with a comparison to the last submitted labeling is provided as **Attachment 2**. Twelve final printed copies of container labeling are included in **Attachment 3**.

Please note that the last patient package insert labeling dated 10/2000 contained references applicable to the 35 mg and 70 mg strengths. Therefore, the patient package insert labeling dated 6/2000 was used as it contains information applicable to the 5 mg, 10 mg and 40 mg strengths. Package insert labeling submitted on 8/2001 contained references applicable only to the 35 mg and 70 mg strengths. The insert labeling dated 8/2001will not be implemented until approval of the 35 mg and 70 mg strengths.

We look forward to your final approval of ANDA #75-710. Should there be any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 15 2002

PE/jb
Enclosures

Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NC to Labeling

NEW CORRESP

January 25, 2002

LABELING AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
LABELING AMENDMENT – FINAL PRINTED LABELING for 5 mg, 10 mg and 40 mg

Dear Mr. Buehler:

This correspondence references a January 14, 2002 Labeling Amendment submitted to the above-referenced ANDA. In accord with a telephone conversation between Angela Payne of your office and Philip Erickson of TEVA Pharmaceuticals USA (TEVA), this letter serves as a replacement cover letter to our aforementioned labeling amendment. The purpose of this revised cover letter is to clarify the enclosures of our original amendment.

Attachment 1 of the amendment contains twelve final copies of the *patient* package insert as well as a comparison to the 6/2000 version. Comparison to this edition was used, as it was the last submitted labeling containing reference to only the 5 mg, 10 mg and 40 mg strengths.

This labeling is submitted in anticipation of the resolution of patent litigation for these strengths. We understand from Lt. Greg Davis that, upon tentative approval of the ANDA, final approval for the 5 mg, 10 mg 40 mg strengths would be possible if litigation completed in TEVA's favor.

The insert revision dated 8/2001 contained references to all of the strengths, so this insert was used for comparison and references for the 35 mg and 70 mg strength were removed. **Attachment 2** of the amendment contains twelve final copies of the insert along with a comparison of the last submitted labeling of 8/2001.

Twelve final copies of container labeling are included in **Attachment 3**.

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 28 2002

We look forward to your continued review of ANDA #75-710. Should there be any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/jb

PE/jb
Enclosures

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Phone: (215) 591 3000
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

February 28, 2002

ORIG AMENDMENT
N/AM.

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
MINOR AMENDMENT – RESPONSE TO DECEMBER 5, 2001 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced pending ANDA. The subject of this amendment is our response to comments from the Office of Generic Drugs (OGD) pertaining to this application. The response to your chemistry comments from the review letter dated December 5, 2001are provided. A copy of this letter is enclosed in **Attachment 1**.

A. Deficiencies:

1. (b) (4)

2.

Acknowledgements:

1. Updated stability data for all strengths are provided in **Attachment 4**.
2. We acknowledge that our labeling information is pending review.

CENTER FOR DRUG EVALUATION AND RESEARCH
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OGD

3. We acknowledge that an acceptable compliance evaluation is needed for approval and that a request has been made for an evaluation from the Office of Compliance.

The information provided herein represents, in our opinion, a complete response to your letter of December 5, 2001 and is submitted towards the continued review of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

April 26, 2002

ORIG AMENDMENT
UNSOLICITED AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
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ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
UNSOLICITED AMENDMENT – ADDITION OF UNIT DOSE PACKAGING

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above-referenced ANDA for the addition of unit dose packaging in the 35 mg and 70 mg strengths. The unit dose packaging site address is as follows:

(b) (4)

A certification of current Good Manufacturing Practices for the above-referenced site is provided in **Attachment 1**.

A packaging and disbursement summary is provided for both 35 mg (Batch Number 1081-120) and 70 mg (Batch Number 1081-102) in **Attachment 2**. Please note that both batches and applicable Certificates of Analysis were presented in the amendments of additional strengths dated August 20, 2001 and October 23, 2000 respectively. Executed packaging directions from (b) (4) are included in **Attachment 3**.

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APR 29 2002
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The following table summarizes the proposed packaging configurations:

Unit Dose	[redacted] (b) (4)	[redacted] (b) (4)
Count	4 Tablets	10 Tablets
Presentation Size	3 x 5	3 x 5
Blister Code Number	[redacted] (b) (4)	[redacted] (b) (4)
Blister		
Foil Code Number		
Foil		
Paper Backing		
Film		
Heat Seal Coating		

Please note that [redacted] (b) (4) has legally changed their name to [redacted] (b) (4) but will still market under the [redacted] (b) (4) name. Appropriate DMF authorizations and technical information as well as [redacted] and Manufacturer Certificates of Compliance are provided in **Attachment 4**.

Stability at accelerated (12 weeks) and controlled room temperature (3 months) conditions for the addition of unit dose packaging for both strengths is included in **Attachment 5**. Please note that stability for the 70 mg strength [redacted] (b) (4) is not available at this time and will be provided to the Agency when available. An updated stability protocol and a stability commitment are also provided in **Attachment 5**.

Four copies of draft carton and blister labeling for the [redacted] (b) (4) and four copies of draft carton and blister labeling for the [redacted] (b) (4) of both the 35 mg and 70 mg strengths are provided in **Attachment 6**. Four copies of an updated combined strength package insert which includes the addition of unit dose packaging and a comparison to the previously submitted insert is provided in **Attachment 7**. We reference a letter dated August 28, 2001 from the Labeling Review Branch that provided us with the reference product's 70 mg [redacted] (b) (4) carton labeling. For ease of review, please find a copy of this letter in **Attachment 8**. Carton labeling for the [redacted] (b) (4) and [redacted] (b) (4) of the reference product's 35 mg and 70 mg strengths is provided in **Attachment 9**. A side-by-side carton label comparison is provided in **Attachment 10**.

This information is submitted for your review and approval. If there are any further questions, please do not hesitate to contact me by telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

N/AF

ORIG AMENDMENT

April 26, 2002

LABELING AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
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ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
LABELING AMENDMENT – RESPONSE TO JANUARY 30, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment in response to a letter dated January 30, 2002 from the Labeling Review Branch #4. Please disregard our submissions dated January 14 and 25, 2002. For ease of review, please find a copy of the January 30, 2002 letter in **Attachment 1**.

We acknowledge that a complete comment on our once weekly container labels for the 35 mg strength (12s and 100s) is deferred. It is TEVA Pharmaceuticals USA's practice to have the established name and strength be the most prominent information that appear on the label and also to differentiate product strengths using color or shading as does the reference listed drug. In addition, the draft container labeling for 5 mg, 10 mg and 40 mg strengths submitted on September 29, 1999 was found to be satisfactory. Twelve final printed copies of container labeling for 5 mg, 10 mg and 40 mg strengths are included in **Attachment 2**.

We also acknowledge that the Agency requests that our package insert should be a combined insert for the 5 mg, 10 mg, 35 mg, 40 mg and 70 mg strengths. As requested, all comments related to the package insert labeling have been addressed. A comparison to our previous revision labeling has been updated accordingly. Please find attached twelve final printed copies of package insert labeling, as well as a comparison to our previous revision in **Attachment 3**.

Finally, we note that the patient information leaflets should be two separate leaflets. The once weekly draft patient information leaflet submitted on March 9, 2001 was found to be satisfactory. Twelve final printed copies of the once weekly patient information leaflet are included in **Attachment 4**. As requested, all comments related to the daily patient information leaflet were addressed in accord with the referenced attached patient information leaflet. A comparison to

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OGD / CDER

our previous revision submitted on October 23, 2000 along with twelve final printed copies of the daily patient information leaflet is included in **Attachment 5**.

This information is submitted for your continued review and approval of this pending ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

April 30, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
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UNSOLICITED AMENDMENT

ORIG AMENDMENT
N/AM

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
UNSOLICITED AMENDMENT – CLARIFICATION OF DRUG SUBSTANCE AND DRUG PRODUCT TERMINOLOGY

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above-referenced ANDA for the clarification of drug substance and drug product terminology. Specifically, "Trihyrate" is to be added to the drug substance when referenced. For the drug product, the label claim is noted as being the "molar" equivalent and "Anhydrous" will be replaced with "the free acid".

All pages of the original ANDA and subsequent strength amendments that need this clarification change have been updated. Pages referring to the 5 mg, 10 mg and 40 mg strengths are provided in **Attachment 1**. Pages referring to the 35 mg strength are provided in **Attachment 2** and pages referring to the 70 mg strength are included in **Attachment 3**.

This information is submitted towards the continued review of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

RECEIVED
MAY 0 1 2002
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Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 16, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. D,457,246, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. D,457,246 issued on May 14, 2002, therefore Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRES

May 16, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Sincerely,

PE/jbp
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Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 17, 2002

NEW CORRESP

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Sincerely,

PE/jbp
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Administrative Offices:
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1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 20, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

Dear Mr. Buehler:

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Sincerely,

PE/jbp
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1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 21, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Sincerely,

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 22, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

Dear Mr. Buehler:

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Sincerely,

PE/jbp
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Administrative Offices:
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FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 23, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

Dear Mr. Buehler:

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Sincerely,

PE/jbp
Enclosures

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1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NTI
MMB 6-4-02
Patent not yet listed in O.B
According to Docket 95-0117 last updated 5/31/02 : Miss Patent certification is pending

PATENT AMENDMENT
NEW CORRESP
NC

May 24, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Sincerely,

PE/jbp
Enclosures

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Administrative Offices:
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1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 28, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

NAI
6/10/02
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Sincerely,

PE/jbp
Enclosures

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Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 29, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

NAL
6/10/02
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Sincerely,

Philip Erickson

PE/jbp
Enclosures

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Administrative Offices:
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North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 30, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

NAI 6/10/02
P.M.I

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PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Sincerely,

Philip Erickson

PE/jbp
Enclosures

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Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 31, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP

NC

VAT 6/10/02
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Sincerely,

PE/jbp
Enclosures

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Administrative Offices:
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1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NC

June 3, 2002

NEW CORRESP
PATENT AMENDMENT

NAI 6/10/02
P.M.P

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Sincerely,

PE/jbp
Enclosures

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Administrative Offices:
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1090 Horsham Road, PO Box 1090
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Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NC
NEW CORRESP

June 4, 2002

PATENT AMENDMENT

NAL 6/10/02
P.M.P

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Sincerely,

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

June 5, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NDE 6/10/02 NEW CORRESP
NC
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Sincerely,

PE/jbp
Enclosures

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JUN 0 6 2002
OGD / CDER

Please file in latest open archival volume

75-710

Telecon

Date: 06-JUN-2002

Time: 1600 H

Firm: TEVA Pharmaceuticals USA

Drug: Alendronate Sodium Tablets, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg

ANDA #: 75-710

Attendees: Gregg Davis, FDA and Debbie Jaskot Davis 06-JUN-2002

Phone #: 215-591-3142

Agenda:

I called Debbie and asked for the following patent certifications and clarifications:

1. TEVA must revise their '570 certification to withdraw reference to the 40 mg strength
2. TEVA must revise their '329 certification to withdraw reference to the 5 mg, 10 mg and 40 mg strengths
3. TEVA must revise their '801 certification to withdraw reference to the 5 mg, 10 mg and 40 mg strengths
4. TEVA must revise their '004 certification to withdraw reference to the 5 mg, 40 mg and 70 mg strengths
5. TEVA must revise their '294 certification to withdraw reference to the 5 mg, 10 mg and 40 mg strengths

Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

June 6, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NAZ 6/10/02
P.M.P

NEW CORRESP

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,592, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,592 issued on June 4, 2002, therefore Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

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Enclosures

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JUN 0 6 2002
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Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NFF MB 6-19-02

June 6, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRES

June 6, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

June 7, 2002

NEW CORRESP

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

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ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NOTE 6-19-02 mtg Patent not yet listed in OB Accepted 6-14-02 Docket 075,047 Lost upon filed. 6-14-02 : this cert is included.

