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) (6), 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, 680 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 review 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	DATE
Markus F. Hertig	Markus F. Herzig, Executive Director Regulatory Affairs and Quality Assurance	January 24, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
732 Louis Drive Warminster, PA 18974	215-956-2200

Please **DO NOT RETURN** this form to this address.

Appendix 1

WITHHOLD 1 PAGE (S)

Appendix 2

WITHHOLD 8 PAGE (S)

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: 1-23-01 Pages (including cover) 2

TO: Markus Herzig

COMPANY: Ornpharma

ADDRESS:

FAX PHONE#: 1-215-443-9531 Our Fax # (301) 827-2075

Voice # (301) 827-2020

MESSAGE:

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Kalyani Bhatt

TITLE: Project Manager

TELEPHONE: 301-827-2020

1. Particle Size Specification/Method/Acceptance Criteria

a). Reference is made to your correspondence dated December 12, 2000, to Ms. Debbie Pagano of PHL-DO. Please refer to Table 1 submitted with this response. We recommend that you propose acceptance criteria for a particle size specification for the Bulk Microspheres based on the data submitted in this table. Your submission should also include a copy of the method used to obtain the data in this Table. Please submit this in the form of revised specifications for bulk microspheres (OraPharma Specifications and Test Methods No. 110), including the particle size specification.

b). At this time, we do not recommend any revision in the Regulatory Specifications for the finished/packaged drug product (OraPharma Specifications and Test Methods No. 112).

2. Please submit whatever response you have to our information requests faxed on November 28 and December 22, 2000 by no later than January 22, 2001. If no information is available at this time, please indicate that under the specific question.

3. This information must be received not later than Monday, January 29, 2001, in order to avoid an impact on the approvability of your NDA.

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:**	1/12/01
Fax No.:	301-827-2091	**No. of pages w/cover:**	5
RE:	NDA-50-781		

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

Dear Ms. Bhatt:

As requested, attached is the safety update submission.

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

Sincerely,

Markus F. Herzig
Executive Director Regulatory Affairs and Quality Assurance

ORAPHARMA, INC.
www.orapharma.com

732 Louis Drive
Warminster, PA 18974

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

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

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

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.

FOR FDA USE ONLY
APPLICATION NUMBER

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

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

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
OraPharma, Inc.	January 12, 2001
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
215-956-2200	215-443-9531
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):	**AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE**
732 Louis Drive Warminster, PA 18974	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)	PROPRIETARY NAME (trade name) IF ANY
Minocycline PTS (Minocycline Periodontal Therapeutic System)	ARESTIN™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)
7 - dimethylamine - 6 - demethyl - 6 - deoxytetracycline hydrochloride	--

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
topical	1 mg	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 314.94)
☐ 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) (6), 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 review 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	DATE
Markus F. Herzig	Markus F. Herzig, Executive Director Regulatory Affairs and Quality Assurance	January 12, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
732 Louis Drive Warminster, PA 18974	215-956-2200

Please DO NOT RETURN this form to this address.

ATTACHMENT 1:

Safety Summary

- Study Protocol OPI-106 was an open label extension at Dr. Persson's site to evaluate patient treatment needs following application wit Arestin™. No further drug treatment occurred in study OPI-106, beyond that which was administered in Protocol OPI-103A in these patients.
  - Patients enrolled 35
  - Patients completed 30
    - o No adverse events reported
- A single patient (compassionate use) was treated under protocol OPI-125.
    - o No adverse events reported
- Five (5) pilot study protocols were submitted to the IND [redacted] and have enrolled the following numbers of patients so far:

Study Number	No. Patients
OPI-123	3
OPI-126	4
OPI-127	5
OPI-128	0
OPI-130	5

  - o No adverse events reported

Conclusion: No further safety information can be added to the report submitted for the 120-day safety update; as only a few additional patients have been treated.

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:	Division of Dermatologic / Dental Drug Products	**Date:**	1/11/01
Fax No.:	301-827-2091	**No. of pages w/cover:**	2
RE:	Marketing Exclusivity		

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

Kalyani:

Attached is Amendment 22.1 regarding the market exclusivity.

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

Thank you,

Markus F. Herzig

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: January 10, 2001

To: Markus F. Herzig	**From:** Kalyani Bhatt
Company: Orapharma, Inc	Division of Division of Dermatologic & Dental Drug Products
Fax number: 215-443-9531	**Fax number:** 301-827-2075
Phone number: 215-956-2200	**Phone number:** 301-827-2020

Subject: Chemistry Micro Review Completed for NDA 50-781

Total no. of pages including cover: 2

Comments:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: ☐ YES ☑ NO

Please see commments from the CMC Microbiology Reviewer.

List of Deficiencies and comments:

1. The sponsor states on page 5 of this submission that a test for *E. coli* as an objectionable organism will be added as a specification. Please provide a test method for detection of *E. Coli* and add the absence of *E. coli* to the drug product specifications.

2. The sponsor also states that they will evaluate alternate testing methodology based on unit dose pooling and testing bulk drug product as a replacement for the current method. The sponsor should note that if they desire to change to an alternate method for routine testing they must inform the agency of this change either as an amendments to this application (prior to the approval of the application) or as a supplement to an approved application.

TIME : JAN 10 '01 17:44
TEL NUMBER : 3018272075
NAME : FDA/DTDP

NBR	FILE	DATE	TIME	DURATION	PGS	TO	DEPT NBR	MODE		STATUS
826	F.3	JAN.10	17:43	00/42	2	912154439531		EC	M	OK

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: 1-8-00 Pages (including cover) 2
TO: Markus Herzig
COMPANY: Orapharma
ADDRESS:
FAX PHONE#: 215-443-9531 Our Fax # (301) 827-2075
Voice # (301) 827-2020

MESSAGE:
Heres a 2nd copy that was faxed to you.

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Kalyani Bhatt
TITLE: PM.
TELEPHONE: 827-2020

CMC Labeling comments: NDA 50-781

Arestin (minocycline hydrochloride) Microspheres, 1 mg

DESCRIPTION

Arestin (minocycline hydrochloride) Microspheres is a subgingival sustained-released product containing the antibiotic minocycline hydrochloride incorporated into a bioresorbable polymer, poly(glycolide-co-dl-lactide) or PGLA, for professional subgingival administration into periodontal pockets. Each unit dose dispenser delivers minocycline hydrochloride equivalent to 1 mg of minocycline free base.

The molecular formula of minocycline hydrochloride is $C_{23}H_{27}N_3O_7 \cdot HCl$, and the molecular weight is 493.94. The structural formula of minocycline hydrochloride is:

HOW SUPPLIED

Arestin (minocycline hydrochloride) Microspheres, 1 mg is supplied in unit doses of 12 ——— in one tray (NDC number) packaged with desiccant in a heat-sealed foil laminate resealable pouch. There are two pouches in each box.

Storage Conditions

Store at 20-25°C (68-77°F): excursions permitted to 15-30°C (59-86°F).
Avoid exposure to excessive heat.

RX only

Manufactured for OraPharma, Inc.

Distributed by: ORAPHARMA, INC.

