

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-762**

**ADMINISTRATIVE**  
**DOCUMENTS/CORRESPONDENCE**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b>  <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		<b>NDA NUMBER</b> 21-762	
		<b>NAME OF APPLICANT / NDA HOLDER</b> Merck & Co., Inc	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
<b>TRADE NAME (OR PROPOSED TRADE NAME)</b> FOSAMAX® PLUS			
<b>ACTIVE INGREDIENT(S)</b> Alendronate; Cholecalciferol		<b>STRENGTH(S)</b> 70 mg (eq); 2800 IU	
<b>DOSAGE FORM</b> Tablet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by the FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
<b>a. United States Patent Number</b> 4621077		<b>b. Issue Date of Patent</b> November 4, 1986	<b>c. Expiration Date of Patent</b> February 6, 2008 (with pediatric exclusivity)
<b>d. Name of Patent Owner</b>  MERCK & CO., INC.		<b>Address (of Patent Owner)</b> P.O. BOX 2000, RY 60-30	
		<b>City/State</b> RAHWAY, NEW JERSEY	
		<b>ZIP Code</b> 07065-0907	<b>FAX Number (if available)</b> 732-594-4720
		<b>Telephone Number</b> 732-594-1249	<b>E-Mail Address (if available)</b>
<b>e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)</b>		<b>Address (of agent or representative named in 1.e.)</b>	
		<b>City/State</b>	
		<b>ZIP Code</b>	<b>FAX Number (if available)</b>
		<b>Telephone Number</b>	<b>E-Mail Address (if available)</b>
<b>f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?</b>		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
<b>g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?</b>		<input type="checkbox"/> Yes	<input type="checkbox"/> No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Claim Number (as listed in the patent)  Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

1

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

- Treatment of osteoporosis in postmenopausal women →
- For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.
- Treatment to increase bone mass in men with osteoporosis →

**5. No Relevant Patents**

For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

<p><b>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</b></p>	<p>Date Signed</p>
	<p>May 4, 2004</p>

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

<input type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p>	
<p>Dianne Brown</p>	
<p>Address</p> <p>Merck &amp; Co., Inc., P.O. Box 2000, RY60-30</p>	<p>City/State</p> <p>Rahway, NJ</p>
<p>ZIP Code</p> <p>07065-0907</p>	<p>Telephone Number</p> <p>(732) 594-1249</p>
<p>FAX Number (if available)</p> <p>(732) 594-4720</p>	<p>E-Mail Address (if available)</p> <p>dianne_brown2@merck.com</p>

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b>  <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		<b>NDA NUMBER</b> 21-762	
		<b>NAME OF APPLICANT / NDA HOLDER</b> Merck & Co., Inc	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
<b>TRADE NAME (OR PROPOSED TRADE NAME)</b> FOSAMAX® PLUS			
<b>ACTIVE INGREDIENT(S)</b> Alendronate; Cholecalciferol		<b>STRENGTH(S)</b> 70 mg (eq); 2800 IU	
<b>DOSAGE FORM</b> Tablet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by the FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
<b>a. United States Patent Number</b> 5358941		<b>b. Issue Date of Patent</b> October 25, 1994	<b>c. Expiration Date of Patent</b> June 2, 2013 (with pediatric exclusivity)
<b>d. Name of Patent Owner</b>  MERCK & CO., INC.		<b>Address (of Patent Owner)</b> P.O. BOX 2000, RY 60-30	
		<b>City/State</b> RAHWAY, NEW JERSEY	
		<b>ZIP Code</b> 07065-0907	<b>FAX Number (if available)</b> 732-594-4720
		<b>Telephone Number</b> 732-594-1249	<b>E-Mail Address (if available)</b>
<b>e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)</b>		<b>Address (of agent or representative named in 1.e.)</b>	
		<b>City/State</b>	
		<b>ZIP Code</b>	<b>FAX Number (if available)</b>
		<b>Telephone Number</b>	<b>E-Mail Address (if available)</b>
<b>f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?</b>		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
<b>g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?</b>		<input type="checkbox"/> Yes	<input type="checkbox"/> No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
--	---