NEW CORRESP
NC

June 7, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

Dear Mr. Buehler:

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
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June 10, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

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ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NTE 6-19-02

June 10, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT-
PATENT CLARIFICATION

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
TELEPHONE AMENDMENT- PATENT CLARIFICATION

Dear Mr. Buehler:

In accord with a June 6, 2002 request made by Gregg Davis of the Office of Generic Drugs in a telephone conversation with Deborah Jaskot of TEVA Pharmaceuticals USA, we provide herein clarification of the patents to which we have certified for Alendronate Sodium Tablets in the above-referenced ANDA. Per Mr. Davis, the Agency has confirmed the patent listings by strength for Fosamax® Tablets with Merck Company and therefore he has requested withdrawal of reference to several patents for certain strengths as outlined below:

U.S. Patent 5,804,570: We note that this patent is listed only for the 5 mg, 10 mg, 35 mg and 70 mg strengths and therefore does not apply to the 40 mg strength. As such, we withdraw reference to the 40 mg strength from our certification for this patent.

U.S. Patent 5,994,329: We note that this patent is listed only for the 35 mg and 70 mg strengths and therefore does not apply to the 5 mg, 10 mg or 40 mg strengths. As such, we withdraw reference to the 5 mg, 10 mg and 40 mg strengths from our certification for this patent.

U.S. Patent 6,015,801: We note that this patent is listed only for the 35 mg and 70 mg strengths and therefore does not apply to the 5 mg, 10 mg or 40 mg strengths. As such, we withdraw reference to the 5 mg, 10 mg and 40 mg strengths from our certification for this patent.

U.S Patent 6,194,004: We note that this patent is listed only for the 10 mg strength, and therefore does not apply to the 5 mg, 35 mg, 40 mg or 70 mg strengths. As such, we withdraw reference to the 5 mg, 35 mg, 40 mg and 70 mg strengths from our certification for this patent.

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NKT
Notes 6-19-02
Patent not yet listed in OB.
According to Docket 955-0071 ist
updated 6-14-02 :: this cert is
NWHM

June 10, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT D,457,246

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. D,457,246, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. D,457,246 issued on May 14, 2002, therefore Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

Philip Erickson

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC
6-19-02
Patent not yet listed in OB According to Dockets 75-017 Instructed 6-14-02
: this cert is invalid.

June 11, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

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PE/jbp
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1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

June 11, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

June 12, 2002

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Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NC
NAI 6/14
- Not listed yet.
P.M.P

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Solid Oral Dosage Forms

June 12, 2002

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Food and Drug Administration
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PATENT AMENDMENT
NEW CORRESP
NC
6/14
NAE
Not listed yet
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC

June 13, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NAI 6/15
Not listed yet.
P.M.P

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Philip Erickson

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NEW CORRESP
NC

June 13, 2002

PATENT AMENDMENT

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6/15 WAL
Not listed yet.
P.M.P

ANDA # 75-710
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PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

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PATENT AMENDMENT

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NEW CORRESP
NC

WAT 6/19
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PM. P

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
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June 17, 2002

PATENT AMENDMENT

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Food and Drug Administration
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NEW CORRESP
NC

6/18
NAI
Not listed yet
P.M.P

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Sincerely,

Deborah Jasnot /for PE

PE/jbp
Enclosures

RECEIVED
JUN 18 2002
OGD / CDER

Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

June 18, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

NFT
6/19 Not listed yet.
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,592, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,592 issued on June 4, 2002, therefore Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

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June 19, 2002

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7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC
NAI
6/20 Not listed yet.
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,406,714, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,406,714 issued on June 18, 2002. Therefore Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

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PATENT AMENDMENT

NEW CORRESP

6/21 NC

NEF Not listed yet.

P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

Dear Mr. Buehler:

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PATENT AMENDMENT

CORRESP
NC

6/19 NAF

Not listed yet.

P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

Dear Mr. Buehler:

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9.1

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June 20, 2002

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PATENT AMENDMENT

6/28 NAE
Not listed yet
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

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LABELING AMENDMENT

ORIG AMENDMENT
NIAF

ANDA# 75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
LABELING AMENDMENT – RESPONSE TO MAY 20, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment in response to a letter dated May 20, 2002 from the Labeling Review Branch #5. For ease of review, please find a copy of the May 20, 2002 letter in **Attachment 1**.

Labeling Deficiencies:

1. We have revised and relocated "(Once Weekly)" so that it is in parenthesis and follows the product name for all appropriate labels and labeling.

2. The city, state, zip code, lot # and expiration date have been added as requested on the 35 mg and 70 mg unit dose blisters. It is TEVA Pharmaceuticals USA's practice to have the established name and strength be the most prominent information that appear on the label and also to differentiate product strengths using color or shading as does the reference listed drug. Please find four copies of draft 35 mg and 70 mg unit dose blister labels and a comparison to our previous revisions in **Attachment 2**.

3. Unit-Dose Cartons: (1x4s) and (20s)

   a. The 1x4 (b) (4) carton will ensure the child resistant concept for this unit-of-use carton. Typically, for a packaging configuration to possess the child resistant attributes, it must require a two step process for medication removal. The (b) (4) carton qualifies as child resistant, specifically, as it has a "peel and push" system. Please note

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that this "peel and push" system is used in the innovator's packaging configuration as well.

b. Please note that the sentence, "Remember to take one Alendronate Sodium Tablet once each week on that same day for as long as your doctor prescribes it", appears on the reference listed drug labels for the 35 mg and 70 mg 1x4 unit-dose cartons provided to us by the Labeling Review Branch on August 28, 2001. Due to this discrepancy, please confirm that this sentence should be removed from our labeling.

c. We have revised the sentence, "There is important additional information about…" to the 1x4 unit dose cartons as requested.

d. "(Once weekly)" has been relocated on the 1x4 unit dose cartons so that it follows the product name.

e. We have added, "Unit-of-Use- dispense in original package", to the 1x4 unit dose cartons as requested.

f. The statement, "This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used", has been added to the 20s unit dose cartons. The (b) (4) cartons are not child resistant and are not intended for dispensing as the cartons are a bulk package.

g. It is TEVA Pharmaceuticals USA's practice to add, "Keep this and all medications out of the reach of children." In accord with this current practice, the previous sentence has been added instead of "Keep out of reach of children."

h. For further clarification, the card configuration has been revised for the 20s unit dose cartons to read "20 Tablets (2x10)" as requested.

Four copies of draft 35 mg and 70 mg 1x4 unit dose cartons as well as a comparison to our previous revision are provided in **Attachment 3**. Four copies of draft 35 mg and 70 mg 20s unit dose cartons with a comparison to our previous revision are provided in **Attachment 4**.

4. The package insert labeling has been revised as requested. Please find four copies of draft package insert labeling and a comparison to our previous revision in **Attachment 5**.

5. Patient Information Leaflets

   a. We note that the once weekly draft patient information leaflet submitted on March 9, 2001 was found to be satisfactory. Twelve final printed copies of the once weekly patient information leaflet were submitted in our Labeling Amendment dated April 26, 2002.

   b. As requested, all comments related to the daily patient information leaflet were addressed in accord with the attached patient information leaflet. Twelve final printed copies of the

daily patient information leaflet along with a comparison to our previous revision were submitted in our Labeling Amendment dated April 26, 2002.

Also provided are four draft copies of our revised once weekly container labels for the 35 mg and 70 mg strengths (12s and 100s) along with a comparison to the previously submitted labels in **Attachment 6**.

This information is submitted for your continued review and approval of this pending ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson 10 A.

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

June 21, 2002

NEW CORRESP
NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

6/25 VAI
Not listed yet.
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

Dear Mr. Buehler:

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
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June 21, 2002

NEW CORRESP
NC

Gary Buehler, Director
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Food and Drug Administration
Document Control Room
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7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

MAI
6/25 not listed yet.
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

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Philip Erickson

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

June 24, 2002

NEW CORRESP

PATENT AMENDMENT

6/26
NAL
Not listed yet
P.M.P

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
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7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

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Sincerely,

Philip Erickson PE

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JUN 25 2002
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

June 24, 2002

NEW CORRESP

PATENT AMENDMENT

6/26
-Not listed yet
P.M.P

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
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7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
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PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

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June 25, 2002

NEW CUMBERLAND
NC

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PATENT AMENDMENT

6/27
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June 25, 2002

NC

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PATENT AMENDMENT

NAE 6/27
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Director, Regulatory Affairs
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June 26, 2002

NEW CORRESP
NC

PATENT AMENDMENT

6/28
NFX
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P.M.P

Gary Buehler, Director
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Philip Erickson 1dg

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PATENT AMENDMENT

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Not listed yet.
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,406,714, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,406,714 issued on June 18, 2002. Therefore Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/jbp
Enclosures

RECEIVED
JUN 2 8 2002
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

June 27, 2002

NEW CORRESP

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

7/5 ~~NAT~~ Not listed yet P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,592, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,592 issued on June 4, 2002, therefore Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

Philip Erickson / DG

PE/jbp
Enclosures

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JUN 2 8 2002
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

10.1

June 28, 2002

PATENT AMENDMENT

NAF - Not listed yet
P.M.P
7/5/02

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

Dear Mr. Buehler:

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Sincerely,

Philip Erickson /dy

PE/jbp
Enclosures

Administrative Offices:
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1090 Horsham Road, PO Box 1090
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Phone: (215) 591 3141
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

June 28, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

7/2/02 NAE
Not listed yet.
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,406,714, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,406,714 issued on June 18, 2002. Therefore Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

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Philip Erickson

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

12

NEW CORRESP

July 1, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

7/9/02 WAF
-Not listed
Yet
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

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Sincerely,

PE/jbp
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRES

July 1, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NAI
- 6/5/02 - Not listed yet.
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

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Sincerely,

PE/jbp
Enclosures

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JUL 2002
OGD Mail Room

7/18/02

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW COURTESY
NC

July 2, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

7/4 Not
Not listed yet.
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

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Sincerely,

PE/jbp
Enclosures

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC

July 2, 2002

PATENT AMENDMENT

7/8 WAE
Not listed yet.
P.M.P

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

Dear Mr. Buehler:

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Sincerely,

Philip Erickson

PE/jbp
Enclosures

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

July 3, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

NAI
-Not listed as
of 7/25/02
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,592

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Sincerely,

PE/jbp
Enclosures

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JUL 0 3 2002
OGD / DDER

Administrative Offices:
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1090 Horsham Road, PO Box 1090
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FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

July 5, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

VAL
7/10 Not listed yet.
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

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Sincerely,

PE/jbp
Enclosures

JUL 2002

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

10.1

NEW CORRESP

NC

July 8, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NAL PMP
- Not listed
Yet as of 7/25/02

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

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Sincerely,

PE/jbp
Enclosures

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JUL 0 2002

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

July 9, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NAI
- Not listed as of 7/25/02
P.Z.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

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Sincerely,

PE/jbp
Enclosures

Administrative Offices:
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1090 Horsham Road, PO Box 1090
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FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

July 10, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NTL
-Not listed as
of 7/25/02
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

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Sincerely,

Philip Erickson

PE/jbp
Enclosures

Administrative Offices:
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Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

10.1

NEW COMPLETE
N C

July 11, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NAE
- Not listed as of 7/25/02.
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

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Sincerely,

PE/jbp
Enclosures

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TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

July 12, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPOND
NC

NAI
- Not listed as
of 7/25/02 — P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

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Sincerely,

PE/jbp
Enclosures

RECEIVED
JUL 15 2002
OGD / CDER

Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

July 15, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT
NEW CORRESP
NC

N41
-Not listed as
of 7/25/02
P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

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Sincerely,

PE/jbp
Enclosures

RECEIVED
JUL 16 2002
OGD / CDER

Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NC

July 16, 2002

NEW CORRESP

PATENT AMENDMENT

Gary Buehler, Director
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Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NAL
-Not listed as
of 7/25/02
L.P.M.P

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,406,714, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,406,714 issued on June 18, 2002. Therefore Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
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JUL 17 2002
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Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

July 17, 2002

NEW CORRESP
NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NAI
-Not listed in OB'
or Current Doc. Page.
P.M.P 7/25/02

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,406,714, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,406,714 issued on June 18, 2002. Therefore Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

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NAI
8/16/02

July 18, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NAI
-Not listed as of 7/25/02
LPM

CORRESP
NO

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,406,714

Dear Mr. Buehler:

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Sincerely,

PE/jbp
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July 31, 2002

ORIG AMENDMENT
MINOR AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
MINOR AMENDMENT – RESPONSE TO JULY 30, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced ANDA in response to a review letter dated July 30, 2002. The referenced review letter is provided in **Attachment 1** for ease of review.