We have the following comments on the container label (submission dated August 16, 2000)

1. Minocycline HCl should be more bold with respect to prominence in relation to the trademark, Arestin
2. The label should include statement - Rx Only
3. Storage statement should be consistent with the above recommendations.
   Store at 20-25°C/60% RH

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:**	1/3/01
Fax No.:	301-827-2075	**No. of pages w/cover:**	7
RE:	NDA-50-781		

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

Ms. Bhatt:

We will officially submit a color copy of the Pouch and Box labels tomorrow.

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

Sincerely,

Markus F. Herzig
Executive Director Regulatory Affairs and Quality Assurance

ORAPHARMA, INC.
www.orapharma.com

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

January 3, 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: Pouch Label and Box Label

Dear Dr. Wilkin:

Reference is made to a teleconference held on December 22, 2000 between Drs. DeCamp, Gautam-Basak and Ms. Bhatt in your Division and representatives from OraPharma, Inc. during which NDA CMC issues were discussed. At the end of the teleconference, the undersigned requested input from the FDA regarding our pouch labels for the Arestin product. The reason for this request is the extremely long lead-time for the production of these labels and I was assured by Dr. DeCamp that we would receive feedback on this pouch label along with the CMC points raised during our teleconference.

In an earlier discussion with Ms. Bhatt, I raised the same issue and was informed that if the same text is being used as in the draft package insert the label may be acceptable unless the Chemistry reviewer has objections to the artwork. Further, in order to complete our filling and packaging validation, we would need to have pouch labels to fulfill the validation procedures.

We have reached the time where we would have to produce the pouch labels at risk and great cost to our company and respectfully ask for your feedback by Friday morning, January 5, 2001.

I will contact Ms. Bhatt on Friday and hope to receive your acceptance for the pouch label. We also included the box label, and if at all possible, would appreciate to receive your feedback as well.

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

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

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

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

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT OraPharma, Inc.	DATE OF SUBMISSION January 3, 2001
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 (trademame) IF ANY ARESTIN™
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 7 - dimethylamine - 6 - demethyl - 6 - deoxytetracycline 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 314.94)
☐ 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 Requesting 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)

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

☐	1. Index		
☒	2. Labeling *(check one)*	☒ Draft Labeling	☐ Final Printed Labelling
☐	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) (6), 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 review 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	DATE
Markus F. Herzig	Markus F. Herzig, Executive Director Regulatory Affairs and Quality Assurance	January 3, 2001

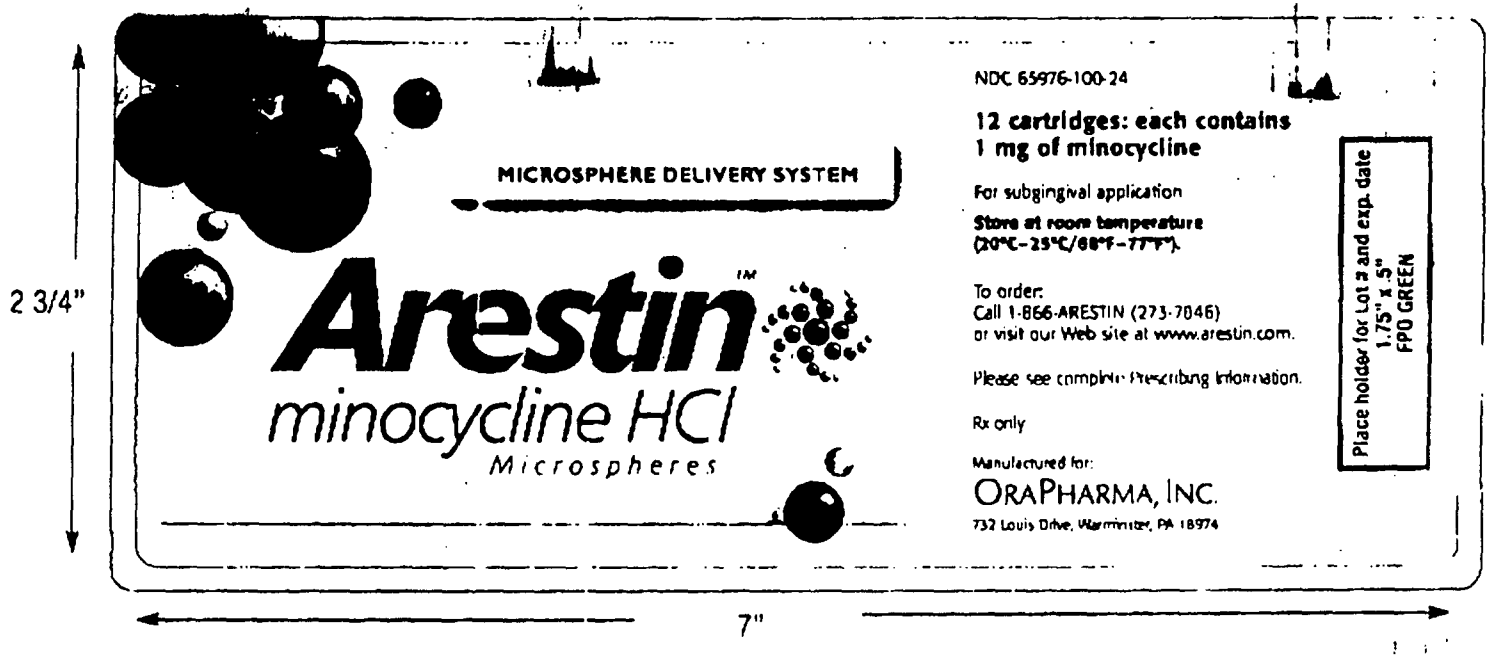
ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
732 Louis Drive Warminster, PA 18974	215-956-2200

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing 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:

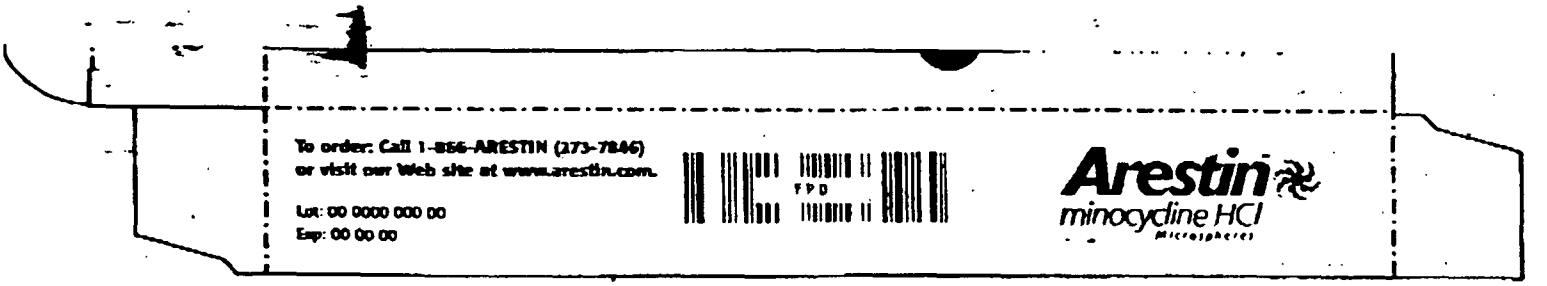
DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please DO NOT RETURN this form to this address.