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
---	--

**5. No Relevant Patents**

For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product.  Yes

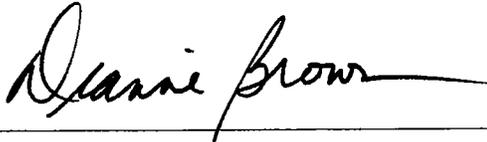
**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)**

Date Signed



May 4, 2004

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Merck & Co., Inc

Address

P.O. Box 2000, RY60-30

City/State

Rahway, NJ

ZIP Code

07065-0907

Telephone Number

(732) 594-1249

FAX Number (if available)

(732) 594-4720

E-Mail Address (if available)

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b>  <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 21-762	
		NAME OF APPLICANT / NDA HOLDER Merck & Co., Inc	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) FOSAMAX® PLUS			
ACTIVE INGREDIENT(S) Alendronate; Cholecalciferol		STRENGTH(S) 70 mg (eq); 2800 IU	
DOSAGE FORM Tablet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by the FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number 5681590		b. Issue Date of Patent October 28, 1997	c. Expiration Date of Patent June 2, 2013 (with pediatric exclusivity)
d. Name of Patent Owner  MERCK & CO., INC.		Address (of Patent Owner) P.O. BOX 2000, RY 60-30	
		City/State RAHWAY, NEW JERSEY	
		ZIP Code 07065-0907	FAX Number (if available) 732-594-4720
		Telephone Number 732-594-1249	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes	<input type="checkbox"/> No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input type="checkbox"/> No
--	--	--

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
---	--

**5. No Relevant Patents**

For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed



May 4, 2004

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Merck & Co., Inc

Address

P.O. Box 2000, RY60-30

City/State

Rahway, NJ

ZIP Code

07065-0907

Telephone Number

(732) 594-1249

FAX Number (if available)

(732) 594-4720

E-Mail Address (if available)

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b>  <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 21-762	
		NAME OF APPLICANT / NDA HOLDER Merck & Co., Inc	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) FOSAMAX® PLUS			
ACTIVE INGREDIENT(S) Alendronate; Cholecalciferol		STRENGTH(S) 70 mg (eq); 2800 IU	
DOSAGE FORM Tablet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by the FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number 5994329		b. Issue Date of Patent November 30, 1999	c. Expiration Date of Patent January 17, 2019 (with pediatric exclusivity)
d. Name of Patent Owner  MERCK & CO., INC.		Address (of Patent Owner) P.O. BOX 2000, RY 60-30	
		City/State RAHWAY, NEW JERSEY	
		ZIP Code 07065-0907	FAX Number (if available) 732-594-4720
		Telephone Number 732-594-1249	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
1	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) - Treatment of osteoporosis in postmenopausal women For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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. - Treatment to increase bone mass in men with osteoporosis
---	--

**5. No Relevant Patents**

For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or methods(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product.  Yes

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Claim Number (as listed in the patent)  2	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) - Treatment of osteoporosis in postmenopausal women —  For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.  - Treatment to increase bone mass in men with osteoporosis —

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Claim Number (as listed in the patent)  3	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) - Treatment of osteoporosis in postmenopausal women —  For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.  - Treatment to increase bone mass in men with osteoporosis —

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Claim Number (as listed in the patent)  4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) - Treatment of osteoporosis in postmenopausal women —  For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.  - Treatment to increase bone mass in men with osteoporosis —

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.3 Claim Number (as listed in the patent)  6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) - Treatment of osteoporosis in postmenopausal women —  For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.  - Treatment to increase bone mass in men with osteoporosis —

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.4 Claim Number (as listed in the patent)  7	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	<p>Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)</p> <p>- Treatment of osteoporosis in postmenopausal women —</p> <p style="text-align: center;">For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.</p> <p>- Treatment to increase bone mass in men with osteoporosis —</p>

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.5 Claim Number (as listed in the patent)  8	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	<p>Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)</p> <p>- Treatment of osteoporosis in postmenopausal women —</p> <p style="text-align: center;">For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.</p> <p>- Treatment to increase bone mass in men with osteoporosis —</p>