A. Deficiencies:

1. (b) (4)

2.

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A report entitled "The Chemical and Physical Stability Results for Accelerated and Controlled Room Temperature Report for Alendronate Sodium Tablets, 70 mg" is provided in **Attachment 4**, which summarizes stability results and provides a regression analysis.

B. All other accrued long-term stability data are provided in **Attachment 5**. For further clarification, the tables below represent the controlled room temperature stability data presented in Attachment 5.

35 mg				
Packaging Size	12s	100s	Unit Dose (b) (4)	Unit Dose (b) (4)
Test interval	12 months	12 months	9 months	9 months

70 mg		
Packaging Size	12s	100s
Test Interval	24 months	24 months

Please note that the long-term stability data for the 5 mg, 10 mg and 40 mg strengths cover the full term of the 24 month proposed expiration period.

This information is submitted for your review. If there are any further questions, please do not hesitate to contact me by telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

NAL
E Thomas
8/19/02

TEVA

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

August 14, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,432,931, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,432,931 issued on August 13, 2002. Therefore, Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

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August 14, 2002

NEW CORRESP

PATENT AMENDMENT

Gary Buehler, Director
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Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

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Sincerely,

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WAI
E Thomas
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August 15, 2002

NEW CORRESP
NC

Gary Buehler, Director
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Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

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Sincerely,

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

August 16, 2002

NEW CORRESP
NC

Gary Buehler, Director
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Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

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Sincerely,

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Philip Erickson, R.Ph.
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August 19, 2002

PATENT AMENDMENT

Gary Buehler, Director
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Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

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Sincerely,

Philip Erickson

PE/jbp
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

August 20, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,432,931, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,432,931 issued on August 13, 2002. Therefore, Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

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E Thomas
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Phone: (215) 591 3141
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

August 21, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

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Sincerely,

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Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

August 22, 2002

NEW CORRESP
NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

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Sincerely,

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3/31/12

Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
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NC
NEW CORRESP

August 23, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

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Sincerely,

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Administrative Offices:
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FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

August 26, 2002

PATENT AMENDMENT

NEW CORRESP

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

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Sincerely,

PE/jbp
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NFI 9/30/02 2 Thomas not yet listed in OB ET

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

August 27, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
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Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP

NC

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PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

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Sincerely,

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2 Thomas

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

August 28, 2002

Gary Buehler, Director
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Food and Drug Administration
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PATENT AMENDMENT

NEW CORRESP
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ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

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Sincerely,

PE/jbp
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NAS not yet listed in OB 9/11/02 E Thomas

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1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

N C

August 29, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,432,931, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,432,931 issued on August 13, 2002. Therefore, Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED
AUG 30 2002
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

NC

August 30, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

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Sincerely,

PE/jbp
Enclosures

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SEP 0 3 2002
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

September 3, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,432,931, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,432,931 issued on August 13, 2002. Therefore, Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

NAI not yet listed in OB 9/11/02 STimms

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

September 4, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,432,931, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,432,931 issued on August 13, 2002. Therefore, Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

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SEP 0 5 2002
OGD / CDER

Not yet listed in OB
Thomas
9/10/02
NA 5 ET

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

NC

September 5, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,432,931, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,432,931 issued on August 13, 2002. Therefore, Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

PE/jbp
Enclosures

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SEP 0 6 2002
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Not yet listed in OB
E Thomas 9/10/02

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC

September 6, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,432,931, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,432,931 issued on August 13, 2002. Therefore, Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

Philip Erickson

PE/jbp
Enclosures

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Not yet listed in OB
2 Thomas
9/10/02
NAI

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NC

September 9, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,432,931, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,432,931 issued on August 13, 2002. Therefore, Teva anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

PE/jbp
Enclosures

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TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

September 10, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

Dear Mr. Buehler:

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Sincerely,

PE/jbp
Enclosures

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SEP 1 1 2002
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Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

September 11, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

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Sincerely,

PE/jbp
Enclosures

RECEIVED
SEP 12 2002
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

September 12, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,432,931

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Sincerely,

PE/jbp
Enclosures

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SEP 13 2002
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3142
FAX: (215) 591 8812

Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

NEW CORRESP
NC NAI 09-OCT-2002

October 7, 2002

TELEPHONE AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS, 5, 10, 35, 40 and 70 mg
TELEPHONE AMENDMENT

Dear Mr. Buehler:

In response to a telephone request made by Lt. Gregory Davis of your Office, Teva is providing the following statements:

1. No suit was brought against Teva within the statutory 45 day period from receipt of notice for U. S. patent no. 6,090,410 for the 5, 10 and 40 mg products.
2. No suit was brought against Teva within the statutory 45 day period from receipt of notice for U. S. patent no. 6,194,004 for the 10 mg product.

This information is provided toward the continued review of this application. If there are any further questions, please do not hesitate to contact me by telephone at (215) 591-3142 or via facsimile at (215) 591-8812.

Sincerely,

Deborah Jaskot

DJ

RECEIVED
OCT 0 8 2002
OGD / CDER

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-710 Applicant Teva Pharmaceuticals USA
Drug Alendronate Sodium Tablets Strength 5mg, 10mg, 35mg, 40mg, 70mg

APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

1. Project Manager, Team 5 Wanda Pamphile — Review Support Br
   DRAFT Package Date 8/28/02 Initials WP
   FINAL Package Date _____ Initials _____

Application Summary:

Original Rec'd date 9/29/99
Date Acceptable for Filing 9/29/99 J
Patent Certification (type) PIV
Date Patent/Exclus.expires See Print out
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD = Fosamax
Date checked 9/11/02 NDA# 20560
Nothing Submitted ☐
Written request issued ☒
Study Submitted ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 7/12/02
Date of Office Bio Review 9/30/99, 7/12/00, 4/27/01, 10/30/02
Date of Labeling Approv. Sum 7/9/02
Date of Sterility Assur. App. _____
Methods Val. Samples Pending Yes ☒ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

2. Gregg Davis **PPIV ANDAs Only** Date 11-OCT-2002 Initials GD — Date 11-OCT-2002 Initials GD
   Supv., Reg. Support Branch

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐
Has case been settled: Yes ☒ No ☒
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☒ No ☒
Comments: TEVA is first for 5, 10, 40 & 70mg all patents - this is a very complicated scenario invoking the 7 1/2 yr clock for 5, 10 & 40mg & the 30 mos clock for 70mg - this application is also split using both definitions of court. *see attached for details

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
Date Checked 12/20/02 KW
Nothing Submitted ☐
Written request issued ☒ 10/31/02
Study Submitted ☐
RLD = Fosamax Tablets 5mg (base), 10mg, 35mg, 40mg + 70mg (base) Merck and Co., Inc.
NDA 20-560

3. Div. Dir./Deputy Dir.
   Chemistry Div. I ~~OCP II~~
   Comments:
   Date 12/6/02
   Initials [illegible]

The conc see from is satisfactory for TA.

REVIEWER:

FINAL ACTION

4. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)
N/A. ANDA 76-184 (Barr) was TA'ed 4/23/02 (35 and 70 mg)
ANDA 75-711 (Teva) was TA'ed 7/24/02 (5, 10, and 40 mg)

Date _____
Initials _____

5. Peter Rickman
Acting Director, DLPS
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable ES dated 7/12/02 (Rec'd 12/20/02) w/o OAI. Data noted Bioequivalence study (single-dose fasting) on the 40 mg strength found acceptable 12/30/99. Dissolution data on 5 mg, 10 mg and 40 mg strengths also found acceptable. Waivers granted to expand to 10 mg strengths. Studies performed by Phoenix Clinical Research, Montreal (Canada) (dosing) and Phoenix International (analytical). These facilities have an acceptable DSI inspectional history. Office-level bio (5, 10, and 40 mg strengths) endorsed 12/30/99. Revised dissolution specs endorsed 4/23/01. Office-level bio endorsed 7/12/00. Bio study for 70 mg strength found acceptable 4/26/01. Dissolution specs also acceptable. Dosing and analytical studies performed by Anapharm. This facility has an acceptable DSI inspection history. Office-level bio endorsed 4/20/01 (70 mg strength). Bio waiver granted for 35 mg strength 10/30/02. Office-level bio endorsed 10/30/01 (35 mg strength).

Date 12/27/02
Initials Per Test for

5. Robert L. West
Acting Deputy Director, OGD

Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☒ No☐; Petition: Yes☐ No☒
Comments: Labeling found acceptable for TA on 7/9/02. CMC acceptable 12/4/02. Methods validation completed and found acceptable.
Patent litigation between TEVA and NDA/patent holders is ongoing.
This application is recommended for tentative approval

Date 12/27/2002
Initials Per Test for

6. Gary Buehler
Director, OGD
Comments:

Date 12/27/2002
Initials Per Test for

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Team Leader, Review Support Branch Wanda Langhale

Date @ 12/27/02
Initials CL

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
1:40 Time notified of approval by phone 1:45 Time approval letter faxed

FDA Notification:
12/27/02 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
12/27/02 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

V:\reports\approval\approvrou2.doc

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

January 2, 2003

NDA/ORIG
NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

NAI
P.M.P
1/13/03

'077- Found Valid
~Teva will appeal.

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
STATUS OF LITIGATION REGARDING U.S. PATENT # 4,621,077

Dear Mr. Buehler:

On December 2, 2002 the United States District Court for the District of Delaware issued a Final Judgement Order regarding litigation between Merck & Co. (the plaintiff) and Teva Pharmaceuticals USA, Inc. and Zenith Goldline Pharmaceuticals, Inc. (the defendants) regarding U.S. Patent # 4,621,077. This order provides ruling in favor of the plaintiff and orders that the pending ANDAs held by the defendants not be approved prior to August 6, 2007, the expiration of U.S. Patent # 4,621,077. A copy of this order is enclosed.

Further, Teva Pharmaceuticals USA, Inc. has filed for an appeal of this court decision. Correspondence regarding this appeal process and its outcome will be provided to this pending application as it becomes available.

This information is submitted for your review and approval. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/rsv
Enclosures

NAI VAF 1/21/03

RECEIVED
JAN 0 3 2003
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 6, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- RECOGNITION OF PEDIATRIC EXCLUSIVITY

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing certification that recognizes the recent issuance of Pediatric Exclusivity to NDA #20-560 for Fosamax® (Alendronate Sodium Tablets) which appears in an April 30, 2003 Patent Term Extension and New Patents docket. A copy of the relevant docket pages is provided herein. In addition, it has also come to our attention that U.S. Patent # 5,804,570 is no longer listed in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations.* Please note that Ms. Maryann Holovack of your office confirmed on May 2, 2003 that Merck & Co. has, in fact, de-listed this patent. As such, reference to U.S. Patent # 5,804,570 has been removed from Teva's patent certification.