Orapharma Pouch Label
7" x 2 3/4" 1/8" corner radius
Unwind position: 4
Acucote 60# Semigloss/40# SCK/AC-34TA



Printed at 60%

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:**	1/3/01
Fax No.:	301-827-2075	**No. of pages w/cover:**	7
RE:	NDA-50-781		

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

Ms. Bhatt:

We will officially submit a color copy of the Pouch and Box labels tomorrow.

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

Sincerely,

Markus F. Herzig
Executive Director Regulatory Affairs and Quality Assurance

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:	Division of Dermatologic/Dental Drug Products	**Date:**	12-22/00
Fax No.:	301-827-2075	**No. of pages w/cover:**	3
RE:	Teleconference Meeting Minutes – November 28, 2000		

☐ *Urgent* ☐ *Reply ASAP* ☐ *Please comment* ☐ *Please review* ☐ *For your information*

Ms. Bhatt,

Attached are my teleconference weekly minutes you requested.

Markus Herzig

FDA Contact Report	Date: November 20, 2000
Project: Arestin	■ **FDA Initiated** □ **OraPharma, Inc. Initiated**
IND #	**NDA #:50-781**
Contact Person:	Ms. K. Bhatt, Project Manager – 302-827-2023 Division of Dermatologic and Dental Drug Product

Teleconference held on December 19, 2000, 2:30 pm.

FDA participants: Dr. W. DeCamp – Chemistry Team Leader
Dr. M. Gautam – Basak – Chemistry Review
Ms. K. Bhatt – Project Manager

OraPharma participants: Dr. R. Lawter – Ex. V. P. Chief Scientific and Technical Officer
Mr. M. Herzig – RA/QA

Dr. DeCamp informed OraPharma that there are several items for which FDA requests additional information and or clarification.

1. In the methods validation volume 2.1 submitted on April 12, he identified that it is incomplete as it did not contain detailed data information. He requested that we submit raw test data for drug substance lot 03868 and final product lot 9366C.

2. Dr. DeCamp asked for a sample of actual dispensers (cartridges) and a sample dispenser handle.

3. He inquired about the telefax FDA sent to OraPharma dated November 28, 2000 regarding particle size distribution specifications for the final product.

4. Dr. DeCamp pointed out that the flow chart in Volume 1.3 (original NDA) and the information provided in volume 1.7 (original NDA), is not consistent and requested clarification.

5. Dr. DeCamp pointed out that our release test results show large variations and asked for our explanation and why such data should be acceptable or the test is suitable.

6. Dr. DeCamp requested a COA from the dispenser components from ——— and specification information for critical dimensions.

As a more general concern, FDA stated that they are not comfortable with our control for the filling of each unit dose cartridge. They are aware of the static build-up and want to know how we intent to control the filling process. Dr. Lawter explained that this is accomplished by our weight check during the filling process and by testing uniformity of dosage units as well as the release testing of minocycline from the product. Additionally, 100% of each unit dose is visually inspected.

Dr. DeCamp asked OraPharma when we would be able to respond to their November 28 telefax which requested particle size distribution specifications for our product. Dr. Lawter explained that we have identified a contract laboratory which will be able to conduct such testing. They are in the process of validating the method after which they would generate the data FDA requested. Dr. Lawter asked Dr. DeCamp if he feels that the [redacted] identified would be satisfactory. Dr. DeCamp stated that as long as the distribution is unimodal as which he believes it is, it would be a reliable method should provide such assurance.

FDA asked whether or not we could use the USP weight variation test to show accuracy of product fill into the unit dose cartridges. Dr. Lawter explained that method is not usable as our dosage of 4.5 mg. is too small to use the USP method. In lieu of such a test, Dr. Lawter stated that we use a test for uniformity of dosage unit.

Mr. Herzig asked if FDA could provide us with feedback on the pouch labels in order for OraPharma to complete filling and packaging violation. He stated that the leadtime for these labels is rather long and it would be very helpful to receive their input. Dr. DeCamp stated that we would receive feedback along with the issues discussed in a telefax from the FDA

Mr. Bhatt then asked Mr. Herzig to prepare the meeting minutes of this conversation which he agreed to prepare and fax to FDA.

We thanked FDA for the information exchange and reiterated that we will work expeditiously to prepare our responses. The conversation was then concluded.

Signature: Paulus F Herzig **Date:** 12/21/00

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: 12/22/00 Pages (including cover) 3

TO: Markus Heizig

COMPANY: Ora pharma

ADDRESS:

FAX PHONE#: 215-443-9531 Our Fax # (301) 827-2075

Voice # (301) 827-2020

MESSAGE:

Markus,
Attached are the CMC issues

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Kalyani Bhatt

TITLE: Project Manager

TELEPHONE: 301 827-2020

CMC comments as discussed at the t -con of December 19, 2000 with OraPharma (NDA 50-781)

1. Method validation package (Vol. 2.1) received on 4/12/2000 is incomplete. Certificate of Analyses for samples listed (i.e. Lot # 03868 for Minocycline hydrochloride Drug Substance and Lot #98336C for the finished drug product) along with full specification test results should be provided.

2. Your response to our CMC Information Request letter faxed on November 27, 2000 is outstanding.

3. Please ship a representative unit dose dispenser/delivery system (i.e. dispenser with handle) including one filled/packaged dosage unit.

4. Provide COA (from ———) and acceptance criteria (from PCI, Inc.) for dispenser cartridge unit.

5. The packaging flow-chart (Vol. 1.3, page 26) and packaging directions for batch no. 98214 (Vol. 1.7, Tab 4.8 Batch Documentation) are not consistent.

   In response, the applicant informed that the packaging directions for batch No. 98214 are for the ——— filling machine. For the to-be-marketed product packaging will be performed using ——— machine.

   A description of the packaging procedure for to be marketed product using ——— filling machine should be provided.

6. On page 186 (Vol. 1.7) you have indicated that the % accountability should be between —— %. The % accountability for batch no. 98214 was about —% with an overall yield of —%. On page 154 you have included a Deviation Report where it is indicated that "There will be no corrective measures at this time". Please explain.

What corrective measures are planned in future for such deviations?

7. Describe various controls that are employed for checking fill weight of the dosage units. This should include information on sampling procedures.

MESSAGE CONFIRMATION

12/22/00 12:24

NO.	MODE	BOX	GROUP
573	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
12/22 12:23	00'43"	912154439531	003/003	OK		0000

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: 12/22/00 **Pages (including cover)** 3

TO: Markus Hezig

COMPANY: Ora pharma

ADDRESS:

FAX PHONE#: 215-443-9531 **Our Fax # (301) 827-2075**

Voice # (301) 827-2020

MESSAGE:

Markus,
Attached

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: November 28, 2000 Number of Pages 2 (Including cover sheet)

TO: Markus Herzig
COMPANY: OraPharma
FAX #: 215-443-9531

MESSAGE: **Please see comments for the submission dated November 3, 2000. NDA 50-781, ARESTIN (minocycline hydrochloride) microspheres 1mg**

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

NDA 50-781-000 ARESTIN (minocycline hydrochloride) microspheres, 1 mg

1.) The proposed specifications for bulk Minocycline Microspheres ("OraPharma Specifications and Test Methods No. 110") and Minocycline Microspheres, 1 mg; 12 Unit Dose Package ("OraPharma Regulatory Specifications and Test Methods No. 112") fail to include a specification for particle size distribution. Please revise specifications to include a specification for particle size distribution.

