Clinical Investigator Financial Certification

This information below is provided in accordance with 21 CFR Part 54 in regard to the following clinical study.

OraPharma, Inc.
Pharmaceutical Company

Minocycline Periodontal Therapeutic System
Investigating Product

Multicenter Phase III Trial of Minocycline Periodontal Therapeutic System (Minocycline PTS): Adjunctive Use in Patients with Adult Periodontitis (OPI-103A & B)
Title of Study/Protocol #

Dr. Ingvar Magnusson
Investigator

Yes ☐ No ☑	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
Yes ☐ No ☑	Do you, your spouse or dependent children have a proprietary interest in **Minocycline Periodontal Therapeutic Systems (Minocycline MPTS)** such as patent rights or rights under a patent, trademark, copyright or licensing agreement? If yes, the nature of the proprietary interest is as follows:
Yes ☐ No ☑	Do you, your spouse or dependent children, or any of you combined have a significant equity interest in **OraPharma, Inc.** such as an ownership interest, stock options or any other financial interest whose value cannot be readily determined through reference to public prices, or any equity in **OraPharma, Inc.** (if it is a publicly traded organization) exceeding $50,000, or any combination of these? If yes, the amount and nature of the equity interest is as follows:
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To the best of my knowledge, the information provided above is correct and complete. I understand that I am obligated to amend this statement and notify **OraPharma, Inc.** promptly if there is any change in this information during the conduct of the clinical studies listed above or during one year after the studies have been completed.

Ingvar Magnusson Signature of Investigator	Sep 8, 1999 Date

Clinical Investigator Financial Certification

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OraPharma, Inc.
Pharmaceutical Company

Minocycline Periodontal Therapeutic System
Investigating Product

Multicenter Phase III Trial of Minocycline Periodontal Therapeutic System (Minocycline PTS): Adjunctive Use in Patients with Adult Periodontitis (OPI-103A & B)
Title of Study/Protocol #

Dr. Richard Oringer
Investigator

Yes ☐ No ☑	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
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Richard Oringer
Signature of Investigator

9-7-99
Date

Clinical Investigator Financial Certification

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OraPharma, Inc.
Pharmaceutical Company

Minocycline Periodontal Therapeutic System
Investigating Product

Multicenter Phase III Trial of Minocycline Periodontal Therapeutic System (Minocycline PTS): Adjunctive Use in Patients with Adult Periodontitis (OPI-103A & B)
Title of Study/Protocol #

Dr. Rutger Persson
Investigator

Yes ☐ No ☒	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
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Signature of Investigator — Date: 9-21-99

Clinical Investigator Financial Certification

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OraPharma, Inc.
Pharmaceutical Company

Minocycline Periodontal Therapeutic System
Investigating Product

Multicenter Phase III Trial of Minocycline Periodontal Therapeutic System (Minocycline PTS): Adjunctive Use in Patients with Adult Periodontitis (OPI-103A & B)
Title of Study/Protocol #

Dr. Donald Adams
Investigator

Yes ☐	No ☒	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
Yes ☐	No ☒	Do you, your spouse or dependent children have a proprietary interest in **Minocycline Periodontal Therapeutic Systems (Minocycline MPTS)** such as patent rights or rights under a patent, trademark, copyright or licensing agreement? If yes, the nature of the proprietary interest is as follows:
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Donald Adams	Sept 14, 1999
Signature of Investigator	Date

Clinical Investigator Financial Certification

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OraPharma, Inc.
Pharmaceutical Company

Minocycline Periodontal Therapeutic System
Investigating Product

Multicenter Phase III Trial of Minocycline Periodontal Therapeutic System (Minocycline PTS): Adjunctive Use in Patients with Adult Periodontitis (OPI-103A & B)
Title of Study/Protocol #

Dr. Connie Drisko
Investigator

Yes ☐ No ☒	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
Yes ☐ No ☒	Do you, your spouse or dependent children have a proprietary interest in **Minocycline Periodontal Therapeutic Systems (Minocycline MPTS)** such as patent rights or rights under a patent, trademark, copyright or licensing agreement? If yes, the nature of the proprietary interest is as follows:
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Signature of Investigator	Date
Connie Drisko	9-9-99

Clinical Investigator Financial Certification

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OraPharma, Inc.
Pharmaceutical Company

Minocycline Periodontal Therapeutic System
Investigating Product

Multicenter Phase III Trial of Minocycline Periodontal Therapeutic System (Minocycline PTS): Adjunctive Use in Patients with Adult Periodontitis (OPI-103A & B)
Title of Study/Protocol #

