

WITHHOLD 8 PAGE (S)

Correspondence from Applicant

12-1-00



ORAPHARMA, INC.

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

December 1, 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: Unit dose Identifier, Draft Labeling

Dear Dr. Wilkin:

Reference is made to a telephone conversation held on December 1, 2000, between Dr. M. Gautam-Basak and Ms. K. Bhatt in your Division and the undersigned from OraPharma, Inc.

Dr. Gautam-Basak requested clarification as to what OraPharma called each individual dosage unit, as OraPharma, Inc. has referred to it by several names (i.e. dispenser, unit dose tip, unit dose dispenser).

I informed Dr. Gautam-Basak that our marketing team has decided to refer to each unit dose as a "cartridge". Dr. Gautam-Basak requested that we submit final revised text for the unit dose cartridge and the package insert.

The enclosed documents; the drawing of a cartridge showing the "OP-1" identifier and the revised draft package insert replacing all older terminology used with the unit dose identifier "cartridge".

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

11-20-00



ORAPHARMA, INC.

www.orapharma.com

732 Louis Drive
Warminster, PA 18974

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

November 20, 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
Minocycline PTS
Amendment: Draft Label Revisions

Dear Dr. Wilkin:

We have received your draft labeling for Arestin (minocycline hydrochloride) Microspheres 1 mg. We appreciate the Division's continued responsiveness to this application and look forward to working with you to facilitate completion of a timely and successful review. The following comments and suggested revisions to your draft labeling focus on three major sections, namely, microbiology, pharmacokinetics and clinical studies. In addition, we have some comments on several miscellaneous additions and changes to our original proposed labeling.

I. Microbiology

A. We request that lines 25-34 of the FDA draft labeling be deleted.

During drug development, FDA agreed with our plans to conduct a study concerning changes in plaque microorganisms using DNA probes. At that time there were no guidelines or precedents in the field for this type of study, and the protocol we submitted and used provided for sampling of only one site in each patient. We were the first sponsor to explore this relatively new technique.

Our microbiology study was designed for safety and as such looked for long-standing alterations in the subgingival microflora across the patient population. Sampling one site per patient and analyzing proportional

changes are acceptable methods to achieve that objective. To study antimicrobial effects on specific organisms, more sensitive methods are called for. These include a larger number of samples per patient, and an analysis of either the change in number of sites harboring the organism, or the reduction in the numbers of a specific organism. A consensus of experts in this area, e.g., Goodman, Socransky and others, is that one sampling site in each patient is inadequate to provide definitive data about the qualitative and quantitative changes in plaque microorganisms. Recent publications support that one site per patient is not adequate to obtain reliable results.

Having said that, we agree with the Agency that this type of work may be of value. Accordingly, if you desire, we would be willing to immediately consider conducting such a trial with a suitable number of sites to establish the relative distribution of microorganisms following treatment.

- B. We propose that lines 35-38 be revised to read:

[

We believe it is important to describe that the sampling in this study was performed at only two centers and only in a single site in each subject, and that these changes were neither statistically nor clinically significant. We believe that this context will enable dental professionals to better understand how the trial was conducted and to put the results in the proper perspective.

II. Pharmacokinetics

- A. In this section we would like to add the following text at line 47:
(NDA PK Section 6.2.4.1 Vol. 1.11 page 20)

[



We believe that it is important to describe the high levels of minocycline that are present in the crevicular fluid over at least 14 days. The sustained release of minocycline from microspheres is a fundamental basis for the original development of this product, and is therefore an important aspect of the mechanism of action of ARESTIN. We believe this should be communicated to the dental professional.

B. In table 1 we added the SEM as requested by the Division.

III. Clinical Studies

A. In this section of the draft labeling, line 64, you changed the mean probing depth baseline range from ~~—~~ mm and ~~—~~ mm to 5.90 and 5.81 mm. The original values reflect the range of the data we presented in Table 2. Please clarify the source of the values in your draft.

B. In the description of the patients that were included in our clinical trials, we propose to insert the following sentence after the word "health" in line 69:

[These patients were prospectively included in the studies and were evaluated as a sub-population. Therefore, we believe it is important to include these populations in the labeling and to disseminate information about these difficult to treat patients.]

C. Concerning Table 2, we request that the Agency reinsert the row containing the 9 months data.

We believe that this information was inadvertently deleted since the title of the table and the statistical description in the footnotes to the table both refer to the 9 months data that were removed from this draft. We also acknowledge our typographical error in describing the data as SD when the table actually presented SEM, and have corrected this description.

- D. On line 85 of your draft labeling, you refer to probing depth reductions of -1.42 mm, -1.10 mm, and -1.18 mm for SRP + ARESTIN, SRP + Vehicle, and SRP alone, respectively. Our original proposed labeling contained the values _____, respectively. Our values are contained in the ISE and we have not been able to determine the source of the values you inserted.
- E. Concerning Table 3, the last row of the data and the text in the labeling describing those data were deleted in your draft. We therefore propose to reinsert both the second row of Table 3 and the text language as follows into the labeling.

_____ resulted in a greater percentage of pockets showing a change in PD of ≥ 2 mm and ≥ 3 mm compared to SRP alone at 9 months, as shown in Table _____

OraPharma evaluated the numbers and percentages of pockets showing a change of pocket depth by ≥ 2 or ≥ 3 mm as was agreed to by the Division reflected in the meeting minutes of the pre-NDA meeting of June 7, 1999. We believe that such information is valuable to the dental professional treating patients.