2.) We have the following comments regarding the amendment dated November 3, 2000.

Particle size distribution data should be provided to demonstrate the sameness of the product filled/packaged using the two different filling machines. Specifically, we suggest the following studies be performed and the results be submitted:

i) A comparison of particle size distribution data for Minocycline Microspheres before and after a complete filling cycle (to mimic the actual filling operation time) using the ——— filling machine;

ii) A summary of the historical particle size distribution data for Minocycline Microspheres filled/packaged using the manually operated filling machine (i.e. ————), if available. If no historic data are available, particle size distribution studies should be performed on available samples from clinical/stability batches and the results submitted.

MESSAGE CONFIRMATION

11/27/00 15:41

NO.	MODE	BOX	GROUP
420	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
11/27 15:41	00'34"	912154439531	002/002	OK		0000

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: November 28, 2000

Number of Pages 2
(Including cover sheet)

TO: Markus Herzig
COMPANY: OraPharma
FAX #: 215-443-9531

MESSAGE: **Please see comments for the submission dated November 3, 2000. NDA 50-781, ARESTIN (minocycline hydrochloride) microspheres 1mg**

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: November 13, 2000

Number of Pages 8
(Including cover sheet)

TO: Markus Herzig
COMPANY: OraPharma
FAX #: 215-443-9531

MESSAGE: **Please submits the variation in values in Table 1 expressed in Standard errors rather than ——————— for NDA 50-781 Minocyline. Please find the enclosed draft label.**

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

WITHHOLD 7 PAGE (S)

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

ORAPHARMA INC.

FAX COVER SHEET

To:	Jonathan K. Wilkin, MD	**From:**	Markus Herzig
Company:	Food and Drug Administration	**Date:**	November 3, 2000
Fax No.:	301-827-2075	**No. of pages w/cover:**	30
RE:	**NDA 50-781**		

☐ *Urgent* ☐ *Reply ASAP* ☐ *Please comment* ☒ *Please review* ☐ *For your information*

Attached is the requested clinical information.

Please let me know if any additional information is needed.

Sincerely,

Markus F. Herzig
Associate Director Regulatory Affairs and Quality Assurance

ORAPHARMA, INC.
www.orapharma.com

732 Louis Drive
Warminster, PA 18974

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

November 3, 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: Requested Clinical Information

Dear Dr. Wilkin:

Reference is made to a teleconference held on November 2, 2000 between Drs. Gilkes, Hyman and Ms. Bhatt from your division and Dr. Lessem and Mr. Herzig from OraPharma, Inc. The medical review team requested additional information. Dr. Hyman identified that a narrative of an SAE patient was missing from the 120 day safety update submitted on June 16, 2000 as amendment 4.1. Further, Dr. Hyman stated that he would like a summary of all the discontinued patients from our studies OPI-103A, OPI-103B, and OPI-104. He informed OraPharma that the statistician stated that the numbers do not add up correctly.

Dr. Hyman asked when we would be able to submit this information and added that he would appreciate it if we could provide it before November 6, 2000 PM as the FDA has a meeting scheduled to discuss this NDA. Dr. Lessem told Dr. Human that we would supply his requested information before the FDA's meeting time.

Attached herewith is the additional narrative for patient 01-027, and copies of all the discontinuation sections from the referenced studies (OPI-103A, OPI-103B, OPI-104 as well as the ISS and ISE).

I hope the information provided clarifies the medical review teams questions, but please don't hesitate to call me if additional information needed.

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

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

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

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

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
OraPharma, Inc.	November 3, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** (Include Area Code)
215-956-2200	215-443-9531
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	**AUTHORIZED U.S. AGENT NAME & ADDRESS** (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE
732 Louis Drive Warminster, PA 18974	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 Periodontal Therapeutic System)	PROPRIETARY NAME (trade name) IF ANY
Minocycline PTS	ARESTIN™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)
7 - dimethylamine - 6 - demethyl - 6 - deoxytetracycline hydrochloride	—

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
topical	1 mg	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 314.94)
☐ 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) (6), 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 review 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	DATE
Markus F. Herzig	Markus F. Herzig, Executive Director Regulatory Affairs and Quality Assurance	November 3, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
732 Louis Drive Warminster, PA 18974	215-956-2200

OBSERVATIONS: Only Five (5) Narratives are provided but the text states there are Six(6) SAEs identified in the 120-day safety update.

ANSWER: The additional narrative is attached for patient 01-027

Patient 01-027 (Investigator Reinhardt) was a 44-year-old female. She was admitted to the hospital for a planned lumbar disc repair on 18 June 1999, 158 days after the first dose of study treatment. This patient had a history of degenerative disc disease since 1994. Concomitantly, the patient had been taking Provella-14 (PremPro) since 1998 and sodium fluoride since 1999. This hospitalization did not delay treatment and the patient continued on study. This event was judged by the Investigator to be unrelated to study drug.

Patient 01-030 (Investigator Reinhardt), a 45-year-old female, was admitted to the hospital for gallbladder surgery on 13 September 1999, 271 days after the first dose of study treatment. This patient had a frequent upset stomach since 10 March 1999 for which she took ranitidine until 9 May 1999 with little improvement. Lansoprazole was taken from 10 May 1999 to 1 September 1999, with no marked improvement. The patient was diagnosed with cholecystitis and admitted into the hospital on 13 September 1999 for a cholecystectomy. She was released on 14 September 1999. The investigator considered this event as not related to study drug. The patient completed the study on 10 December 1999.

Patient 03-007 (Investigator Hart), a 38-year-old female, was admitted to the hospital for pneumonia on 3 March 1999, 76 days after the first dose of study treatment. She became ill on 1 March 1999 and her physician diagnosed her with pneumonia and fluid in the lungs. The patient was treated with azithromycin from 01 March 1999 until 03 March 1999. Once admitted into the hospital, this patient was treated with ceftriaxone and ciprofloxacin until she was discharged on 06 March 1999. This patient had a relevant medical history of sinus problems and ear infections since 1998. Concomitantly, the patient had been taking R-tannate and cyclobenzaprine since 1998. The investigator considered this event as not related to study drug. This patient completed the study on 28 December 1999.

Patient 03-009 (Investigator Hart), a 49-year-old female, was admitted to the hospital for a ruptured appendix on 27 October 1999, 339 days after the first dose of study treatment. The patient underwent an emergency appendectomy on 27 October 1999. The patient remained in the hospital for four days and was released without complication on 30 October 1999. Concomitantly, the patient had been taking fluoxetine since 1995. The investigator considered this event as not related to study drug.

Patient 03-047 (Investigator Hart), a 57-year-old male, was admitted to the hospital for angina on 14 October 1999, 269 days after the first dose of study treatment. The patient presented himself to his physician with the chief complaint of chest pain and pain in left arm. Results of a coronary arteriogram revealed total occlusion of a non-dominant right coronary artery. A coronary angioplasty and stainless steel stent placement were performed on 15 October 1999. The patient was released from the hospital without complication on 16 October 1999. The patient completed the study on 14 January 2000. The patient had no past history of cardiovascular disease, however, a family history did exist. Subsequent to this procedure, the patient was concomitantly taking atenolol, aspirin, vitamin E, and nitroglycerin. The following medications were given during the angioplasty procedure: fentanyl, versed, heparin, mannitol, nitroglycerin, neosynephrine, abciximab, and clopidogrel. The investigator considered this event as not related to study drug.