Dr. Robert Genco
Investigator

Yes ☐ No ☒	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
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Signature of Investigator	Date 9/2/04

Clinical Investigator Financial Certification

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OraPharma, Inc.
Pharmaceutical Company

Minocycline Periodontal Therapeutic System
Investigating Product

Multicenter Phase III Trial of Minocycline Periodontal Therapeutic System (Minocycline PTS): Adjunctive Use in Patients with Adult Periodontitis (OPI-103A & B)
Title of Study/Protocol #

Dr. John Rapley
Investigator

Yes ☐ No ☒	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
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Signature of Investigator	12/8/99 Date

Clinical Investigator Financial Certification

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OraPharma, Inc.
Pharmaceutical Company

Minocycline Periodontal Therapeutic System
Investigating Product

Multicenter Phase III Trial of Minocycline Periodontal Therapeutic System (Minocycline PTS): Adjunctive Use in Patients with Adult Periodontitis (OPI-103A & B)
Title of Study/Protocol #

Dr. Ira Lamster
Investigator

Yes ☐ No ☑	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
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Signature of Investigator	9/3/99 Date

Clinical Investigator Financial Certification

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OraPharma, Inc.
Pharmaceutical Company

Minocycline Periodontal Therapeutic System
Investigating Product

Multicenter Phase III Trial of Minocycline Periodontal Therapeutic System (Minocycline PTS): Adjunctive Use in Patients with Adult Periodontitis (OPI-103A & B)
Title of Study/Protocol #

Dr. David Paquette
Investigator

Yes ☐ No ☑	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
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Signature of Investigator	11 Nov 1999 Date

Clinical Investigator Financial Certification

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OraPharma, Inc.
Pharmaceutical Company

Minocycline Periodontal Therapeutic System
Investigating Product

Multicenter Phase III Trial of Minocycline Periodontal Therapeutic System (Minocycline PTS): Adjunctive Use in Patients with Adult Periodontitis (OPI-103A & B)
Title of Study/Protocol #

Dr. Sigmund Socransky
Investigator

Yes ☐ No ☒	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
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Sigmund L Socransky	09/07/1999
Signature of Investigator	Date

Clinical Investigator Financial Certification

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Pharmaceutical Company

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Multicenter Phase III Trial of Minocycline Periodontal Therapeutic System (Minocycline PTS): Adjunctive Use in Patients with Adult Periodontitis (OPI-103A & B)
Title of Study/Protocol #

Dr. Thomas Van Dyke
Investigator

Yes ☐ No ☒	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
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Signature of Investigator	Date
	9/14/95

Clinical Investigator Financial Certification

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Pharmaceutical Company

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Title of Study/Protocol #

Dr. Larry Wolff
Investigator

Yes ☐ No ☒	Do you, your spouse or dependent children have a financial arrangement with **OraPharma, Inc.**, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be grater for a favorable clinical result, compensation in the form of an equity interest in **OraPharma, Inc.** or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
Yes ☐ No ☒	Do you, your spouse or dependent children have a proprietary interest in **Minocycline Periodontal Therapeutic Systems (Minocycline MPTS)** such as patent rights or rights under a patent, trademark, copyright or licensing agreement? If yes, the nature of the proprietary interest is as follows:
Yes ☐ No ☒	Do you, your spouse or dependent children, or any of you combined have a significant equity interest in **OraPharma, Inc.** such as an ownership interest, stock options or any other financial interest whose value cannot be readily determined through reference to public prices, or any equity in **OraPharma, Inc.** (if it is a publicly traded organization) exceeding $50,000, or any combination of these? If yes, the amount and nature of the equity interest is as follows:
Yes ☐ No ☒	Have you, your spouse or dependent children, or any of you combined received payments from **OraPharma, Inc.** such as an ownership interest, stock options or any other financial interest whose value cannot be readily determined through reference to public prices, or any equity interest in **OraPharma, Inc.** (if it is a publicly traded organization) exceeding $50,000, or any combination of these? If yes, the amount and nature of the equity interest is as follows:
Yes ☐ No ☒	Have you, your spouse or dependent children, or any of you combined received payments from **OraPharma, Inc.** in excess of $25,000, exclusive of the costs of conducting the clinical studies, such as honoraria, a grant or grants to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation? If yes, the amount and nature of the payment is as follows:

To the best of my knowledge, the information provided above is correct and complete. I understand that I am obligated to amend this statement and notify **OraPharma, Inc.** promptly if there is any change in this information during the conduct of the clinical studies listed above or during one year after the studies have been completed.