Please find enclosed herein an updated Patent Certification and an updated Exclusivity Statement. Since the enclosed Patent Certification and Exclusivity Statement are not revised with regard to intent, re-notification to the holder of NDA # 20-560, Merck, is not deemed necessary. It is Teva Pharmaceuticals USA's opinion that submission of this information does not constitute a "new" patent certification requiring the submission of information as cited in 21 CFR 314.95(a) as these requirements have already been fulfilled.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/rsv
Enclosures

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MAY 7 - 2003
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Administrative Offices:
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Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

July 31, 2003

NEW CORRESP

UNSOLICITED AMENDMENT

NC

NAE 8/28/03

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
UNSOLICITED AMENDMENT – ADDENDUM TO MAY 6, 2003 PATENT AMENDMENT

Dear Mr. Buehler:

We submit herewith an Unsolicited Amendment to the above-referenced pending ANDA for the purpose of revising the Exclusivity Statement provided in our May 6, 2003 correspondence. More specifically, typographical errors have been corrected to show the appropriate expiration year. Please find enclosed herein a revised Exclusivity Statement.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/jb
Enclosure

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AUG 0 1 2003
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1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

September 24, 2003

NEW CORRESP

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively approved ANDA for the purpose of providing an additional patent certification statement. TEVA has recently become aware of the existence of U.S. Patent No. 6,623,755, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, TEVA wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,623,755 issued on September 23, 2003. Therefore, TEVA anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

In accord with FDA's final rule "Application for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of ANDAs Certifying That a Patent Claiming a Drug is Invalid or Will Not Be Infringed", it is TEVA's understanding that Notice is not required to be sent to the NDA holder or patent owner for this patent as TEVA is already subject to a thirty month stay for Alendronate Sodium Tablets.

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Sincerely,

PE/jbp
Enclosures

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SEP 2 4 2003
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

September 24, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

September 25, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
N/C

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

PE/jbp
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SEP 26 2003
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Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC

September 26, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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PE/jbp
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Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC

September 29, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

September 29, 2003

NEW CORRESP
NC

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

PE/jbp
Enclosures

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NAI
10-9-03

Administrative Offices:
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Phone: (215) 591 3141
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

September 30, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

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Sincerely,

PE/jbp
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Administrative Offices:
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North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 1, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC.

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

PE/jbp
Enclosures

OCT 0 2 2003

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 2, 2003

NEW CORRESP
NC

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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PE/jbp
Enclosures

OCT 0 6 2003

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FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 3, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

PE/jbp
Enclosures

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OCT 0 6 2003
OGD/CDER

NAI
'755 Not listed in OB
Marianne M Bim
10/22/03

Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
(NC)

October 6, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

NC

October 7, 2003

PATENT AMENDMENT

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Food and Drug Administration
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRES.

NC

October 8, 2003

PATENT AMENDMENT

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Food and Drug Administration
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PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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TEVA Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively approved ANDA for the purpose of providing an additional patent certification statement. TEVA has recently become aware of the existence of U.S. Patent No. 6,623,755, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, TEVA wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,623,755 issued on September 23, 2003. Therefore, TEVA anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

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Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

PE

OCT 0 9 2003

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

October 9, 2003

PATENT AMENDMENT

NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

Dear Mr. Buehler:

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PE/jbp
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OCT 1 0 2003

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Phone: (215) 591 3141
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 10, 2003

PATENT AMENDMENT

NEW CORRESP
NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

PE/jbp
Enclosures

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OCT 1 4 2003
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Philip Erickson, R.Ph.
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October 13, 2003

Gary Buehler, Director
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Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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PE/jbp
Enclosures

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OCT 1 4 2003
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 14, 2003

Gary Buehler, Director
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Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESPONDENCE
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

PE/jbp
Enclosures

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OCT 1 5 2003
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NAI
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

October 15, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

PE/jbp
Enclosures

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OCT 16 2003
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NAI
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NOT in 013
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 16, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

PE/jbp
Enclosures

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OCT 17 2003
OGD/CDER

NAI NOT 7/03
10/27/03

TEVA

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FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC

October 17, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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RECEIVED
OCT 20 2003
OGD/CDER

Sincerely,

PE/jbp
Enclosures

NAI
NOT in OB
Bin
10/27/03

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 20, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
No

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

Phil D Erickson

PE/jbp
Enclosures

RECEIVED
OCT 21 2003
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NAI
Christine Bina
Not in OB
10/27/03

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1090 Horsham Road, PO Box 1090
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Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 21, 2003

NEW CORRESP
NC

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

PE/jbp
Enclosures

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10/27/03

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FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP

NC

October 22, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

PE/jbp
Enclosures

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OCT 23 2003
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NAL Not in 505 or dockets 10/29/03

TEVA

Administrative Offices:
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Philip Erickson, R.Ph.
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NEW CORRESP
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October 23, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

Philip Erickson

RECEIVED
OCT 24 2003
OGD/CDER

PE/jbp
Enclosures

NAI 1755 not in OB or dockets 10/31/03

Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 24, 2003

Gary Buehler, Director
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Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

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Sincerely,

PE/jbp
Enclosures

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OCT 27 2003
OGD/CDER

NAI
1755 not in
OB or Docket 3 Bin
10/31/03

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Philip Erickson, R.Ph.
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October 27, 2003

Gary Buehler, Director
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7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
DC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively approved ANDA for the purpose of providing an additional patent certification statement. TEVA has recently become aware of the existence of U.S. Patent No. 6,623,755, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, TEVA wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,623,755 issued on September 23, 2003. Therefore, TEVA anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

In accord with FDA's final rule "Application for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of ANDAs Certifying That a Patent Claiming a Drug is Invalid or Will Not Be Infringed", it is TEVA's understanding that Notice is not required to be sent to the NDA holder or patent owner for this patent as TEVA is already subject to a thirty month stay for Alendronate Sodium Tablets.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

RECEIVED
OCT 28 2003
OGD/CDER

PE/jbp
Enclosures

NAI
-955 not listed
06 or dockets
11/6/03

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC

October 28, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively approved ANDA for the purpose of providing an additional patent certification statement. TEVA has recently become aware of the existence of U.S. Patent No. 6,623,755, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, TEVA wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,623,755 issued on September 23, 2003. Therefore, TEVA anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

PE/jbp
Enclosures

RECEIVED
OCT 29 2003
OGD/CDER

NAI
'755 not listed in
OB or dockets
11/6/03

TEVA

Administrative Offices:
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1090 Horsham Road, PO Box 1090
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Phone: (215) 591 3141
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC

October 29, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively approved ANDA for the purpose of providing an additional patent certification statement. TEVA has recently become aware of the existence of U.S. Patent No. 6,623,755, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, TEVA wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,623,755 issued on September 23, 2003. Therefore, TEVA anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

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Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED
OCT 30 2003
OGD/CDER

NAI patent '755 not listed in OB or dockets S. Middleton
11/13/03

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 30, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW/CORRESP
(NC)

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively approved ANDA for the purpose of providing an additional patent certification statement. TEVA has recently become aware of the existence of U.S. Patent No. 6,623,755, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, TEVA wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,623,755 issued on September 23, 2003. Therefore, TEVA anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

In accord with FDA's final rule "Application for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of ANDAs Certifying That a Patent Claiming a Drug is Invalid or Will Not Be Infringed", it is TEVA's understanding that Notice is not required to be sent to the NDA holder or patent owner for this patent as TEVA is already subject to a thirty month stay for Alendronate Sodium Tablets.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED
OCT 31 2003
OGD/CDER

NAI patent 1755 not listed in OB or dockets S. Middleton
11/13/03

Administrative Offices:
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North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESP
NC

October 31, 2003

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,623,755

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively approved ANDA for the purpose of providing an additional patent certification statement. TEVA has recently become aware of the existence of U.S. Patent No. 6,623,755, which on its face, has been assigned to Merck and Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Fosamax® Tablets, TEVA wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,623,755 issued on September 23, 2003. Therefore, TEVA anticipates that Merck, as owner of NDA 20-560 for Fosamax® Tablets and owner of this patent, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

In accord with FDA's final rule "Application for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of ANDAs Certifying That a Patent Claiming a Drug is Invalid or Will Not Be Infringed", it is TEVA's understanding that Notice is not required to be sent to the NDA holder or patent owner for this patent as TEVA is already subject to a thirty month stay for Alendronate Sodium Tablets.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

RECEIVED
NOV 0 3 2003
OGD/CDER

PE/jbp
Enclosures

NAI
'077 - found valid - in US Court of Appeals. - 329 still under appeal.
3/25/04

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
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philip.erickson@tevausa.com

February 20, 2004

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

XP

ANDA # 75-710
ALENDRONATE SODIUM TABLETS
FINAL OUTCOME OF PATENT LITIGATION FOR U.S. PATENT 4,621,077

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an amendment to the above-referenced ANDA to provide the result of patent litigation for U.S. Patent 4,621,077. As reported to the Agency in a January 2, 2003 patent amendment, TEVA was sued by Merck and Company for the '077 patent and Merck prevailed in that litigation. The decision was appealed by TEVA in the United States Court of Appeals for the Federal Circuit. On October 30, 2003, the Court of Appeals affirmed the decision of the District Court in a 2-1 vote. Please find enclosed a copy of both the affirming order and the dissenting order. The '077 patent is listed for all strengths of Alendronate Sodium Tablets.

With respect to litigation for U.S. Patent 5,994,329, Merck prevailed at the District Court level, and TEVA has filed an appeal. The outcome of the appeal is awaited, and will be reported to the Agency once available. The '329 patent affects only the 35 mg and 70 mg strengths of Alendronate Sodium Tablets.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

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Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

April 29, 2005

ORIG AMENDMENT
N-AA

UNSOLICITED AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-710
ALENDRONATE SODIUM TABLETS, 5mg, 10 mg, 35 mg, 40 mg and 70 mg
UNSOLICITED AMENDMENT – ALTERNATE SOURCE OF THE DRUG SUBSTANCE

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above referenced tentatively approved Abbreviated New Drug Application to provide for an alternate source of the drug substance, Alendronate Sodium Trihydrate, (b) (4). The proposed source is:

Assia Chemical Industries, Ltd. (Teva-Tech)
Ramat Hovav
Emek Sara, Beer Sheva 84874, Israel

The following information is enclosed in support of the change:

Attachment 1: A letter of authorization from Assia Chemical Industries Ltd., granting the Agency permission to review the Drug Master File for Alendronate Sodium Trihydrate on behalf of Teva Pharmaceuticals USA. Please note that Assia submitted their DMF documentation to the Food and Drug Administration on April 28, 2005. As such, a DMF number has yet to be assigned.

Attachment 2: Report comparing the chemical and physical properties of the drug substance from the proposed source Teva – Tech and the source submitted in the original Abbreviated New Drug Application (b) (4)

Attachment 3: Drug substance procedures manual (R19668RM, Version 3.0, Official Date: 3/7/02).

Attachment 4: Teva USA and Teva-Tech (Plantex) Certificates of Analysis for the proposed Teva- Tech drug substance (Drug Substance Lot No.14121 and 14124) used in the exhibit batch (Exhibit Batch Lot No. 1615-096).

Attachment 5: A summary of the ingredients used in the manufacture of the exhibit batch (drug substance and excipients) and their respective Certificates of Analysis.

Attachment 6: Copy of the Executed Batch record, Packaging Record, and Packaging Disbursement Summary for Alendronate Sodium Tablets, 40 mg manufactured using the proposed drug substance source, Teva-Tech.

Attachment 7: Teva Finished Product Certificate of Analysis for drug product manufactured with proposed Teva-Tech drug substance (Exhibit Batch Lot No. 1615-096) and Teva Finished product Certificate of Analysis for drug product manufactured with the originally submitted drug substance supplied by (b) (4) (reference validation batches 17267, 17268, 17269).

Attachment 8: Dissolution Profiles comparing drug product manufactured with Teva-Tech drug substance ((Exhibit Batch Lot No. 1615-096) and drug product manufactured with a drug substance supplied by (b) (4) (reference validation batches 17267, 17268, 17269).

Attachment 9: 12 weeks accelerated (40°C75%RH) and 12 months controlled room temperature stability data on Alendronate Sodium Tablets. Based on stability data, we propose the retention of the product's 24-month expiry.

Policy and Procedure Guide #22-90 states that only one batch; the bioequivalency strength, is needed for a second or subsequent source of NDS to support all strengths. Please be advised that although two separate bioequvalency studies were conducted for the drug product contained within ANDA # 75-710, specifically the 40 mg and 70 mg strengths, we request that the data submitted herein be deemed supportive for all strengths of Alendronate Sodim Tablets. Our request is based on the fact that 5 mg, 10 mg, 40mg and 70 mg strengths are dose similar formulations and the 35mg and 70 mg are dose proportional.