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.6 Claim Number (as listed in the patent) 9	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	<p>Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)</p> <p>- Treatment of osteoporosis in postmenopausal women</p> <p style="text-align: center;">For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.</p> <p>- Treatment to increase bone mass in men with osteoporosis</p>

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.7 Claim Number (as listed in the patent) 16	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	<p>Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)</p> <p>- Treatment of osteoporosis in postmenopausal women</p> <p style="text-align: center;">For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.</p> <p>- Treatment to increase bone mass in men with osteoporosis</p>

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.8 Claim Number (as listed in the patent) 17	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) - Treatment of osteoporosis in postmenopausal women  For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.  - Treatment to increase bone mass in men with osteoporosis

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.9 Claim Number (as listed in the patent) 18	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) - Treatment of osteoporosis in postmenopausal women  For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.  - Treatment to increase bone mass in men with osteoporosis

4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.10 Claim Number (as listed in the patent)  19	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	<p>Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)</p> <p>- Treatment of osteoporosis in postmenopausal women —</p> <p style="text-align: center;">For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.</p> <p>- Treatment to increase bone mass in men with osteoporosis —</p>

4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.11 Claim Number (as listed in the patent)  21	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	<p>Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)</p> <p>- Treatment of osteoporosis in postmenopausal women —</p> <p style="text-align: center;">For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.</p> <p>- Treatment to increase bone mass in men with osteoporosis —</p>

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.12 Claim Number (as listed in the patent)  22	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) - Treatment of osteoporosis in postmenopausal women  For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.  - Treatment to increase bone mass in men with osteoporosis

<b>4. Method of Use</b>	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.13 Claim Number (as listed in the patent)  23	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2A If the answer to 4.2 is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) - Treatment of osteoporosis in postmenopausal women  For the treatment of osteoporosis, FOSAMAX® PLUS increases bone mass and reduces 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.  - Treatment to increase bone mass in men with osteoporosis

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed



May 4, 2004

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Merck & Co., Inc

Address

P.O. Box 2000, RY60-30

City/State

Rahway, NJ

ZIP Code

07065-0907

Telephone Number

(732) 594-1249

FAX Number (if available)

(732) 594-4720

E-Mail Address (if available)

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b>  <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 21-762	
		NAME OF APPLICANT / NDA HOLDER Merck & Co., Inc	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) FOSAMAX® PLUS			
ACTIVE INGREDIENT(S) Alendronate; Cholecalciferol		STRENGTH(S) 70 mg (eq); 2800 IU	
DOSAGE FORM Tablet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by the FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number 6090410		b. Issue Date of Patent July 18, 2000	c. Expiration Date of Patent June 2, 2013 (with pediatric exclusivity)
d. Name of Patent Owner  MERCK & CO., INC.		Address (of Patent Owner) P.O. BOX 2000, RY 60-30	
		City/State RAHWAY, NEW JERSEY	
		ZIP Code 07065-0907	FAX Number (if available) 732-594-4720
		Telephone Number 732-594-1249	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes	<input type="checkbox"/> No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2: Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**3: Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4: Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
---	--

**5: No Relevant Patents**

For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed



May 4, 2004

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Merck & Co., Inc

Address

P.O. Box 2000, RY60-30

City/State

Rahway, NJ

ZIP Code

07065-0907

Telephone Number

(732) 594-1249

FAX Number (if available)

(732) 594-4720

E-Mail Address (if available)

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.



Michele R. Flicker  
Michele R. Flicker  
Director  
Regulatory Affairs

May 12, 2004  
Date

## MEMORANDUM OF TELECON

DATE: April 8, 2005

APPLICATION NUMBER: NDA 21-762

BETWEEN:

Name: Michele Flicker  
Phone: 732-594-1502  
Representing: Merck & Co., Inc.

AND

Name: Randy Hedin  
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Date of Final Draft Package Insert

I spoke with Dr Flicker, and confirmed that the date of submission of the final draft Package Insert (PI) in the approval letter dated April 7, 2005 is not correct. The correct date of submission of the final draft PI is April 1, 2005 (Email) and April 5, 2005 (hardcopy).