Larry Wolff — Signature of Investigator

September 3 1999 — Date

Correspondence from Applicant

01-30-01

ORAPHARMA, INC.
www.orapharma.com

732 Louis Drive
Warminster, PA 18974

215/956-2200 Tel
215/443-9531 Fax

January 30, 2001

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 50-781
Arestin (minocycline hcl) microspheres, 1mg
Amendment: Correction to NDA Amendment 24.1, 24.2

Dear Dr. Wilkin:

Reference is made to OraPharma, Inc.'s submission of January 25, 2001 Amendment #24.1 and 24.2.

During our QA check of the submission the following typographical error was detected in volume 24.2.

In our haste to submit the requested CMC information by the timeframe given, under point 2, appendix #2, Table 1, we inadvertently referenced filling machine [redacted] as [redacted]

Attached is the corrected table with the correction in bold. Please replace the table in Volume 24.2 in the original and archival copies.

If you have any questions regarding this submission, please contact me at (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director, Regulatory Affairs and Quality Assurance

Form FDA.356h
Submitted in duplicate
Desk copy to K. Bhatt

DUPLICATE

Correspondence from Applicant
1-25-01

ORAPHARMA, INC.
www.orapharma.com

732 Louis Drive
Warminster, PA 18974
215/956-2200 Tel
215/443-9531 Fax

Fed Ex'd
Priority Delivery
1/25/01
K. Bhatt

January 25, 2001

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 50-781
Arestin (minocycline hcl) microspheres, 1mg
Amendment: No. 24.1, FDA Requested CMC Information

Dear Dr. Wilkin:

Reference is made to a teleconference between Drs. DeCamp and Gautam-Basak and Ms. K. Bhatt in your Division and Dr. Lawter and Mr. Herzig of OraPharma, Inc. on December 19, 2000. During this teleconference Dr. DeCamp identified a number of issues OraPharma needed to address. The teleconference was followed up by a telefax dated December 22, 2000 which provided the items in writing.

Attached/enclosed are OraPharma, Inc.'s responses to these items. For completeness, I restated the FDAs requests followed by our responses. For item 3 we have enclosed a dispenser/cartridge handle and a pouch containing 12 filled unit dose cartridges in the desk copy package address to Ms. K. Bhatt.

As I indicated in my telefax copy of January 24, 2001, regarding the particle size specifications for the bulk microspheres, this information is included in this amendment submission as the last tab in volume 2.

If you have any questions regarding this submission, please contact me at (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director, Regulatory Affairs and Quality Assurance

Form FDA 356h
Submitted in duplicate
Desk copy to K. Bhatt (containing the dispenser handle and a 12 cartridge pouch of drug product)

Correspondence from Applicant

12.01

ORAPHARMA, INC.
www.orapharma.com

732 Lo
Warminster,
215/956-
215/443-

January 12, 2001

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

NDA ORIG AMENDMENT
SU

RE: NDA 50-781
Arestin (minocycline hcl) microspheres, 1mg
Amendment: Clinical – Final Safety Update

Dear Dr. Wilkin:

Reference is made to a telephone call on January 11, 2001 between Ms. K. Bhatt in your Division and the undersigned. Ms. Bhatt requested OraPharma, Inc. to provide a final safety update for the above referenced NDA.

Attachment 1 summarized the clinical safety since our 120-day safety update submission of June 16, 2000 (amendment 4.1 – 4.14). As the summary shows there were no additional safety reports to submit, as no studies were ongoing until the start-up recently of some pilot-studies.

If you have any questions regarding this submission, please contact me at (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director, Regulatory Affairs and Quality Assurance

Form FDA 356h
Submitted in duplicate

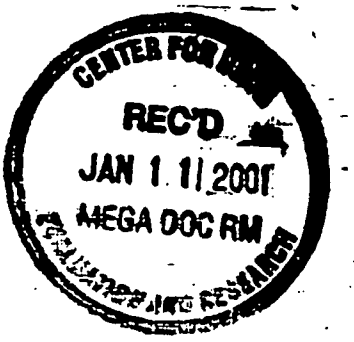
Correspondence from Applicant

01-10-01

PHARMA, INC.
www.orapharma.com

732 Louis Drive
Warminster, PA 18974

215/956-2200 Tel
215/443-9531 Fax



January 10, 2001

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

NDA 0NG AMENDMENT
BC

RE: NDA 50-781
Arestin (minocycline hcl) microspheres, 1mg
Amendment: CMC Amendment

Dear Dr. Wilkin:

This CMC amendment contains updated dispenser (cartridge) components specifications and test methods (STM). These revisions were made to reflect commercial production of these components. At the same time, typographical errors were also corrected.