This information is submitted for your review and approval. If you have any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile (215) 591-8812.

Sincerely,

PE/ak
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

December 12, 2006

ORIGINAL

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ADDENDUM TO TEVA'S 4/29/05 MINOR AMENDMENT

ORIG AMENDMENT
AC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg and 70 mg
ADDENDUM TO TEVA'S 4/29/05 MINOR AMENDMENT (PROPOSAL OF AN ALTERNATE SOURCE OF THE DRUG SUBSTANCE)

RECEIVED
DEC 13 2006
OGD / CDER

Dear Mr. Buehler:

Regarding the above-referenced tentatively-approved Abbreviated New Drug Application, TEVA Pharmaceuticals USA submits herewith an addendum to our April 29, 2005 minor amendment. Said amendment provided for an alternate source of the drug substance, Alendronate Monosodium Trihydrate, (b) (4), and was supported by a 40 mg strength batch. To further support use of this alternate material, we submit herewith a 70 mg strength batch manufactured using the proposed API.

The source proposed in TEVA's April 29, 2005 amendment, and further supported herein is:

Assia Chemical Industries, Ltd. (Teva-Tech)
Ramat Hovav
Emek Sara, Be'er Sheva 84874, Israel

The following information is enclosed herein:

Attachment 1: Letter of authorization for Assia Chemical Industries' DMF for Alendronate Monosodium Trihydrate (#18327). Please note that at the time of TEVA's April 29, 2005 amendment, a number had not yet been assigned to Assia's Drug Master File. A statement from Assia regarding OVIs is also provided.

Attachment 2: A report comparing the chemical and physical properties of the drug substance manufactured by Assia Chemicals and drug substance manufactured by the original source, (b) (4) Specifically, a comparison of lots of drug substance that were used in the exhibit and reference finished product batches is presented.

Attachment 3: TEVA and supplier Certificates of Analysis for the proposed Assia drug substance (TEVA Lot #17365; Assia Lot #728400103) used in the manufacture of the Alendronate Sodium Tablets, 70 mg exhibit batch (Lot 1917-019).

Attachment 4: A summary of the ingredients used in the manufacture of exhibit batch #1917-019 (drug substance and excipients) and their respective Certificates of Analysis. Please refer to **Attachment 3** for the Certificate of Analysis for the drug substance.

Attachment 5: Copy of the executed batch record, packaging record (packaged at (b) (4) (b) (4), and Packaging Disbursement Summary for Alendronate Sodium Tablets, 70 mg (Lot 1917-019) manufactured using the proposed drug substance manufactured by Assia.

Please note that TEVA added (b) (4) as a contract packager to this ANDA via an April 26, 2002 Unsolicited Amendment- Addition of Unit Dose Packaging. (b) (4) has changed its name to (b) (4) (b) (4), and therefore the documents contained herein reflect the new name. A letter outlining the name change is provided in this attachment for your reference.

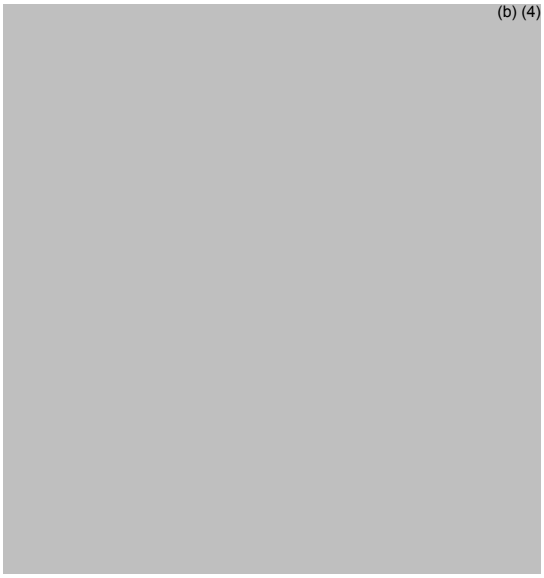
Attachment 6: Teva finished product Certificates of Analysis for Lot No. 1917-019 manufactured with the proposed Assia drug substance and for drug product manufactured with the originally submitted drug substance supplied by (b) (4) (reference batches 20362D, 20363D and 20364D).

Attachment 7: Comparative dissolution profiles generated for drug product manufactured with Assia drug substance (Lot No. 1917-019) and drug product manufactured with material supplied by (b) (4) (reference batches 20362D, 20363D and 20364D). Also provided in this report are f_1 calculations showing the comparability of the dissolution of the exhibit batch to that of the three reference batches.

Attachment 8: 12-week accelerated (40°C75%RH) and 3-month controlled room temperature stability data for Alendronate Sodium Tablets, 70 mg (Lot 1917-019). Based on these data, we propose retention of the product's 24-month expiry.

In addition, the following contract facilities are proposed as alternate sites for labeling of packaged finished drug product for future commercial batches. The sites may be used to apply container labels and/or package outsert labeling. Upon completion of this operation, the labeled and outserted product will be returned to Teva Pharmaceuticals USA's warehouse for holding. Commercial distribution will commence only after final approval of this ANDA is granted.

In support of the use of these labeling facilities, statements of cGMP compliance and a Generic Drug Enforcement Act Statement for each site are enclosed in **Attachment 9**.



This information is submitted for your review and approval. Should you have any questions on the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile (215) 591-8812.

Sincerely,

Philip Erickson/RS

PE/jbp
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

May 18, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

AMENDMENT

N-000-MC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg 35 mg, 40 mg and 70 mg
AMENDMENT – CLARIFICATION OF LEGAL STATUS

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced tentatively approved ANDA for the purpose of providing a clarification of legal status with regard to multiple patents listed for the reference listed drug, Fosamax® Tablets.

The table below summarizes patent numbers, expiration dates, the strengths of the drug product protected by each patent and Teva's legal status with regard to each patent.

U.S. Patent #	**Expiration Date (Patent + PED)**	**TEVA's Certification**	**Applicable Strengths**	**Suit filed** Yes/ No	**Suit Status**
4,621,077	2/6/08	PIV	All 5 strengths	Yes	Patent upheld
5,358,941	6/02/13	PIV	All 5 strengths	Yes	Suit dismissed
5,681,590	6/02/13	PIV	All 5 strengths	Yes	Suit dismissed
5,849,726	12/06/15	PIV	All 5 strengths	Yes	Suit dismissed
6,008,207	12/06/15	PIV	All 5 strengths	Yes	Suit dismissed
6,090,410	6/02/13	PIV	All 5 strengths	Yes: 35mg and 70mg only	Suit dismissed
5,994,329	1/17/19	PIV	35mg and 70mg only	Yes	Patent invalid
6,015,801	1/17/19	PIV	35mg and 70mg only	Yes	Suit dismissed

U.S. Patent #	Expiration Date (Patent + PED)	Certification	Applicable Strengths	Suit filed Yes/ No	Suit Status
6,225,294	1/17/19	PIV	35mg and 70mg only	Yes	Suit dismissed
6,194,004	6/02/13	PIV	10mg only	No	N/A

Enclosed in **Attachment 1**, please find printouts of the all patent listings from the electronic Orange Book.

Please note that U.S. Patent # 5804570 had been listed at the time of filing of the original ANDA, however, it had since been de-listed from the Orange Book and thus is not addressed herein.

Reference is made to our February 20, 2004 patent amendment to this ANDA in which we informed the Agency of an appeal filed by TEVA Pharmaceuticals USA in the United States Court of Appeals for the Federal Court with regard to U.S. Patent 5,994,329. We hereby inform the Agency that on January 28, 2005, the Court of Appeals vacated the judgment of the district court in a 2-1 vote and held the claims of said patent invalid and not infringed. Enclosed in **Attachment 2**, please find a copy of both the affirming order and the dissenting order.

A copy of the court decision which upheld the U.S. Patent # 4,621,077 was provided to the Agency in the aforementioned February 20, 2004 Patent Amendment.

Additionally, enclosed in **Attachment 3**, please find the court dismissal orders with regard to U.S. Patent Nos. 5,358,941, 5,681,590, 5,849,726, 6,008,207, 6,090,410, 6,015,801 and 6,225,294. For ease of your review, the table below summarizes patent numbers, relevant product strengths and civil action numbers for the corresponding suits.

U.S. Patent #	Applicable Strengths	Civil Action #
5,358,941	40 mg 5 mg, 10 mg	00-035 (JJF) 00-052 (JJF)
	35 mg, 70 mg	01-048 (SLR)
5,681,590	40 mg 5 mg, 10 mg	00-035 (JJF) 00-052 (JJF)
	35 mg, 70 mg	01-048 (SLR)
5,849,726	40 mg 5 mg, 10 mg	00-035 (JJF) 00-052 (JJF)
6,008,207	40 mg 5 mg, 10 mg	00-035 (JJF) 00-052 (JJF)
	35 mg, 70 mg	01-048 (SLR)
6,090,410	35 mg, 70 mg	01-048 (SLR)
6,015,801	35 mg, 70 mg	Consolidated Action 01-048 (JJF)
6,225,294	35 mg, 70 mg	Consolidated Action 01-048 (JJF)

In summary, please note that all patents except for the U.S. Patent # 4,621,077 (the '077 patent) have been either deemed invalid and not infringed or have been dismissed by the courts.

Therefore, Teva's ANDA # 75-710 for Alendronate Sodium Tablets is eligible for final approval upon expiration of the '077 patent and its associated pediatric exclusivity on February 6, 2008.

We draw your attention to our April 29, 2005 minor amendment and a December 12, 2006 addendum to this amendment, which provided for an alternate source of the drug substance. To this date, we have not received comments from the Agency with regard to these submissions.

We look forward to your review and final approval of the above-referenced tentatively approved ANDA. Should you have any questions, please feel free to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson PE

PE/dl
Enclosures

Pediatric Use Labeling Package

Product Name: Fosamax® (Alendronate Sodium) Tablets

Approval of generic applications expected on 2/7/2008

Background

The Reference Listed Drug, Fosamax® tablets [NDA 20-560, Merck Research Laboratories] received 3 years Waxman-Hatch marketing exclusivity for miscellaneous exclusivity (M-51 – information added to labeling regarding osteogenesis imperfecta study), which will expire December 21, 2008.

On January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) was signed into law ("Best Pharmaceuticals for Children Act" (BPCA). Section 11). The Act addresses the approval of drugs under 505(j) when pediatric information protected by exclusivity has been added to the labeling. BPCA section 11(a)(2) [21 USC 355a(l)(2)] amends section 505(j) of the FD&C Act to allow approval of an ANDA that omits a pediatric indication or other aspect of labeling pertaining to pediatric use when that labeling is protected by patent or exclusivity. A labeling statement stating that the ANDA is not labeled for pediatric use because of marketing exclusivity is required. In addition, the statute directs FDA to include in the ANDA labeling a statement of any appropriate pediatric contraindications, warnings, or precautions considered necessary.

1. Are there any issues of safety or effectiveness for the remaining conditions of use when the protected pediatric information is removed from the labeling?
2. Are the proposed labeling statements acceptable?
3. Are there any statements of appropriate pediatric contraindications, warnings, or precautions that should be included in the generic drug labeling?