- F. OraPharma requests that the following information be added to the "Clinical Studies" section of the labeling at line 90:
"In both studies, the following patient subgroups were prospectively analyzed: smokers, patients over and under 50 years of age, and patients with a previous history of cardiovascular disease."

In smokers, the mean reduction in pocket depth at 9 months was less in all treatment groups than in non-smokers, but the reduction in mean pocket depth at 9 months with _____ ARESTIN™ was significantly greater than in SRP alone or in SRP + vehicle – TABLE 4.

The patient subgroups described above were predefined in the statistical analysis plan, and were prospectively analyzed as an integral part of the clinical studies. These analyses were reviewed by the pre-NDA meeting on June 7, 1999, and in the statistical analysis plan submitted to the Division Oct. 22, 1999, (IND _____ Serial number 106), after a teleconference between representatives from your Division, Biostatistics and OraPharma, Inc. on Oct. 21, 1999. The IND submission was made prior to unblinding the studies and starting the analysis. The results of each of these analyses were highly statistically significant. They confer information we believe should be in the labeling because it addresses clinically important and difficult to treat segments of the patient population.

Since deeper pockets are also difficult to treat, the studies were also prospectively analyzed in this regard. The data showed statistically significant differences between SRP + ARESTIN versus SRP alone. Again, we believe this is important information for the dental professional.

IV. Miscellaneous Additions/Changes

◦ A. Description

On line 9 we would like to insert: _____

An important characteristic of the polymer chosen for ARESTIN's™ development is its ability to hydrolyze and cause the microspheres to adhere to the tissues of the periodontal pocket, thereby facilitating sustained drug levels. We believe that it is important for the dental professional to be aware of this characteristic of the product in order to use it properly and to better inform the patient of the procedure and the patient's expectations.

B. Dosage and Administration

We recommend uniformly changing the words "tips/dispensers" to the word "cartridge" in this Section and in any other mention in the labeling. In addition, at the end of this section, line 210, we propose to add: _____

We believe that this is very important information to include in this section, since it directly affects how the product is applied. In the clinical studies, no adhesive or dressing was used, since the product itself is inherently bio-adhesive.

C. How Supplied

As we submitted in our NDA amendment 14.1 on November 9, 2000, we added as requested by the Chemistry Review Team a product identifier to each cartridge:

"Each unit dose cartridge contains the product identifier "OP-1".

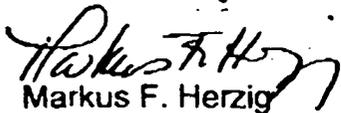
In the remaining sections of the draft labeling, up to "Dosage and Administration," we are in agreement with the Agency's proposed revisions, and have only edited minor spelling mistakes and similar clerical errors.

Additionally, we want to alert you that the figures 1 through 3 in the Dosage & Administration Section will be updated with the hands wearing surgical gloves as is standard in the dental profession, as soon as the art work becomes available.

We look forward to the Agency's review of our response to your draft, and to continuing to work closely with the Division. In the future, we hope to continue to further the knowledge of periodontal disease and treatments.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT OraPharma, Inc.	DATE OF SUBMISSION November 20, 2000
TELEPHONE NO. (Include Area Code) 215-956-2200	FACSIMILE (FAX) Number (Include Area Code) 215-443-9531
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 732 Louis Drive Warminster, PA 18974	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Markus F. Herzig 732 Louis Drive Warminster, PA 18974

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 50-781

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Minocycline PTS (Minocycline Periodontal Therapeutic System)	PROPRIETARY NAME (trade name) IF ANY ARESTIN™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 7 - dimethylamine - 6 - demethyl - 6 - doxycycline hydrochloride	CODE NAME (If any) --	
DOSAGE FORM: topical	STRENGTHS: 1 mg	ROUTE OF ADMINISTRATION: Subgingival

(PROPOSED) INDICATION(S) FOR USE: Adjunctive therapy to scaling and root planing procedures in patients with adult periodontitis

APPLICATION INFORMATION

APPLICATION TYPE (check one)

NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.84)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b) (1) 505 (b) (2) 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one)

ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION

PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

REASON FOR SUBMISSION Requested Information

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

NA

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NA

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d) (1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
- 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
- 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
- 9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
- 10. Statistical section (e.g. 21 CFR 314.50 (d) (8), 21 CFR 601.2)
- 11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
- 12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k) (1))
- 17. Field copy certification (21 CFR 314.50(k) (3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. OTHER (Specify)

CERTIFICATION

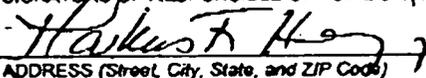
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

- 1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
- 2. Biological establishment standards in 21 CFR Part 600.
- 3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
- 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
- 5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
- 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
- 7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Markus F. Herzig, Executive Director Regulatory Affairs and Quality Assurance	DATE November 20, 2000
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ADDRESS (Street, City, State, and ZIP Code) 732 Louis Drive Warminster, PA 18974	TELEPHONE NUMBER 215-956-2200
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Washington, DC 20201

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Correspondence from Applicant

11-16-00