OBSERVATION: There are discrepancies in the numbers of discontinued patients in the studies OPI-103A, OPI-103B and OPI-104.

ANSWER: The sections containing the discontinuation information from the individual reports as well as the ISS and ISE are provided.

The discontinuations from study OPI-103A and OPI-103B are six (6) in each study and are appropriately summarized in the ISE with 12 discontinuations (part 1).

The discrepancy which was identified occurred in study OPI-104. The individual study report lists only nine (9) discontinuations whereby the ISS included ten (10) discontinuations.

The explanation is that in the study report the patient who only underwent SRP and was not treated with minocycline PTS was not included, whereby this patient was counted in the ISS. The Part 2 attachment contains the section from the report of Study OPI-104 as well as the post-text table 2.1 which identifies the discontinued patient. As listed on page 3 of 8 (pagination page 15) patient 016 provides the explanation for the discontinuation.

For completeness I have attached copies from the ISS as well as the 12-month update.

PART 1

OPI – 103A 9 Months

INFORMATION

Table 10.1A. Patient Evaluation Groups

	Treatment Group		
	MPTS N=121	Vehicle N=123	S/RP Alone N=124
Number (%) of Patients			
Randomized	121	123	124
Treated	121 (100.0)	123 (100.0)	124 (100.0)
Completed	115 (95.0)	112 (91.1)	114 (91.9)
Discontinued	6 (5.0)	11 (8.9)	10 (8.1)
Analyzed for Efficacy			
Intent-to-treat	121 (100.0)	123 (100.0)	124 (100.0)
Evaluable	110 (90.9)	111 (90.2)	112 (90.3)
Analyzed for Safety	121 (100.0)	123 (100.0)	124 (100.0)

Source: **Post-text Table 1.**

A total of 27 (7.3%) patients discontinued the study after treatment; similar numbers of patients across treatment groups discontinued the study. Most of these patients (15/27, 55.6%) were lost to follow-up. Only one patient, a Vehicle patient, discontinued the study due to an AE. Patient 1040458 (Vehicle) was discontinued due to an SAE of myocardial infarction. Study completion status, by patient, is provided in **Appendix 16.2, Listing 2.1**. Study discontinuations are summarized in **Section 14, Post-text Table 8** and provided in **Table 10.1B** below.

Table 10.1B. Study Discontinuations (Safety Sample)

	Treatment Group		
	MPTS N=121	Vehicle N=123	S/RP N=124
Number (%) of Patients			
Total Number of Discontinuations	6 (5.0)	11 (8.9)	10 (8.1)
Discontinuations among smokers[1]	4 (7.8)	3 (6.0)	6 (12.0)
Discontinuations among nonsmokers	2 (2.9)	8 (11.0)	4 (5.4)
Reason			
Adverse event	0 (0.0)	1 (0.8)	0 (0.0)
Protocol violation	0 (0.0)	2 (1.6)	0 (0.0)
Withdrawal of consent	1 (0.8)	1 (0.8)	3 (2.4)
Female became pregnant	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	3 (2.5)	6 (4.9)	6 (4.8)
Patient rescue	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (1.7)	1 (0.8)	1 (0.8)

[1] Percentage of discontinuations among smokers and non-smokers is computed out of the number of smokers and non-smokers, respectively.

Source: **Post-text Table 8.**

OPI – 103B, 9 MONTH

Table 10.1B. Study Discontinuations (Safety Sample)

	Treatment Group		
	MPTS N=128	Vehicle N=126	S/RP Alone N=126
Number (%) of Patients			
Total Number of Discontinuations	6 (4.7)	8 (6.3)	11 (8.7)
Discontinuations among smokers[1]	1 (2.6)	3 (7.5)	7 (17.1)
Discontinuations among nonsmokers	5 (5.6)	5 (5.8)	4 (4.7)
Reason			
Adverse event	1 (0.8)	0 (0.0)	0 (0.0)
Protocol violation	1 (0.8)	0 (0.0)	0 (0.0)
Withdrawal of consent	1 (0.8)	4 (3.2)	2 (1.6)
Female became pregnant	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	3 (2.3)	4 (3.2)	7 (5.6)
Patient rescue	0 (0.0)	0 (0.0)	1 (0.8)
Other	0 (0.0)	0 (0.0)	1 (0.8)

[1] Percentage of discontinuations among smokers and nonsmokers is computed out of the number of smokers and nonsmokers, respectively.

Source: Post-text Table 8.

10.2 PROTOCOL VIOLATIONS

By-patient listings of protocol deviations and violations are provided in **Appendix 16.2, Listing 2.2**. One patient, an MPTS patient, discontinued the study due to a protocol violation. Patient 2091031 (MPTS) was discontinued due to prophylactic teeth cleaning.

Most protocol deviations were due to the following:

- Visit 6 occurred after the visit window,
- A scheduled Visit 6 assessment was not performed on any baseline treatment teeth, and
- A scheduled Visit 4 or Visit 5 treatment was not given to 20% or more of baseline treatment teeth **(Section 14, Table 1)**.

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYZED

For this trial, three study samples were used in the analysis of data. The Intent-to-treat (ITT) sample included all randomized patients.

The Evaluable sample included all ITT patients who met the following criteria:

10.2 PROTOCOL VIOLATIONS

By-patient listings of protocol deviations and violations are provided in **Appendix 16.2, Listing 2.2**. Two (1.6%) Vehicle patients discontinued the study due to a protocol violation; one non-smoking patient (PID 1020122) was incorrectly randomized as a smoker, and the other patient (PID 1060603) was discontinued at the sponsor's directive because he was enrolled past the enrollment cut-off date. Both of these Vehicle patients were treated only at Baseline, and both were discontinued ≤ 18 days after entering the study.

Most protocol deviations were due to the following:

- Visit 6 occurred after the visit window,
- a scheduled Visit 6 assessment was not performed on any baseline treatment teeth, and
- a scheduled Visit 4 or Visit 5 treatment was not given to 20% or more of baseline treatment teeth (**Section 14, Table 1**).

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYZED

For this trial, three study samples were used in the analysis of data. The Intent-to-treat (ITT) sample included all randomized patients.

The Evaluable sample included all ITT patients who met the following criteria:

- Patient had ≥ 4 teeth with 6 mm ≤ PD ≤ 9 mm at Screening,
- Patient's randomized stratum and the actual stratum were consistent,
- Scheduled Baseline treatment was given to ≥ 80% of the patient's qualifying teeth,
- Scheduled Visit 4 treatment was given to ≥ 80% of Baseline treatment teeth,
- Scheduled Visit 5 treatment was given to ≥ 80% of Baseline treatment teeth,
- Scheduled Visit 6 assessment was performed on at least 1 Baseline treatment tooth, and
- Visit 6 assessments were done within the study window.