*{See appended electronic signature page}*

---

Randy Hedin  
Senior Regulatory Management Officer

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

/s/

-----  
Randy Hedin  
4/8/05 01:46:23 PM  
CSO

**Division of Metabolic and Endocrine Drug Products**  
**PROJECT MANAGER LABELING REVIEW**

**Application Number:** NDA 21-762  
**Name of Drug:** Fosamax Plus D (alendronate sodium 70 mg & 2800 I.U. vitamin D<sub>3</sub>) Tablets  
**Sponsor:** Merck & Co. Inc.

**Material Reviewed**

**Submission Dates:**

- March 31, 2005 submission containing draft labeling for the patient package insert (PPI) for Fosamax Plus D.

**Background and Summary Description:**

Merck & Co., Inc. submitted a New Drug Application (NDA) dated May 24, 2005, which is a combination of Fosamax and Vitamin D<sub>3</sub>. This combination product contains a nutritional supplement, and a prescription drug, and is also a 505(b)(2) application because it relies on the literature for the labeling of the vitamin D<sub>3</sub>. The application is seeking an indication for the treatment of osteoporosis in postmenopausal women, and the treatment to increase bone mass in men with osteoporosis.

**Review**

Patient Package Insert

The draft PPI submitted March 31, 2005 (No Identifier Number and No Revision Date), was compared to the Final Printed Labeling (FPL) PPI submitted January 18, 2005 (Identifier # 7969415, revision date December 2004) for Fosamax once-weekly. The following document entitled, "January 18, 2005 Fosamax Last Approved" shows all the items deleted from the last approved PPI (circled), and the document entitled, "PPI March 31, 2005" shows all additions to the PPI (circled).

## Text Comparison

### Documents Compared

PPI March 31, 2005.pdf

PPI January 18, 2005 Fosamax Last Approved.pdf

### Summary

224 word(s) differ

189 word(s) added

436 word(s) deleted

**APPEARS THIS WAY  
ON ORIGINAL**

6 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

## **Conclusions**

An approval letter should be issued.

Reviewed by: Randy Hedin, R.Ph., Senior Regulatory Management Officer

*{See appended electronic signature page}*

**APPEARS THIS WAY  
ON ORIGINAL**

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

/s/

-----  
Randy Hedin  
4/8/05 04:05:37 PM  
CSO

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-762	Efficacy Supplement Type SE-	Supplement Number
Drug: Fosamax Plus D		Applicant: Merck & Co., Inc.
RPM: Randy Hedin	HFD-510	Phone # 301-827-6392
<p>Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)                      (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</b></p> <p><input type="checkbox"/> Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Vitamin D</p>	
<b>❖ Application Classifications:</b>		
<ul style="list-style-type: none"> <li>• Review priority</li> </ul>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<ul style="list-style-type: none"> <li>• Chem class (NDAs only)</li> </ul>		
<ul style="list-style-type: none"> <li>• Other (e.g., orphan, OTC)</li> </ul>		
<b>❖ User Fee Goal Dates</b>		March 24, 2005
<b>❖ Special programs (indicate all that apply)</b>		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
<b>❖ User Fee Information</b>		
<ul style="list-style-type: none"> <li>• User Fee</li> </ul>		<input checked="" type="checkbox"/> Paid UF ID number 4764
<ul style="list-style-type: none"> <li>• User Fee waiver</li> </ul>		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<ul style="list-style-type: none"> <li>• User Fee exception</li> </ul>		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
<b>❖ Application Integrity Policy (AIP)</b>		
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "No," continue with question (5).*

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

*If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>• Exclusivity summary</li> <li>• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	Pending
<ul style="list-style-type: none"> <li>• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	<input checked="" type="checkbox"/> Yes, Application # 20-560 <input type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	July 15, 2004

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	March 31, 2005
• Original applicant-proposed labeling	May 24, 2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS, Tradename, October 25, 2004 DMETS, PPI, December 6, 2004 DMETS, PPI, March 30, 2005 DDMAC, PPI, November 10, 2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	May 24, 2004 February 18, 2005
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	March 31, 2005
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	None
• Pre-Approval Safety Conference (indicate date; approvals only)	None
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	None
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	None