Request for consultation for Fosamax® Tablets

Division of Metabolism and Endocrinology Products

Division consult request form.pdf

Formatted Table

Side by side comparison (Table) of previously approved and proposed alendronate sodium tablets labeling related to the Waxman-Hatch exclusivity

Alendronate BPCA CONSULT COMPARIS

Fosamax Tablets (NDA 20-560/SLR-046) Approved November 11, 2005	Fosamax NDA 20-560SLR046.pdf
Fosamax Tablets (NDA 20-560/SE1-038) (Waxman Hatch Marketing Exclusivity) Approved December 21, 2005	Fosamax NDA 20-560SE1-038.pdf
Patent and Exclusivity Information for Fosamax® Tablets	Alendronate patent and exclusivity.pdf
Office of Pediatric Drug Development and Program Initiatives recommendation	PMHS Recommendation.pdf

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: Mary H. Parks, M.D. Director, Division of Metabolism and Endocrinology Products Office of Drug Evaluation II Center for Drug Evaluation and Research			FROM: Ruby (Chi-Ann) Wu, chi-ann.wu@fda.hhs.gov, HFD-613, Labeling Review Branch, Office of generic Drugs	
DATE: September 21, 2007	IND NO.	NDA NO. 20-560 (tablets) (combined insert with 21-575 (Fosamax Oral Solution)	TYPE OF DOCUMENT: Proposed Labeling for original generic applications	DATE OF DOCUMENT
NAME OF DRUG Fosamax® (Alendronate Sodium) Tablets		Official Drug Name: Alendronate Sodium Tablets	CLASSIFICATION OF DRUG Bisphosphonate-inhibitor of osteoclast-mediated bone resorption	DESIRED COMPLETION DATE October 26, 2007
NAME OF FIRM: Merck				

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL	PRE NDA MEETING	RESPONSE TO DEFICIENCY LETTER
PROGRESS REPORT	END OF PHASE II MEETING	FINAL PRINTED LABELING
NEW CORRESPONDENCE	RESUBMISSION	LABELING REVISION
DRUG ADVERTISING	SAFETY/EFFICACY	ORIGINAL NEW CORRESPONDENCE
ADVERSE REACTION REPORT	PAPER NDA	FORMULATIVE REVIEW
MANUFACTURING CHANGE/ADDITION	CONTROL SUPPLEMENT	■OTHER: **Pediatric Labeling**

MEETING PLANNED BY _____

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDI ES PROTOCOL REVIEW OTHER	CHEMISTRY PHARMACOLOGY BIOPHARMACEUTICS OTHER

III. BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
PROTOCOL– BIOPHARMACEUTICS	BIOAVAILABILITY STUDIES
IN–VIVO WAIVER REQUEST	PHASE IV STUDIES

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g., POPULATION EXPOSURE ASSOCIATED DIAGNOSES	SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC REACTIONS *(List below)*	POISON RISK ANALYSIS
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS

A 3-year Waxman Hatch exclusivity was granted to Merck for Fosamax® (Alendronate Sodium) Tablets. This exclusivity will expire on December 21, 2008. See attached for additional information.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY
Ruby (Chi-Ann) Wu	Electronic-DFS and email

FORM FDA 3291 (7/83)

3 pages of draft labeling have been removed (b)(4)

Copy of Reference Listed Drug labeling removed

Patent and Exclusivity Search Results from query on Appl No 020560 Product 004 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020560	004	4621077	AUG 06,2007			U-114
020560	004	4621077*PED	FEB 06,2008			U-114
020560	004	5358941	DEC 02,2012			
020560	004	5358941*PED	JUN 02,2013			
020560	004	5681590	DEC 02,2012			
020560	004	5681590*PED	JUN 02,2013			
020560	004	5849726	JUN 06,2015			
020560	004	5849726*PED	DEC 16,2015			
020560	004	5994329	JUL 17,2018			
020560	004	5994329*PED	JAN 17,2019			
020560	004	6008207	JUN 06,2015			
020560	004	6008207*PED	DEC 06,2015			
020560	004	6015801	JUL 17,2018			U-353
020560	004	6015801*PED	JAN 17,2019			U-353
020560	004	6090410	DEC 02,2012			
020560	004	6090410*PED	JUN 02,2013			
020560	004	6225294	JUL 17,2018			
020560	004	6225294*PED	JAN 17,2019			

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020560	004	M-51	DEC 21,2008

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

5. U.S. Patent Nos. RE 36481 and RE 36520 were relisted for Zocor (NDA 19-766) pursuant to the decision and related order in Ranbaxy Labs. v.Leavitt, No. 05-1838 (D.D.C. April 30, 2006). The '481 and '520 patents remained listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act were triggered and run. For additional information on this matter, please refer to Docket Nos. 2005P-0008 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through July, 2007
Patent and Generic Drug Product Data Last Updated: August 16, 2007

Exclusivity Codes

This page defines the exclusivity codes.

Code	Definition
M-51	INFORMATION ADDED TO LABELING REGARDING OSTEOGENESIS IMPERFECTA STUDY

View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
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Orange Book Data Updated Through July, 2007
Patent and Generic Drug Product Data Last Updated: August 16, 2007

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

/s/

Ruby Wu

8/16/2007 05:49:22 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: September 21, 2007

From: Hari Cheryl Sachs, MD, Medical Officer
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff

Through: Lisa Mathis, MD, OND Associate Director
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff

To: Gary Buehler, RPh, Director
Office of Generic Drugs

Re: Proposed labeling for alendronate tablets

Office Question:
The Office of Generic Drugs (OGD) has consulted the Pediatric and Maternal Health Staff (PMHS) to request a review of the proposed labeling for the generic product alendronate tablets.

Material Reviewed:
Consult from OGD
Fosamax® labeling (November 2, 2005), pediatric labeling changes for Fosamax® (December 21, 2005), and labeling revision (December 28, 2006)
Comparison chart of labeling for the generic drug and Fosamax®
Patent and exclusivity data for NDA 20-560 Fosamax® tablets and 21-575 Fosamax® oral solution

Background:
Best Pharmaceuticals for Children Act
Signed into law on January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) addresses the approval of drugs under 505(j) when pediatric information protected by exclusivity has been added to the labeling. BPCA section 11(a)(2) [21 USC 355a(l)(2)] states:

"(2) LABELING...The Secretary may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling... include--

(A) a statement that, because of marketing exclusivity for a manufacturer, ...

(i) the drug is not labeled for pediatric use; or

(ii) in the case of a drug for which there is an additional pediatric use, ... the drug is not labeled for the pediatric use ...

(B) a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary."

Regulatory History for alendronate

On September 29, 1995, the FDA approved Merck, Fosamax® (alendronate) tablets, NDA 20-560) for the treatment of postmenopausal osteoporosis in women and Paget's disease of bone in men and women. The labeling indicated that safety and effectiveness in pediatric patients have not been established.

Labeling has since been expanded to include the indications of prevention of osteoporosis (April 25, 1997), the prevention of fractures in the treatment of postmenopausal osteoporosis (April 25, 1997), treatment of glucocorticoid-induced osteoporosis in men and women (June 16, 1999) and to increase bone mass in men with osteoporosis (Sept 29, 2000). Fosamax® oral solution (NDA 21-575) was approved on September 17, 2003; labeling is combined for both dosage forms.

On December 21, 2005, the FDA approved revisions to the Fosamax® Tablets (NDA 20-560) labeling to reflect that effectiveness has not been established in children, specifically, that although alendronate improved lumbar spine bone mineral density z score, treatment did not reduce fracture risk and to describe adverse events, including delayed fracture healing and non-union. Based on the pediatric studies performed in response to the alendronate WR, GSK was awarded three years of Waxman-Hatch exclusivity (M-51 Information added to labeling regarding osteogenesis imperfecta study), which expires on December 21, 2008. In addition, Merck was awarded pediatric exclusivity for the alendronate moiety, resulting in six additional months protection for every alendronate product marketed by Merck with patent protection or exclusivity. The longest additional protection for tablet expires December 6, 2015 and the oral solution, Jan 17, 2019.

NDA-20-560 Fosamax tablets

PATENT	**Patent Expiration Date**
4621077	Aug 6, 2007
4621077 PED	Feb 6, 2008
5358941	Dec 2, 2012
5358941 PED	Jun 2, 2013
5681590	Dec 2, 2012
5681590 PED	Jun 2, 2013
5849726	Jun 6, 2015
5849726 PED	Dec 6, 2015
6008207	Jun 6, 2015
6008207 PED	Dec 6, 2015

6090410	Dec 2, 2102
6090410 PED	Jun 2, 2013
6194004	Dec 2, 2012
6194004 PED	June 2, 2013
EXCLUSIVITY	**Exclusivity Expiration Date**
M-51	December 21, 2008

NDA-21-575 Fosamax oral solution

PATENT	**Patent Expiration Date**
4621077	Aug 6, 2007
4621077 PED	Feb 6, 2008
5462932	May 17, 2014
5994329	Jul 17, 2018
5994329 PED	Jan 17, 2019
6015801	Jul 17, 2018
6015801 PED	Jan 17, 2019
6225294	Jul 17, 2018
6225294 PED	Jan 17, 1019
EXCLUSIVITY	**Exclusivity Expiration Date**
D-87 (addition of once-weekly dosing for the treatment to increase bone mass in men with osteoporosis)	April 16, 2007
M-51	December 21, 2008

Several ANDAs have been submitted for alendronate tablets using Fosamax® Tablets (NDA 20-560) as the reference listed drug.

Discussion:
Since the labeling was changed due to the pediatric studies, the package insert for Fosamax® has been revised, along with the post-marketing adverse experience section. Parts of the labeling have been updated to reflect new information derived from the pediatric study that was performed. These sections include:

Pharmacokinetics: Special Populations (Pediatric)
Precautions: Pediatric Use
Adverse Reactons: Clinical Studies: Osteogenesis imperfecta
Patient Package Insert: General information

OGD suggests that all the new pediatric information be retained because including information that the drug was ineffective as well as unsafe is important safety information. Moreover, the disclaimer, which may be interpreted as saying the drug is approved may be potentially misleading.

Pharmacokinetics: Special Populations (Pediatric)
Labeling under this section now states that bioavailability in children is similar to adults but alendronate is not indicated for use in children.

Reviewer comment: PMHS agrees that the current disclaimer in this case can be misinterpreted. However, the information that the drug is ineffective (and potentially unsafe) in children will be effectively communicated in the Precautions: Pediatric Use section. Omitting the pK information will not in itself impact on the safe use of the generic product. PMHS suggests omitting the specific PK information while retaining the statement:

"alendronate is not indicated for use in children"

and using a revised disclaimer:

"Due to Merck's marketing exclusivity rights this drug product is not labeled for pediatric use. Descriptive pediatric pharmacokinetic information is approved for Merck's alendronate tablets and oral solution."

Precautions: Pediatric Use
The Precautions: Pediatric use section describes the clinical study in pediatric patients with osteogenesis imperfecta, highlighting that despite changes in bone mineral density, aldendronate did not reduce the risk of fracture and increased the risk of adverse events (namely delayed fracture healing). OGD recommends that this information is important for the practioner to weigh the risk/benefit.

Reviewer comment: PMHS concurs that the increased risk of an adverse event coupled with the lack of efficacy is critical to the safe use of this product. Retaining this information also avoids a potentially misleading disclaimer.

Adverse Reactions: Clinical Studies: Osteogenesis imperfecta
The Clinical Studies: OI subsection of Adverse Reactions section reiterates that alendronate is not indicated for use in children and contains additional adverse events that were not described previously in children, vomiting and fever, flu-like reactions and/or mild lymphocytopenia.

Reviewer comment: Since these AEs in children are not described elsewhere, PMHS concurs that the increased risk of adverse events coupled with the lack of efficacy is essential to the safe use of this product. Retaining this information also avoids a potentially misleading disclaimer.

Patient Package Insert: General Information about using FOSAMAX safely and effectively
Previously, the PPI only contained the statement that alendronate and all medicines should be stored out of the reach of children. The statement that alendronate is not indicated for use in children has been added.

Reviewer comment: PMHS concurs that the information that alendronate is not indicated for use in children is essential and should be retained.

Recommendation

PMHS agrees that most of the information related to pediatric studies should be retained in the generic labeling as the information impacts on the weighing of risk/benefit and the safe use of this product. With a modified disclaimer, the specific pharmacokinetic information can be safely "carved out."