The Safety sample included all randomized patients.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

In this study, 479 patients were screened at nine study centers (**Section 14, Post-text Table 2.1**). Of these, 121, 123 and 124 patients were randomized to receive MPTS, Vehicle, or S/RP, respectively. Of the randomized patients, most

ISE

Table 8.7-E. Study Discontinuations – Pivotal Studies (ITT Sample)

	Treatment Group		
	MPTS N=249 N (%)	Vehicle N=249 N (%)	S/RP Alone N=250 N (%)
Total Number of Discontinuations	12 (4.8)	19 (7.6)	21 (8.4)
Discontinuations among smokers[1]	5 (5.6)	6 (6.7)	13 (14.3)
Discontinuations among non-smokers	7 (4.4)	13 (8.2)	8 (5.0)
Reason			
Adverse event	1 (0.4)	1 (0.4)	0 (0.0)
Protocol violation	1 (0.4)	2 (0.8)	0 (0.0)
Withdrawal of consent	2 (0.8)	5 (2.0)	5 (2.0)
Female became pregnant	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	6 (2.4)	10 (4.0)	13 (5.2)
Patient rescue	0 (0.0)	0 (0.0)	1 (0.4)
Other	2 (0.8)	1 (0.4)	2 (0.8)

[1] Percentage of discontinuations among smokers and non-smokers is computed out of the number of smokers and non-smokers, respectively.
Source: Post-text Table 4.

8.7.6.3. COMPLIANCE

A drug accountability log, which includes the number of tips dispensed per patient, may be found in **Appendix 8.7.12.4, Listing 3**. Since study treatment was professionally administered in a clinical setting, patient compliance was not an issue.

8.7.7. SUMMARY OF EFFICACY RESULTS

8.7.7.1. PHASE 3 CONTROLLED, PIVOTAL STUDIES (OPI-103A, OPI-103B)

Integrated efficacy data from the two Phase 3, well-controlled pivotal studies are provided in **Appendix 8.7.12.1**. Supplementary efficacy analyses from nonparametric covariance adjusted extended Mantel-Haenszel procedure testing are provided in **Appendix 8.7.12.2**. Descriptive statistics for PD are provided in **Appendix 8.7.12.3**.

In summary tables where treatment comparison p-values are determined, comparisons are done based on LS means. The LS means were adjusted for covariates (defined in **Section 8.7.5.1**). When mean values are discussed in text, the adjusted means will be used.

PART 2

OPI- 104
9 Months Information

Table 10.1A Patient Disposition

Number (%) of Patients	MPTS N = 173	%
Enrolled and Treated	173	
Ongoing at Month 9	164	94.8%
Prematurely Discontinued	9	5.2%

Source: **Post-text Table 2.1**.

At Month 9, 94.8% (164/173) of the patients were still participating in the study.

Study discontinuations are summarized in **Table 10.1B**. A by patient listing, is provided in **Appendix 16.2.1, Patient Data Listing 2.2**. Study discontinuations are provided in **Section 14.1, Post-text Table 2.2**.

Table 10.1B Study Discontinuations (ITT Sample)

Number (%) of Patients	MPTS N=173	%
Total Number of Discontinuations	9	5.2%
Reason		
Protocol violation	2	1.2%
Withdrawal of consent	3	1.7%
Lost to follow-up	1	0.6%
Other	3	1.7%

Source: **Post-text Tables 2.1 and 2.2**.

A total of nine (5.2%) patients prematurely discontinued from the study after receiving study medication. Three (1.7%) patients discontinued due to withdrawal of consent for treatment: patient 02-011 withdrew consent on Day 36, patient 04-004 withdrew consent on study Day 115; and patient 05-013 withdrew consent on study Day 162. Three (1.7%) patients discontinued for "other" reasons. All three patients (03-011, 03-021, and 03-048) moved out of state during the study and discontinued treatment on study Days 124, 16[illegible] and 184, respectively. Two (1.2%) patients discontinued the study due to protocol violations related to concomitant medication: patient 05-012 and patient 05-016 were removed from study on Day 32 and Day 14, respectively, due to an exclusionary medication. One (0.6%) patient (02-014), was lost to follow-up.

10.2 PROTOCOL VIOLATIONS

A by-patient display of protocol deviations/violations is provided in **Appendix 16.2.2, Patient Data Listing 2.2**. Two (1.2%) patients had protocol violations that led to study discontinuation. Both patients were included in the Intent-to-Treat sample.

- Patient 05-012 was administered an exclusionary medication on Day 32 which necessitated the patients' removal from study.
- Patient 05-016 was on an exclusionary medication for > 10 days which necessitated the patient's removal from study on Day 14.

Patient Data Listing 2.1

Study Completion Status

Treatment: Minocycline PTS

Patient	Completed Study	Date of Completion or Withdrawal	Study Duration (Days)	Reason for Discontinuation	Investigator Comments
Investigator: Reinhardt, R. (01)					
001	ONGOING				
002	ONGOING				
003	ONGOING				
004	ONGOING				
005	ONGOING				
006	ONGOING				
007	ONGOING				
008	ONGOING				
009	ONGOING				
010	ONGOING				
011	ONGOING				
012	ONGOING				
013	ONGOING				
014	ONGOING				
015	ONGOING				
016	ONGOING				
017	ONGOING				
018	ONGOING				
019	ONGOING				
020	ONGOING				
021	ONGOING				
022	ONGOING				
023	ONGOING				
024	ONGOING				
025	ONGOING				
026	ONGOING				
027	ONGOING				
028	ONGOING				

Patient Data Listing 2.1

Study Completion Status

Treatment: Minocycline PTS

Patient	Completed Study	Date of Completion or Withdrawal	Study Duration (Days)	Reason for Discontinuation	Investigator Comments
Investigator: Reinhardt, R. (01)					
029	ONGOING				
030	ONGOING				
031	ONGOING				
032	ONGOING				
033	ONGOING				
034	ONGOING				
035	ONGOING				
036	ONGOING				
037	ONGOING				
038	ONGOING				
039	ONGOING				
040	ONGOING				
041	ONGOING				
042	ONGOING				
043	ONGOING				
044	ONGOING				
045	ONGOING				
046	ONGOING				
047	ONGOING				
048	ONGOING				
049	ONGOING				
050	ONGOING				
051	ONGOING				
Investigator: Gunsolley, J. (02)					
001	ONGOING				
002	ONGOING				

Patient Data Listing 2.1

Study Completion Status

Treatment: Minocycline PTS

Patient	Completed Study	Date of Completion or Withdrawal	Study Duration (Days)	Reason for Discontinuation	Investigator Comments
Investigator: Gunsolley, J. (02)					
003	ONGOING				
004	ONGOING				
005	ONGOING				
006	ONGOING				
007	ONGOING				
008	ONGOING				
009	ONGOING				
010	ONGOING				
011	NO	12FEB99	401	WITHDRAWAL OF CONSENT	
012	ONGOING				
013	ONGOING				
014	NO	15JUL99	186	LOST TO FOLLOW-UP	
015	ONGOING				
016#	NO	13JAN99	-	OTHER	PATIENT WAS DISCONTINUED DUE TO UNRESTORED CARIES AFTER S/RP BUT BEFORE TREATMENT.
017	ONGOING				
018	ONGOING				
019	ONGOING				
020	ONGOING				
021	ONGOING				
022	ONGOING				
023	ONGOING				
024	ONGOING				
Investigator: Hart, T. (03)					
001	ONGOING				

Excluded from analysis. No treatment administered.