<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Team Leader, April 4, 2005 Division Director, April 7, 2005
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	March 14, 2005
❖ Microbiology (efficacy) review(s) (indicate date for each review)	None
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	March 14, 2005
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	None
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	None
❖ Demographic Worksheet (NME approvals only)	None
❖ Statistical review(s) (indicate date for each review)	None
❖ Biopharmaceutical review(s) (indicate date for each review)	April 5, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	None
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	None Requested
• Bioequivalence studies	March 14, 2005
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	March 25, 2005
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	March 25, 2005
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: March 22, 2005 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	June 25, 2004 March 1, 2005
❖ Nonclinical inspection review summary	None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	None
❖ CAC/ECAC report	None

**Appendix A to NDA/Efficacy Supplement Action Package Checklist**

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

/s/

-----  
Randy Hedin  
4/7/05 04:31:58 PM

# MEMORANDUM

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

**DATE:** March 30, 2005

**TO:** David Orloff, M.D., Director  
Division of Metabolic and Endocrine Drug Products, HFD-510

**VIA:** Randy Hedin, Regulatory Health Project Manager,  
Division of Metabolic and Endocrine Drug Products, HFD-510

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** DSRCS Review #2 of the Patient Labeling (PPI) for  
Fosamax Plus D (alendronate sodium/cholecalciferol) Tablets,  
NDA 21-762

## **Background and Summary**

The sponsor submitted a draft revised PPI on March 29, 2005, in response to FDA PPI comments dated March 22, 2005, for Fosamax Plus D (alendronate sodium/cholecalciferol) Tablets, NDA 21-762 and a teleconference held March 28, 2008.

Please refer to the DSRCS Patient Labeling review dated December 6, 2004. This review was done jointly with DDMAC. DSRCS reviews materials from a patient comprehension perspective and DDMAC reviews materials from a promotional perspective. The wording was simplified, made consistent with the PI, promotional language and other unnecessary information was removed (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and the PPI was put it in the format that we recommend for all patient information. The proposed changes were done through known research and experience to improve risk communication to a broad audience of varying educational backgrounds.

## **Comments and Recommendations**

1. We stand by the proposed PPI revisions outlined in our December 6, 2004, review and forwarded to the sponsor on March 22, 2005, for the following reasons:
  - The sponsor increased the overall reading level of the PPI from an 8<sup>th</sup> to a 9<sup>th</sup> grade reading level (Flesch-Kincaid scale used). For optimum comprehension, it is recommended that patient information materials be written at less than an 8<sup>th</sup> grade reading level (reading level 8 or less) and

have a reading ease of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). About 50% of American adults (90 million people) have difficulty understanding and acting upon health information, notes the Institute of Medicine (IOM) in its April 2004 report, "Health Literacy: A Prescription to End Confusion." The IOM defines health literacy as "The ability to obtain, process, and understand basic health information and services needed to make appropriate health decisions... Health literacy is not to be confused with the ability to read, although at least a quarter of Americans read at the fifth grade level or below, while the majority of patient education materials are written at or above the 10th-grade level."

- The sponsor minimizes and dilutes the important safety message that should be the focus of the section "**What is the most important information I should know about Fosamax Plus D?**" by not describing the serious and significant esophageal side effects up-front, and by adding information that could be placed in another section. The PPI appears to follow the headings outlined in 21 CFR 208 (Medication Guide regulations). The "What is the most important information I should know" section should be used to describe significant public health concerns and what the patient should do or consider because of the concerns. Based on the professional labeling, the serious esophageal effects would constitute the most important information and thus should be the focus of this section.
- The sponsor's revisions include the use of hyphens, slashes and abbreviations, (e.g., 6 to 8 ounces revised to 6-8 oz), and technical terms. Hyphens and slashes, and abbreviations are not comprehended by lower literate patients. Technical terms, if necessary, should appear in parentheses after the consumer-friendly term is used, e.g., stomach area (abdomen),
- The sponsor added "have severe kidney disease" to the section "**Who should not take Fosamax Plus D?**", which does not appearing the CONTRAINDICATIONS section of the PI.

- The sponsor

-----  
This information contains clinical trial information which is difficult for many patients to interpret and is not written in the first person for the patient.