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

/s/

Ruby Wu
9/21/2007 09:28:50 AM

Administrative Offices:
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1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

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October 19, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/AC

ANDA # 75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg, and 70 mg
TELEPHONE AMENDMENT – RESPONSE TO OCTOBER 19, 2007 REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced, pending Abbreviated New Drug Application in response to an October 19, 2007 telephone request made by Dr. Benjamin Danso of your Office. Specifically, Dr. Danso inquired about the use of [redacted] (b) (4) as a contract testing facility.

Please be informed that we hereby request the withdrawal of all the [redacted] (b) (4) facilities. [redacted] (b) (4) proposed in this application.

We look forward to your continued review and approval of the above-referenced ANDA. Additionally, we note that upon receipt of BPCA language from the Agency, Teva will submit updated labeling in final print format. Should you have any questions, please feel free to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/dm
Enclosures

RECEIVED
OCT 22 2007
OGD

Administrative Offices:
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1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

ORIG AMENDMENT

N/AC

November 20, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT
FINAL APPROVAL REQUESTED
(CONTAINS LABELING)

ANDA #75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg, and 70 mg
MINOR AMENDMENT – FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith a minor amendment to request final approval of the above-referenced tentatively approved ANDA in accord with a December 27, 2002 tentative approval letter received for this file. As noted in our May 18, 2007 Correspondence to this file, the only patent for which suit was filed against Teva and was subsequently upheld by the court was U.S. Patent # 4,621,077 (the '077 patent). Said patent and its corresponding pediatric exclusivity will expire on February 6, 2008. Therefore, TEVA respectfully requests final approval of this ANDA upon the expiration of pediatric exclusivity associated with the '077 patent. Please note that all patents except for the U.S. Patent # 4,621,077 (the '077 patent) have been either deemed invalid or the respective suits have been dismissed by the courts. For your convenience, a copy of the December 27, 2002 tentative approval letter is provided in **Attachment 1**.

The following documentation is submitted toward the final approval of this application:

- Twenty-four month controlled room temperature stability data for TEVA's 35 mg and 70 mg ANDA batches as well as additional submitted batches are provided in **Attachment 2.** Full 24 month controlled room temperature stability for the original executed batches of 5 mg, 10 mg, and 40 mg have already been submitted to this file. The following table summarizes the controlled room temperature stability data presented in Attachment 2.

Active Ingredient Manufacturer	[redacted] (b) (4)					
Strengths	35 mg		35 mg		70 mg	
Batch No.	1081-120		1081-120		1081-102	
Packaging Size	12s	100s	Unit Dose (4s) [redacted] (b) (4)	Unit Dose (2x10s) [redacted] (b) (4)	Unit Dose (4s) [redacted] (b) (4)	Unit Dose (2x10s) [redacted] (b) (4)
Test Interval	24 mos.	24 mos.	24 mos.		24 mos.	

Please note that we submitted an amendment on April 29, 2005 for an alternate source of the drug substance (Teva API Group). Provided in Attachment 2 are updated controlled room temperature stability reports for the batches submitted in support of this alternate API source.

Active Ingredient Manufacturer	Teva API Group/Assia Chemical Industries, Limited (Teva-Tech)	
Strengths	40 mg	70 mg
Batch No.	1615-096	1917-019
Packaging Size	100s	Unit Dose (4s) [redacted] (b) (4)
Test interval	24 months	12 months

- In addition we are proposing herein an additional 30 count packaging configuration for the 5 mg, 10 mg, and 40 mg strengths only. The proposed new configuration is approved for use for Tizanidine HCl Tablets, 4 mg (ANDA #76-284). The following table provides a summary of the new configuration.

Count	30 Tablets
Component Number	(b) (4)
Bottle Manufacturer	
Bottle Size	
Bottle Resin Manufacturer	
Bottle Resin	
Colorant Manufacturer	
Colorant	
Component Number	
Cap Manufacturer	
Cap Type	
Inner Shell Resin Manufacturer	
Inner Shell Resin	
Outer Shell Resin Manufacturer	
Outer Shell Resin	
Closure Colorant Manufacturer	
Closure Colorant	
Closure Seal Manufacturer	
Closure Seal Composition	
Closure Adhesive Manufacturer	
Closure Adhesive	

- The DMF letters of authorization, technical data, and the USP <661> and <671> testing for the proposed packaging components are provided in **Attachment 3**.

- Blank Production Scale Packaging Batch Records for the proposed 30 count configuration for the 5 mg, 10 mg, and 40 mg strengths are provided in **Attachment 4**.

- Stability summary reports for 12 weeks accelerated (40±2°C/75%±5%RH) stability conditions are provided in **Attachment 5**. Based on these data, we propose a 24-month expiration dating for the 30 count configuration proposed herein. This is in accord with the proposed 24 month expiration dating for all other packaging configurations and is in accord with our stability protocol.

Labeling:
We have updated our labeling for containers and are also providing labels for the unit dose blister card configurations and cartons. The following table summarizes the final print labeling provided on a CD in **Attachment 6**. The final print labels are provided in PDF and WORD formats and the corresponding comparisons are provided in PDF format.

Strength	Packaging Size	Label Type	Version (PDF & WORD)	Comparison (PDF)
5 mg, 10 mg, 40 mg	30s	Container	Rev. B 2/2007†	No comparison file due to new configuration
5 mg, 10 mg, 40 mg	100s	Container	Rev. B 2/2007†	Rev. B/2007 to Iss. 9/99
10 mg	1000s	Container	Rev. B 2/2007†	
35 mg	12s	Container	Iss. 2/2007	Iss. 2/2007 to Iss. 6/2002
35 mg	100s	Container	Iss. 2/2007	
70 mg	12s	Container	Iss. 2/2007	Iss. 2/2007 to Iss. 6/2002
70 mg	100s	Container	Iss. 2/2007	
35 mg	4s	Unit Dose Blister Card	Iss. 10/2007	Iss. 10/2007 to Iss. 6/2002
35 mg	4s	Carton	Iss. 2/2007	Iss. 2/2007 to Iss. 6/2002
35 mg	20s (2x10)	Unit Dose Blister Card	Iss. 2/2007	Iss. 2/2007 to Iss. 6/2002
35 mg	20s (2x10)	Carton	Iss. 3/2007	Iss. 3/2007 to Iss. 6/2002
70 mg	4s	Unit Dose Blister Card	Iss. 10/2007	Iss. 10/2007 to Iss. 6/2002
70 mg	4s	Carton	Iss. 2/2007	Iss. 2/2007 to Iss. 6/2002
70 mg	20s (2x10)	Unit Dose Blister Card	Iss. 2/2007	Iss. 2/2007 to Iss. 6/2002
70 mg	20s (2x10)	Carton	Iss. 3/2007	Iss. 3/2007 to Iss. 6/2002

†The container labeling (30s, 100s, 1000s) in WORD format for all daily dose strengths (5 mg, 10 mg, 40 mg) is: (CL) Rev. B 2-2007 (all CL daily).doc.

Please note that we have not included the final print package insert and patient package insert at this time. Upon receipt of BPCA language from the Agency, Teva will submit the updated labeling in final print format.

All procedure manuals for drug substance, excipients, and the finished product have been revised in accord Compendial updates as required. No other substantive changes have been made to the chemistry, manufacturing or control documents pertaining to this ANDA since they were last submitted.

The information provided herein is submitted toward the final approval of ANDA #75-710 for Alendronate Sodium Tablets, 5 mg, 10 mg, 35 mg, 40 mg, and 70 mg on February 6, 2008. Should there be any questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/lf
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
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ORIG AMENDMENT
N/A

December 28, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

LABELING AMENDMENT
& UPDATED EXCLUSIVITY STATEMENT

RECEIVED
DEC 28 2007
OGD

ANDA # 75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg, and 70 mg
LABELING AMENDMENT – RESPONSE TO DECEMBER 26, 2007 EMAIL CORRESPONDENCE & UPDATED EXCLUSIVITY STATEMENT

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith a labeling amendment to the above-referenced, tentatively-approved Abbreviated New Drug Application in response to a December 26, 2007 email correspondence received from Ruby Wu of the Division of Labeling and Program Support. A copy of the December 26, 2007 correspondence is provided in **Attachment 1** for reference. Comments are addressed as presented in Ms. Wu's correspondence.

1. General Comment: We have corrected the typographical error such that all labeling for the 70 mg strength now references the correct statement of "Each tablet contains 91.37 mg…"
2. Container labels for once-daily strengths: We acknowledge that the labels submitted in the November 20, 2007 amendment were found satisfactory.
3. Container labels for once weekly strengths: We have added "Once Weekly" above the established name for the 35 mg, and have relocated "Once Weekly" to appear above the established name for the 70 mg. In addition, we have corrected the bar code to match the NDC number for the bottle of 12s.
4. Unit-dose blisters (35 mg and 70 mg: 5x2): We have made the requested change.
5. Unit-dose blisters (35 mg and 70 mg: 4s): We have made the requested change.
6. Unit-dose carton (35 mg and 70 mg: 2x10): We have made the requested changes.
7. Unit-of-use carton (35 mg and 70 mg: 1x4s): We have made the requested revisions.
8. Professional Insert: We have revised our package insert in accord with the text provided in the December 26, 2007 email. In addition, we acknowledge the listing of exclusivity M-51 in the Orange Book for the reference drug product, and provide an updated exclusivity statement in **Attachment 2**.

9. Patient Weekly-Dose Leaflet: We have revised our PPI for the weekly dose to be in accord with the text provided on December 26, 2007.
10. Patient Daily-Dose Leaflet: We have revised our PPI for the weekly dose to be in accord with the text provided on December 26, 2007.

In accord with the labeling changes noted above, please find a disc in **Attachment 3** that contains all container labels, blister labels and carton labels in final print form in both Word and PDF formats. The disc also contains TEVA's revised package insert and patient leaflets in final print in Word and PDF formats. Please note the insert has been prepared in accord with the format used by the RLD such that there are two inserts that are identical, with the exception that one contains the daily-dose patient leaflet while the other contains the weekly-dose patient leaflet. In addition, the disc also contains side-by-side comparisons of each labeling piece with the version last submitted to the Agency.

We look forward to your continued review and approval of the above-referenced ANDA. Should you have any questions, please feel free to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

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D/Ac

January 10, 2008

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
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7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

ANDA # 75-710
ALENDRONATE SODIUM TABLETS, 5 mg, 10 mg, 35 mg, 40 mg, and 70 mg
TELEPHONE AMENDMENT – RESPONSE TO JANUARY 9, 2008 REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced, pending Abbreviated New Drug Application in response to a January 9, 2008 telephone request made by Mr. Simon Eng of your Office. Specifically, Mr. Eng inquired about the use of (b) (4) as a contract testing facility.

Please be informed that we hereby request the withdrawal of (b) (4), for use in QC testing of commercial finished product.

We look forward to your approval of the above-referenced ANDA. Should you have any questions, please feel free to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/rsv
Enclosures

RECEIVED
JAN 11 2008
OGD

From: West, Robert L
Sent: Monday, February 04, 2008 1:36 PM
To: Danso, Benjamin
Cc: Cai, Bing; Bykadi, Gururaj
Subject: FW: ALENDRONATE SODIUM TABLETS - DISSOLUTION

Ben:

Please file a copy of this email in DFS under TEVA's ANDA 75-710 for Alendronate Sodium Tablets USP.

Thanks,

Bob

From: Buehler, Gary J
Sent: Monday, February 04, 2008 1:32 PM
To: West, Robert L
Subject: RE: ALENDRONATE SODIUM TABLETS - DISSOLUTION

Looks like all the bases are covered.

Gary

From: West, Robert L
Sent: Monday, February 04, 2008 1:31 PM
To: Buehler, Gary J
Subject: ALENDRONATE SODIUM TABLETS - DISSOLUTION

Gary:

Last Friday, I send an email to Theresa Kehoe, Medical Officer for Merck's Fosamax in DMEP. This morning, I called her and I asked if there were any clinical significance to the current 15 minute specification in USP (former specification was 30 minutes). She contacted the new drug chemist who confirmed that the specification was added for quality control purposes only. I told her of my concern in the labeling that the product has a propensity to cause esophagitis and that there are numerous statements in the labeling about this. She also contacted the clinical pharmacology reviewer.