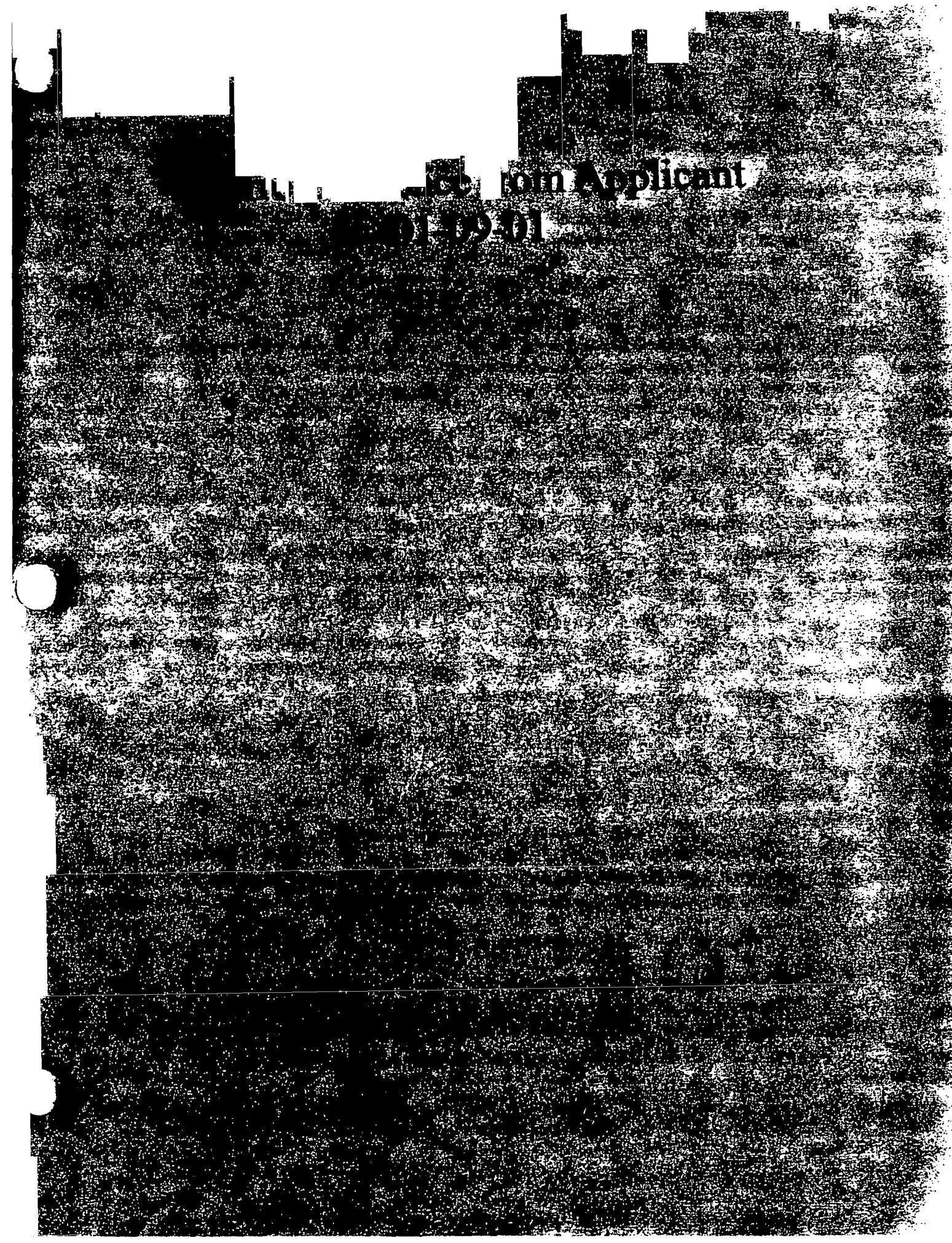
If you have any questions regarding this submission, please contact me at (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director, Regulatory Affairs and Quality Assurance

Form FDA 356h
Submitted in duplicate

ORIGINAL



ORAPHARMA, INC.
www.orapharma.com

215/956-2200 Tel
215/443-9531 Fax

January 9, 2001

NDA ORIG AMENDMENT

XR

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 50-781
Arestin (minocycline hcl) microspheres, 1mg
Amendment: Marketing Exclusivity

Dear Dr. Wilkin:

Reference is made to a telephone call on January 9, 2001 by Ms. K. Bhatt in your Division with the undersigned in which she requested OraPharma, Inc. to officially request marketing exclusivity for the above referenced product according to the patents covering this product.