- The purpose of Prescription Patient Information is to provide important drug product information to enhance its safe and effective use ; not to provide extensive disease state information. Extensive disease state information should be placed at the end of the leaflet or be provided as a separate information sheet.
2. The sponsor states in the **PI, PRECAUTIONS section, Information for patients subsection**, "Physicians should instruct their patients to read the patient package insert before starting therapy with FOSAMAX

PLUS D and to reread it each time a prescription is renewed.”

3. Revise the PPI (using consumer-friendly language) to include any relevant revisions to the PI.
4. We continue to recommend revising the existing Fosamax Patient Information Leaflet using the recommendations suggested in December 6, 2004, review for Fosamax Plus D.

Please call us if you have any questions.

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

/s/  
-----

Jeanine Best  
3/30/05 03:44:31 PM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
3/30/05 03:49:15 PM  
DRUG SAFETY OFFICE REVIEWER  
for Gerald Dal Pan

3 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

       § 552(b)(4) Draft Labeling

## MEMORANDUM OF TELECON

DATE: February 9, 2005

APPLICATION NUMBER: NDA 21-762

BETWEEN:

Name: Michele Flicker  
Phone: 732-594-1502  
Representing: Merck & Co. Inc.

AND

Name: Randy Hedin  
Division of Metabolism and Endocrine Drug Products, HFD-510

SUBJECT: Tradename for alendronate & vitamin D

I spoke with Michele Flicker concerning the tradename for alendronate & vitamin D, NDA 21-762. I stated that the Team reviewing the Fosamax Plus NDA submission discussed the tradename, and felt that the tradename "Fosamax Plus" was promotional. I asked if Merck would consider the tradename "Fosamax Plus D." Dr. Flicker stated that she would discuss it with her team, and get back to me.

---

Randy Hedin  
Senior Regulatory Management Officer

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

/s/

-----  
Randy Hedin  
3/15/05 10:38:14 AM  
CSO

## MEMORANDUM

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

**DATE:** December 6, 2004

**TO:** David Orloff, M.D., Director  
Division of Metabolic and Endocrine Drug Products, HFD-510

**VIA:** Randy Hedin, Regulatory Health Project Manager,  
Division of Metabolic and Endocrine Drug Products, HFD-510

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** DSRCS Review of the Patient Labeling for Fosamax Plus  
(alendronate sodium/cholecalciferol) Tablets, NDA 21-762

### **Background and Summary**

The attached patient labeling represents the revised risk communication materials for Fosamax Plus (alendronate sodium/cholecalciferol) Tablets, NDA 21-762. It has been reviewed by our office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted by the sponsor on May 24, 2004. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

We also have the following comment:

We recommend revising the existing Fosamax Patient Information Leaflet using the recommendations suggested in the following Fosamax Plus PPI.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised documents in Word if requested by the review division. Please call if you have any questions.

C

6 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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

/s/

-----  
Jeanine Best  
12/6/04 10:30:26 AM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
12/6/04 11:06:11 AM  
DRUG SAFETY OFFICE REVIEWER  
for Gerald Dal Pan

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

---

**DATE:** November 10, 2004

**FROM:** Lynn Panholzer, Pharm.D., Regulatory Reviewer, DDMAC

**TO:** Jeanine Best, MSN, RN, PNP, Patient Product Information Specialist,  
ODS

**Re: Comments on patient package insert (PPI) for alendronate sodium/cholecalciferol (Fosamax Plus); NDA 21-762**

Thank you for forwarding a copy of the PPI to DDMAC for review. The following comments were based on the version of the draft PPI received from DSRCS via e-mail on October 12, 2004.

**What is the most important information I should know about FOSAMAX PLUS?**

•

We note that this sentence was deleted from the entire draft PPI. Under **PRECAUTIONS**, *Dosing Instructions* in the draft PI, it states that “

**Who should not take FOSAMAX PLUS?**

“Do not take FOSAMAX PLUS if you:

- have low levels of calcium in your blood”

We recommend that a

- “Have severe kidney disease”

We note the following recommendations/comments/revisions from DSRCs related to the bulleted statement above:



Although the PPI revised according to these recommendations indirectly suggests that there is potential risk associated with use of the product in kidney disease patients, it does not convey the message as strongly as the applicant's original proposal. We are therefore concerned that the revised presentation may minimize the importance of the risk associated with use of the product in patients with severe renal impairment.