She agreed that the 15 minute specification in the current USP has no clinical significance.

USP has provided a letter to TEVA (on USP letterhead) stating that the USP monograph "will be revised to include tolerances that will apply to all approved manufacturers, (e.g., addition of another Dissolution test with a concomitant labeling requirement). USP intends to publish this revision in an upcoming issue of the Pharmacopeial Forum and the corresponding official date for the new Dissolution test will be indicated. The Intent to Revise Notice will also be posted on the USP Website.

Paul has endorsed TEVA's ANDA (b) (4) and forwarded it to me.

Bob

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

/s/

Simon Eng
2/5/2008 07:58:54 AM
CSO

Simon Eng
2/5/2008 07:59:09 AM
CSO

U.S. Pharmacopeia
The Standard of Quality

January 31, 2008

Deborah A. Jaskot
Vice President, Regulatory Affairs
Teva Pharmaceuticals USA
1090 Horsham Road PO Box 1090
North Wales, PA 19454-1090

William P. Rickman
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Jaskot and Mr. Rickman:

The Biopharmaceutics Expert Committee will propose a revision to the Alendronate Sodium Tablets monograph. The monograph will be revised to include tolerances that will apply to all approved manufacturers (e.g., addition of another Dissolution test with a concomitant labeling requirement).

It is anticipated that the revision proposal will be published in an upcoming issue of *Pharmacopeial Forum* and the corresponding official date for the new Dissolution test will be indicated.

This Intent to Revise Notice also will be posted on the USP Website, under Notices/Intent to Revise.

Should you have any questions, please contact Margareth Marques, Ph.D., Senior Scientist and Liaison to the Biopharmaceutics Expert Committee (301-816-8106) or mrm@usp.org.

Sincerely yours,

Darrell R. Abernethy, M.D., Ph.D.
Chief Science Officer

cc: Roger Williams, M.D.
Susan S. de Mars
Anthony DeStefano, Ph.D.
Angela G. Long
Margareth Marques, Ph.D.
Karen Russo, Ph.D.
Dee Sawicki, Teva

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www.usp.org

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/s/

Simon Eng
2/5/2008 09:47:03 AM
CSO

Simon Eng
2/5/2008 09:47:16 AM
CSO

OGD APPROVAL ROUTING SUMMARY

ANDA # 75710 Applicant TEVA Pharmaceuticals USA
Drug Alendronate Sodium Tablets, 5 mg (base), 10 mg (base), 35 mg (base), 40 mg (base) and 70 mg (base) Strength(s) _____

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 11 Jan 2008 Date 2/5/08
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)
Pediatric Exclusivity System
RLD = _____ NDA# 20-560
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐ Study Submitted ☐
Has case been settled: Yes ☒ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval
Comments:

5 and 40 mg: Originally submitted on 9/29/99 with PIVs to the '077, '941, '590 and '726 patents. ANDA filed with PIV cert on 9/29/99(LO dated 11/15/99). RRs for '077, '941, '590, '656, '726 and '570 dated 12/7/99 and litigation filed on 1/19/2000, CA 00-035 in D of DE. TEVA then submitted a PIV cert to the '207 on 2/14/2000(RR dated 3/13/00) and to the '410 on 9/20/2000(RR dated 10/10/2000. TEVA sued on the '207 on 4/18/2000 in an amendment to the 00-035 complaint.

10 mg: Originally submitted on 9/29/99 with PIVs to the '077, '941, '590, '726. ANDA filed with PIV cert on 9/29/99(LO dated 11/15/99). RRs dated 12/7/99 and litigation filed on 1/19/2000. TEVA then submitted a PIV cert to the '207 on 2/14/2000(RR dated 3/13/00), the '410 on 9/19/2000(RR dated 10/10/2000) and to the '004 on 3/21/01(RR dated _____)

70 mg: Originally submitted as a new strength amendment on 10/23/2000 with PIV certs to the '077, '570, '941, '590, '207 and '726 patents. TEVA provided RRs for each of these patents dated 12/15/2000. On 12/15/00 TEVA also provided a PIV cert to the '329 and '801 patents with a RR dated on 12/15/00 as well. TEVA asserts that both the '329 and '801 patents were listed when their new strength amendment was submitted on 10/23/2000. This explains the 12/15/00 RRs dated the same day as the other PIV certs to these patents. Mary Ann Holovac provided Marty with patent listing dates of 4/12/00 for the '329 and 5/8/00 for the '801. TEVA was sued on 1/15/01 on both the '329 and '801 patents. TEVA provided a PIV cert to the '294 patent on 5/23/01 with the RR associated with this cert dated 8/27/2001.

35 mg Originally submitted as a new strength amendment on 8/20/2001 with PIV certs to the '077, '941, '590, '726, '329, '207, '801, '410, and '294 patents. RRs for all of these patents were dated 9/28/2001. TEVA was sued in the D of DE for infringement of the '077, '941, '590, '726, '329, '207, '410, '801, and '294 patents. CA 01-278 filed on the D of DE, 30 months=3/28/04.

TEVA was sued in the District of DE on the '077, '941, '590, '726, '329, '207, '801, '294 and the '410 patents(35 mg and 70 mg only). These CA were 00-035, 01-675 and 01-728. TEVA was not sued with respect to the '004.

On 5/21/2007 TEVA provided an update of the status of any pending litigation for these drug products. In this submission TEVA states that they were sued on all patents for all strengths with the exception of the '004 patent which covered the 10 mg strength. Furthermore, TEVA notified the Agency that the various lawsuits that applied to the '941, '590, '726, '207, '410, '801 and '294 patents were dismissed. TEVA lost their litigation with respect to the '077 patent and won their litigation on the '329 patent(Federal Circuit found claims invalid and not infringed, DC decision was vacated) which only applied to the 35 and 70 mg strengths. This 5/21/07 amendment also includes Court Dismissals for all other court cases.

TEVA is the first filer outright for the 5 mg, 10 mg, 40 mg and 35 mg strengths. TEVA shares 180 day exclusivity on the 70 mg strength. TEVAs ANDA is eligible for Full

Approval with respect to all strengths on 2/6/2008.

2. Project Manager, Benjamin Danso Team 5 — Date 1/10/08 — Date _____
Review Support Branch — Initials for Ben/Simon — Initials _____

Original Rec'd date 9/29/99
Date Acceptable for Filing _____
Patent Certification (type) IV
Date Patent/Exclus.expires 2/6/08
Citizens' Petition/Legal Case Yes ☐ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☐
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver

EER Status Pending ☒ Acceptable ☐ OAI ☐
Date of EER Status _____
Date of Office Bio Review _____
Date of Labeling Approv. Sum 1/10/08
Date of Sterility Assur. App. n/a
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☒ Date 12/27/2002
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer:
Date _____
Name/Initials _____

Labeling Team Leader:
Date 2/5/08
Name/Initials rlw/for

Comments:
From: Grace, John F
Sent: Friday, January 11, 2008 10:25 AM
To: Wu, Ruby (Chi-Ann); Eng, Simon
Subject: RE: 75710/TEVA/Alendronate Tablets, 5 mg, 10 mg, 40 mg daily, & 35 mg and 70 mg once weekly, labeling AP sign-off

concur

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, January 10, 2008 4:19 PM
To: Eng, Simon
Cc: Grace, John F
Subject: RE: 75710/TEVA/Alendronate Tablets, 5 mg, 10 mg, 40 mg daily, & 35 mg and 70 mg once weekly, labeling AP sign-off

John,

The labeling AP signed off today remains acceptable.

Ruby

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ — Date 1/31/08
OGD Regulatory Counsel, Post-MMA Language Included ☐ — Initials DTR
Comments: Changes to AP ltr saved to V drive.

5. Div. Dir./Deputy Dir. — Date 2/1/08
Chemistry Div. I — Initials PS

Comments: 30 minute dissolution timepoint. Intent to revise by USP.

6. Frank Holcombe **First Generics Only** — Date 2/5/08
Assoc. Dir. For Chemistry — Initials rlw/for
Comments: (First generic drug review)

N/A. This ANDa was granted tentative approval on December 27, 2002. In addition, multiple other ANDAs have received tentative approval for this drug product.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Fosamax Tablets 5 mg (base), 10 mg (base), 40 mg (base) - daily
35 mg (base) and 70 mg (base) - once weekly dosing.
Merck & Co., Inc. NDA 20-560 (003, 001, 002, 004, 005)

8. Peter Rickman Date2/5/08
Director, DLPS Initialsrlw/for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes ☐No ☐; Petition: Yes☐ No☐
Comments:This ANDA was granted tentative approval on December 27, 2002. Final approval was blocked at that time by ongoing patent litigation. Refer to the administrative sign-off form completed at that time. On April 29, 2005, TEVA submitted a "major" amendment to the ANDA to provide for Assia Chemical Industries as an alternate supplier for the API. TEVA provided an additional submission dated December 12, 2006, to support the earlier request for an additional API supplier. On May 18, 2007, TEVA presented a summary of the legal status of its ANDA and provided a request for final approval effective February 6, 2008 upon the expiration of the '077 patent (with pediatric extension added). TEVA submitted updated CMC information on November 20, 2007, and restated its request for final approval effective February 6, 2008.

Final-printed labeling (FPL) found acceptable for approval 1/10/08. TEVA has addressed the M-51 labeling exclusivity under a Best Pharmaceuticals for Children Act (BPCA) labeling template endorsed by the agency.

CMC found acceptable for approval (Chemistry Review #8) 2/1/08.

OR

8. Robert L. West Date 2/5/08
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments:Acceptable EES dated 1/11/08 (Verified 2/5/08). No "OAI" Alerts noted.

Refer to the regulatory and litigation history summary provided above by M. Shimer for the legal/regulatory basis for the approval of this ANDA. Other than the patents and exclusivity noted, there are no other patents or exclusivity listed in the current "Orange Book" for this drug product.

With regard to the USP dissolution specification of 15 minutes, TEVA has obtained a letter dated January 31, 2008, from Darrell R. Abernethy, M.D., Ph.D., Chief Science Officer of USP. The letter informs TEVA and the agency that the USP monograph for Alendronate Sodium Tablets USP will be revised to include tolerances that will apply to all approved manufacturers (e.g., addition of another Dissolution test with a concomitant labeling requirement). It is anticipated by USP that the revision proposal will be published in an upcoming issue of Pharmacopeial Forum and the corresponding official date for the new Dissolution test will be indicated. A copy of this letter will be placed in DFS. As some of TEVA's lots may not meet the current USP dissolution specification (which replaced an earlier USP specification of 30-minutes that was in effect at the time of the tentative approval), this proposal has been found acceptable by Division of Chemistry I.

I have also discussed whether the change to a 15-minute dissolution time was necessiated because of clinical concerns related to possible side-effects of the drug product (esophagitis) with Dr. Theresa Kehoe, the medical officer for Merck's Fosamax in DMEP/OND. She agreed that the current 15 minute specification in USP has no clinical significance. I summary of my conversation has also been filed in DFS for this ANDA.

This ANDA is recommended for final approval effective upon the expiration of the 077 patent on February 6, 2008. The agency has confirmed that TEVA is eligible for 180-day generic drug exclusivity for each strength; i.e., 5 mg, 10 mg, 40 mg

and 35 mg and 70 mg (once-weekly). TEVA will share 180-day exclusivity for the 70 mg tablet strength with Barr Laboratories.

9. Gary Buehler Date 2/5/08
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Benjamin Danso Team 5 Date2/6/08

Review Support Branch Initials se
for_____

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
8amTime notified of approval by phone
8amTime approval letter faxed

FDA Notification:
2/6/08Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
2/6/08Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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

/s/

Simon Eng
2/6/2008 08:20:48 AM