OraPharma, Inc. herewith requests market exclusivity until August 17, 2010 for Arestin™. August 17, 2010 is the date when the latest two patents (patent no. 5236355 and patent no. 5622498) expire.

If you have any questions regarding this submission, please contact me at (215) 956-2207.

I also attached a copy of the cover letter dated June 5, 2000 (amendment 3.1) in which OraPharma, Inc. provided microbiology feedback to questions raised by Dr. Riley, for which we would appreciate receiving feedback as we have worked on finding a more sensitive method to measure bioburden.

Sincerely,

Markus F. Herzig
Executive Director, Regulatory Affairs and Quality Assurance

Form FDA 356h
Submitted in duplicate

ORIGINAL

[redacted]

[redacted]rrespondence from Applicant

[redacted]01-03-01

you have any questions regarding this submission, please contact me at (215) 956-
207.

ncerely,

arkus F. Herzig
xecutive Director, Regulatory Affairs and Quality Assurance

orm FDA 356h
ubmitted in duplicate

Correspondence from Applicant
12-7-00

ORAPHARMA, INC.

www.orapharma.com

732 Louis Drive
Warminster, PA 18974

215/956-2200 Tel
215/443-9531 Fax

December 7, 2000

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 50-781
Arestin (minocycline hcl) microspheres, 1mg
Amendment: Labeling

Dear Dr. Wilkin:

Reference is made to our draft package insert submitted in our original NDA on February 17, 2000 and our revision to your first draft submitted on December 1, 2000.

Reference is also made to a telephone conversation on December 6, 2000, with Ms. K. Bhatt from your Division and the undersigned. Ms. Bhatt informed OraPharma that our request to change the product unit dose referenced to in earlier correspondence as "tips" or "dispensers" to "cartridge(s)" is acceptable.

As requested, we have made the changes throughout the 2nd FDA draft label which OraPharma received via fax on December 5, 2000.

In table 4, we have identified a discrepancy which we could not verify. In the 5 mm data of Study OPT-103B your table lists the change as –1.32 mm. Our data shows that number as -1.63 mm. We note that Table 4 now presents PD changes based on varying depths in mm rather than percentages, and as study subgroups. We prefer this presentation, but since it is presented as study subgroups (at least for baseline PD ≥ 6 mm and ≥ 7 mm) we suggest it might be prudent to combine these data (see following table). This would make the data presentation more consistent with Table 3.

Table 4: Mean Pocket Depth Change in Patients with Mean Baseline PD ≥ 5 mm, ≥ 6 mm and ≥ 7 mm at 9 Months from Two Multicenter U.S. Clinical Trials

Mean Baseline Pocket Depth	SRP Alone	SRP + Vehicle	SRP + ARESTIN™
≥ 5 mm at Baseline			
≥ 6 mm at Baseline			
≥ 7 mm at Baseline			

*Statistically significant comparison between SRP + ARESTIN™ and SRP alone

OraPharma, Inc. would like to express our appreciation for the work your Division executed in the revised drafting of the package insert.

If you have any questions regarding this submission, please contact me at (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director, Regulatory Affairs and Quality Assurance

Form FDA 356h
Submitted in duplicate

OraPharma, Inc.
732 Louis Drive
Warminster, PA 18974
215-956-2200
Facsimile: 215-443-9531

ORAPHARMA INC.

FAX COVER SHEET

To:	Ms. Kalyani Bhatt, Project Manager	**From:**	Markus Herzig
Company:	FDA	**Date:**	December 7, 2000
Fax No.:	301-827-2075	**No. of pages w/cover:**	1
RE:	NDA-50-781		

[X] *Urgent* [ ] *Reply ASAP* [ ] *Please comment* [ ] *Please review* [ ] *For your information*

Dear Ms. Bhatt:

As requested, attached is the revised draft package insert regarding the change from "tips" and" dispenser" to "cartridges".

We have identified a discrepancy in Table 4 and request corrections. Additionally, we propose a different presentation of Table 4.

If you have any questions, please don't hesitate to contact me.

Sincerely,

Markus F. Herzig
Executive Director Regulatory Affairs and Quality Assurance