A recommendation against use of this product in patients with more severe renal insufficiency (creatinine clearance <35 mL/min) appears in three separate locations in the draft PI, including a bolded recommendation in the **CLINICAL PHARMACOLOGY** section, and statements in the **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections. We also note that the PPIs of other bisphosphonate products (Fosamax, once weekly Fosamax, Actonel) contain similar statements that the products are not to be taken by patients if they have severe kidney disease. Therefore, we



**How should I take FOSAMAX PLUS?**

Please contact me if you have any questions regarding my comments. My number is (301) 827-3903.

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

/s/

-----  
Lynn Panholzer  
11/10/04 11:41:59 AM  
CSO

15 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

  D   § 552(b)(5) Deliberative Process

       § 552(b)(4) Draft Labeling



NDA 21-762

**FILING COMMUNICATION**

Merck & Co., Inc.  
Attention: Michele Flicker, M.D., Ph.D.  
Director, Regulatory Affairs  
P.O. Box 2000,  
Mail Drop: RY 33-200  
Rahway, NJ 07065

Dear Dr. Flicker:

Please refer to your May 24, 2004 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax Plus (alendronate sodium 70 mg/2800 I.U. vitamin D<sub>3</sub>) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on July 23, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue and request that you submit the following information:

Submit individual in vitro dissolution data from the combination tablet, with descriptive statistics (mean, median, range, and standard deviation) and plots, for alendronate and vitamin D<sub>3</sub>, in three dissolution media, to determine acceptable in vitro dissolution methods and acceptance criteria for alendronate and vitamin D<sub>3</sub>.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. Please respond to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Randy Hedin, Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
Chief, Project Management Staff  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
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/

-----  
Randy Hedin  
7/16/04 09:24:23 AM



Is the application affected by the Application Integrity Policy (AIP)? YES NO X  
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? YES X NO

• Was form 356h included with an authorized signature? YES X NO

**If foreign applicant, both the applicant and the U.S. agent must sign.**

• Submission complete as required under 21 CFR 314.50? YES X NO

If no, explain:

• If an electronic NDA, does it follow the Guidance? N/A YES X NO

**If an electronic NDA, all certifications must be in paper and require a signature.**

Which parts of the application were submitted in electronic format?

Additional comments:

• If in Common Technical Document format, does it follow the guidance? N/A YES X NO

• Is it an electronic CTD? N/A YES X NO

**If an electronic CTD, all certifications must be in paper and require a signature.**

Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information submitted on form FDA 3542a? YES X NO

• Exclusivity requested? YES, \_\_\_\_\_ years NO X

Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES X NO

**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,

*"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."*

Applicant may not use wording such as "To the best of my knowledge . . ."

- Financial Disclosure forms included with authorized signature?  
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)      YES    X    NO
- Field Copy Certification (that it is a true copy of the CMC technical section)?      YES    X    NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS?      YES    X    NO  
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers:      IND 32,033
- End-of-Phase 2 Meeting(s)?      Date(s) \_\_\_\_\_      NO X  
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)?      Date(s) \_\_\_\_\_      NO X  
If yes, distribute minutes before filing meeting.

**Project Management**

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?      YES      NO X
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS?      YES    X    NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS?      N/A      YES      NO X
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?      N/A X      YES      NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?      N/A    X    YES    NO
- Has DOTCDP been notified of the OTC switch application?      YES      NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?      YES      NO X

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment?      YES    X    NO  
If no, did applicant submit a complete environmental assessment?      YES    NO  
If EA submitted, consulted to Nancy Sager (HFD-357)?      YES    NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES   X   NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? NA X   YES   NO

**If 505(b)(2) application, complete the following section:**

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES   NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES   NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES   NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].*

\_\_\_ 21 CFR 314.50(i)(1)(ii): No relevant patents.

\_\_\_ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.