Patient Data Listing 2.1

Study Completion Status

Treatment: Minocycline PTS

Patient	Completed Study	Date of Completion or Withdrawal	Study Duration (Days)	Reason for Discontinuation	Investigator Comments
Investigator: Hart, T. (03)					
002	ONGOING				
003	ONGOING				
004	ONGOING				
005	ONGOING				
006	ONGOING				
007	ONGOING				
008	ONGOING				
009	ONGOING				
010	ONGOING				
011	NO	12APR99	124	OTHER	MOVED TO FLORIDA
012	ONGOING				
013	ONGOING				
014	ONGOING				
015	ONGOING				
016	ONGOING				
017	ONGOING				
018	ONGOING				
019	ONGOING				
020	ONGOING				
021	NO	20MAY99	165	OTHER	PATIENT MOVED OUT OF STATE
022	ONGOING				
023	ONGOING				
024	ONGOING				
025	ONGOING				
026	ONGOING				
027	ONGOING				

Patient Data Listing 2.1

Study Completion Status

Treatment: Minocycline PTS

Patient	Completed Study	Date of Completion or Withdrawal	Study Duration (Days)	Reason for Discontinuation	Investigator Comments
Investigator: Hart, T. (03)					
028	ONGOING				
029	ONGOING				
030	ONGOING				
031	ONGOING				
032	ONGOING				
033	ONGOING				
034	ONGOING				
035	ONGOING				
036	ONGOING				
037	ONGOING				
038	ONGOING				
039	ONGOING				
040	ONGOING				
041	ONGOING				
042	ONGOING				
043	ONGOING				
044	ONGOING				
045	ONGOING				
046	ONGOING				
047	ONGOING				
048	NO	14JUL99	184	OTHER	PATIENT MOVED OUT OF STATE
049	ONGOING				
Investigator: Dean, J. W. (04)					
001	ONGOING				
002	ONGOING				

Patient Data Listing 2.1

Study Completion Status

Treatment: Minocycline PTS

Patient	Completed Study	Date of Completion or Withdrawal	Study Duration (Days)	Reason for Discontinuation	Investigator Comments
Investigator: Dean, J. W. (04)					
003	ONGOING				
004	NO	08APR99	115	WITHDRAWAL OF CONSENT	
005	ONGOING				
006	ONGOING				
007	ONGOING				
008	ONGOING				
009	ONGOING				
010	ONGOING				
011	ONGOING				
012	ONGOING				
013	ONGOING				
014	ONGOING				
015	ONGOING				
016	ONGOING				
017	ONGOING				
018	ONGOING				
019	ONGOING				
020	ONGOING				
021	ONGOING				
022	ONGOING				
023	ONGOING				
024	ONGOING				
025	ONGOING				
Investigator: Shapiro, B. (05)					
001	ONGOING				

Patient Data Listing 2.1

Study Completion Status

Treatment: Minocycline PTS

Patient	Completed Study	Date of Completion or Withdrawal	Study Duration (Days)	Reason for Discontinuation	Investigator Comments
Inveatigator: Shapiro, B. (05)					
002	ONGOING				
003	ONGOING				
004	ONGOING				
006	ONGOING				
007	ONGOING				
008	ONGOING				
009	ONGOING				
010	ONGOING				
011	ONGOING				
012	NO	28JAN99	32	PROTOCOL VIOLATION	PATIENT WAS EXCLUDED DUE TO DISCOVERY OF PRE-MEDICATION
013	NO	01JUN99	162	WITHDRAWAL OF CONSENT	PATIENT DECIDED HE DID NOT WANT TO PARTICIPATE IN THE STUDY ANYMORE.
014	ONGOING				
015	ONGOING				
016	NO	21JAN99	14	PROTOCOL VIOLATION	PATIENT ON EXCLUDED MEDICATION (BIAXIN) FOR 10 MORE DAYS.
017	ONGOING				
018	ONGOING				
019	ONGOING				
021	ONGOING				
022	ONGOING				
023	ONGOING				
024	ONGOING				
025	ONGOING				

Patient Data Listing 2.1

Study Completion Status

Treatment: Minocycline PTS

Patient	Completed Study	Date of Completion or Withdrawal	Study Duration (Days)	Reason for Discontinuation	Investigator Comments
Investigator: Shapiro, B. (05)					
026	ONGOING				
027	ONGOING				

ISS

Table 8.8-J. Study Discontinuations in the Safety Sample (Combined Studies)

	Treatment Group		
	MPTS N=423 N (%)	Vehicle N=249 N (%)	S/RP Alone N=250 N (%)
Total Number of Discontinuations	22 (5.2)	19 (7.6)	21 (8.4)
Discontinuations among smokers	7 (4.3)	6 (6.7)	13 (14.3)
Discontinuations among non-smokers	15 (5.7)	13 (8.2)	8 (5.0)
Reason			
Adverse event	1 (0.2)	1 (0.4)	0
Protocol violation	3 (0.7)	2 (0.8)	0
Withdrawal of consent	5 (1.2)	5 (2.0)	5 (2.0)
Female became pregnant	0	0	0
Lost to follow-up	7 (1.7)	10 (4.0)	13 (5.2)
Patient rescue	0	0	1 (0.4)
Other	6 (1.4)	1 (0.4)	2 (0.8)

Note: All patients in OPI-104 received MPTS as treatment; therefore, patient columns under Vehicle and S/RP contain data identical to that presented for the pivotal studies.
Note: Percentages of discontinuations among smokers and non-smokers were computed out of the number of smokers and non-smokers, respectively.
Source: **Post-text Table 8.2.**

Protocol deviations and violations are provided by patient for the combined studies in **Appendix 8.8.22.3, Listing 2.2**.

8.8.6. ADVERSE EVENTS

Adverse events (AEs) were categorized by body system and preferred term based on the COSTART dictionary standardization of terminology. During the clinical trials, periodontitis was recorded as an AE when a baseline pocket depth increased ≥ 3 mm during the study. The preferred term of tooth disorders grouped investigator terms of tooth fractures, problems with fillings (amalgams) and hot/cold sensitivity; the primary term of tooth caries grouped root surface decay, recurrent decay and dental caries; and the preferred term of dental pain grouped toothache, pain associated with teeth, and discomfort after dental procedures.

All AEs presented and discussed in this ISS are those considered to be either "pretreatment AEs" or "treatment emergent AEs." AEs that occurred between screening and Study Day 1 were considered to be pretreatment AEs. Study Day 1 was defined as the final day of S/RP for the S/RP alone group and the first day of treatment for the MPTS and Vehicle groups (treatment often occurred on the final day of S/RP, but could have occurred up to 48 hours afterward).

OPI – 104

12 Months

10. STUDY PATIENTS

10.1 DISPOSITION AND EVALUABILITY OF PATIENT

A total of 174 patients were enrolled into the study at Screening (Visit 1). Of these 174 patients, 173 were treated with study medication. One patient (02-016) was discontinued from the study prior to receiving study drug due to unrestored caries after S/RP. This patient was excluded from the Intent-to-Treat population. Patient disposition is provided in **Section 15.2.1, Post-text Tables 2.1, and 2.2,** and summarized below in **Table 10.1A.**

Table 10.1A Patient Disposition at 12 Months

Number (%) of Patients	MPTS N = 173	%
Enrolled and Treated	173	
Completed Study	158	91.3%
Prematurely Discontinued	15	8.7%

Source: **Post-text Table 2.1.**

A by-patient listing of the Intent-to-Treat population may be found in the original report (Appendix 16.2.1, Patient Data Listing 1).