ATTACHMENT

**MEMO OF FILING MEETING**

DATE: July 7, 2004

BACKGROUND:

Oral alendronate sodium is a bisphosphonate which specifically inhibits osteoclast-mediated bone resorption. Alendronate has been shown to be efficacious and generally safe and well tolerated for the treatment of osteoporosis in men and postmenopausal women, glucocorticoid-induced-osteoporosis, and Paget's disease of the bone. The original marketing application for Fosamax was approved on September 29, 1995. This application is for once-weekly alendronate 70mg/2800 I.U. vitamin D<sub>3</sub> combination tablet for the treatment of osteoporosis in postmenopausal women, and treatment to increase bone mass in men with osteoporosis

ATTENDEES and ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Theresa Kehoe
Secondary Medical:	None
Statistical:	None
Pharmacology:	Gemma Kuijpers
Statistical Pharmacology:	None
Chemistry:	David Lewis
Environmental Assessment (if needed):	David Lewis
Biopharmaceutical:	Johnny Lau
Microbiology, sterility:	None
Microbiology, clinical (for antimicrobial products only):	None
DSI:	
Regulatory Project Management:	Randy Hedin
Other Consults:	

Per reviewers, are all parts in English or English translation? YES X NO  
 If no, explain:

CLINICAL FILE  X  REFUSE TO FILE \_\_\_\_\_

- Clinical site inspection needed: YES NO X
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A X YES NO

CLINICAL MICROBIOLOGY NA  X  FILE \_\_\_\_\_ REFUSE TO FILE \_\_\_\_\_



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

/s/

-----  
Randy Hedin  
7/15/04 08:08:57 AM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-762

Merck & Company, Inc.  
Attn: Michele R. Flicker, M.D., Ph.D.  
Director, Regulatory Affairs  
P.O. Box 2000, Mail Drop RY 33-200  
Rahway, NJ 07065

Dear Dr. Flicker:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Fosamax™ Plus (alendronate sodium – 70 mg/2800 I.U. Vitamin D <sub>3</sub> combination) Tablets
Review Priority Classification:	Standard (S)
Date of Application:	May 24, 2004
Date of Receipt:	May 24, 2004
Our Reference Number:	NDA 21-762

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 23, 2004 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be March 24, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

NDA 21-762

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic & Endocrine Drug Products, HFD-510  
Attention: Fishers Document Room, 8B45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

Randy Hedin, R.Ph.  
Senior Regulatory Management Officer  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
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/

-----  
Randy Hedin  
6/3/04 09:28:45 AM

# PRESCRIPTION DRUG USER FEE COVER SHEET

**See Instructions on Reverse Side Before Completing This Form**

This form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates are available on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

APPLICANT'S NAME AND ADDRESS

Amgen Co., Inc.  
5600 Town Pike, BLA-20  
Rockville, MD 20852-1448

Thomas M. Erb, Ph.D.

PHONE NUMBER (Include Area Code)

301-344-7597

PRODUCT NAME

XTMPPLUS (Alendronate sodium/vitamin D combination) Tablets

APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NO 21762

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES  NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA)

6. USER FEE I.D. NUMBER

4764

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

HAS AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See Item 8, reverse side if answered YES)

The reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
HFD-99  
Town Pike  
Rockville, MD 20852-1448

Food and Drug Administration  
CDER, HFD-94  
and 12420 Parklawn Drive, Room 3046  
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

NAME OF AUTHORIZED COMPANY REPRESENTATIVE

Thomas M. Erb

TITLE

Executive Director, Regulatory Affairs

DATE

May 3, 2004

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- 1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Melissa King	TITLE Controller, Merck Corporate Finance
FIRM/ORGANIZATION Merck & Co., Inc.	
SIGNATURE 	DATE 4/21/04

#### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

## DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning See Table D-1, who participated as a clinical investigator in the submitted study Alendronate Sodium - 70mg/Vitamin D3 2800 I.U. Combination Tablets, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

*Please mark the applicable checkboxes.*

any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Melissa King	Controller, Merck Corporate Finance
FIRM/ORGANIZATION	
Merck & Co., Inc.	
SIGNATURE	DATE
	4/2/04

### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857