Study discontinuations are summarized in **Table 10.1B**. A by-patient listing is provided in **Appendix 15.2.2, Patient Data Listing 2.2**. Study discontinuations are provided in **Section 15.2.1, Post-text Table 2.2.**

Table 10.1B Study Discontinuations at 12 Months (ITT Sample)

Number (%) of Patients	MPTS N=173	%
Total Number of Discontinuations	15	8.7%
Reason		
Adverse Event	1	0.6%
Protocol Violation	2	1.2%
Withdrawal of Consent	3	1.7%
Patient Rescue	1	0.6%
Lost to Follow-up	3	1.7%
Other	5	2.9%

Source: **Post-text Tables 2.1 and 2.2.**

A total of 15 (8.7%) patients prematurely discontinued from the study after receiving study medication.

- Three (1.7%) patients discontinued due to withdrawal of consent for treatment: patient 02-011 withdrew consent on Day 36, patient 04-004 withdrew consent on study Day 115; and patient 05-013 withdrew consent on study Day 162.
- Five (2.9%) patients discontinued for "other" reasons. Four of these five patients (03-011, 03-021, 03-048, and 02-001) moved during the study and discontinued treatment on study Days 124, 165, 184, and 388, respectively. The fifth patient (02-013) was unable to keep his scheduled appointments due to conflicts with his work schedule and discontinued on Day 376.

- Three (1.7%) patients (02-014, 03-041, and 04-012), were lost to follow-up.
- Two (1.2%) patients discontinued the study due to protocol violations related to concomitant medication: patient 05-012 and patient 05-016 were removed from study on Day 32 and Day 14, respectively, due to an exclusionary medication.
- One patient (02-006) was discontinued secondary to needing rescue therapy. The patient had multiple PD increases of 3+.
- One patient (01-003) was discontinued due to a fatal adverse event of aneurysm that occurred on Day 344. This is a new event since the last report. A narrative of this event may be found in **Section 12.3.2.**

10.2 PROTOCOL VIOLATIONS

A by-patient display of protocol deviations/violations is provided in **Post-text Table 2.2**. Two (1.2%) patients had protocol violations that led to study discontinuation. Both patients were included in the Intent-to-Treat sample.

- Patient 05-012 was administered an exclusionary medication on Day 32 which necessitated the patients' removal from study.
- Patient 05-016 was on an exclusionary medication for > 10 days which necessitated the patient's removal from study on Day 14.

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYZED

The Intent-to-Treat (ITT) sample included all patients with at least one site treated with study medication. One hundred seventy three (173) patients received study medication.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics for the 173 patients that received study drug are presented in **Table 11.2A**.

11.2.1 Concomitant Medications

Concomitant medications taken during the 12-month study period are listed by preferred term in **Post-text Table 14.2, Patient Data Listing 13**.

Use of concomitant medications was reported by a total of 129 (74.6%) patients during the 12-month study period. The most commonly reported concomitant medications were ibuprofen (17.9%, 31/173), acetylsalicylic acid (17.3%, 30/173), and paracetamol (13.9%, 24/173). Other frequently used medications were naproxen (5.8%, 10/173), conjugated estrogens (6.4%, 11/173), and amfebutamone (4.0%, 7/173). Amoxicillin was taken by 4.6% (8/173) of patients, atenolol was taken by 4.0% (7/173) of patients, and Provella-14 and metoprolol were taken by 3.5% (6/173) of patients. Amlodipine, azithromycin, guaifenesin multivitamins, atorvastatin, medroxyprogesterone, pseudoephedrine, omeprazole, were each taken by 2.9% (5/173) of patients. Ascorbic acid, calcium, fluoxetine, levothyroxine and nanne repetabs were each taken by 2.3% (4/173) of patients. All other concomitant medications were taken by less than 2% of patients.

Since medical history data were not changed since the submission of the 9-Month CSR, the original data are in Post-text Table 12, and Patient Data Listing 9 (9-Month CSR).

Whereby this patient was counted in the ISS. The past 2 attachment contains the section from the report of study OPI-104 as well as the post-text table 2.1 which identifies the discontinued patient. As listed on page 30 of 8 (pagination page 15) patient 016 provides the explanation for the discontinuation.

For completeness I have attached copies from the ISS as well as the 12-month update.

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: 10/13/00 Pages (including cover) 2

TO: Sammie Beam

COMPANY: OPDRA

ADDRESS:

FAX PHONE#: 301-480-8173 Our Fax # (301) 827-2075

Voice # (301) 827-2020

MESSAGE: Sammie, NDA 50-781

Here's the letter from ORPHARM

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Kalyani Bhatt

TITLE: PM

TELEPHONE: 827-2049

MESSAGE CONFIRMATION

10/13/00 09:32

NO.	MODE	BOX	GROUP
093	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
10/13 09:32	00'36"	301 480 8173	002/002	OK		0000

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: 10/13/00 **Pages (including cover)** 2

TO: Sammie Beam

COMPANY: OPDRA

ADDRESS:

FAX PHONE#: 301-480-8173 **Our Fax # (301) 827-2075**

Voice # (301) 827-2020

MESSAGE: Sammie,

Here's the letter from ORPHALM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: ~~June 28, 2000~~ Resent 10-5-00

Number of Pages 2
(Including cover sheet)

TO: Markus Herzig
COMPANY: OraPharma
FAX #: 215-443-9531

MESSAGE: Please see the following comments regarding your NDA 50-781, Minocycline PTS, 1mg in reference to the trade name.

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075 2091

MESSAGE CONFIRMATION

10/06/00 10:03

NO.	MODE	BOX	GROUP
052	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
10/06 10:03	00'18"	912154439531	001/001	OK		0000

This is in response to a May 8, 2000 meeting request from Orapharma, Inc for a meeting to discuss their proposed proprietary name of Arestin PTS.

The tradename will be acceptable on the following conditions.

1.) The firm has agreed to undertake a comprehensive effort to update any and all reference sources that contain a mention of the discontinued ARESTIN (trimethobenzamide) product. We would ask for a written commitment to that effect and that the firm provide the Agency with documentation of their search and the actions taken to remedy any reference book notations.

2.) We would also request that a post-marketing commitment be made to (1) treat all expedited reports and (2) be willing to change the name of the product if post-marketing reports are received that led to a patient receiving the wrong drug (trimethobenzamide).

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 20, 2000 Number of Pages 2 (Including cover sheet)

TO: Markus Herzig
COMPANY: OraPharma
FAX #: 215-443-9531

MESSAGE: Please find comments from the Biopharmaceutic reviewer of your original NDA 50-781 Minocycline PTS 1 mg. Please send this as soon as possible so we may expedite the review process.

1.) Extraction procedure of Minocycline from human serum and saliva.

2.) Method of quantitations of Minocycline with proper documentation from human saliva at concentrations above 10 mcg/mL as the validation of the assay was done in the concentration range of ———.

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

MESSAGE CONFIRMATION

09/20/00 12:55

J.	MODE	BOX	GROUP
333	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
09/20 12:55	00'23"	912154439531	001/001	OK		0000

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 20, 2000

Number of Pages 2
(Including cover sheet)

TO: Markus Herzig
COMPANY: OraPharma
FAX #: 215-443-9531

MESSAGE: Please find comments from the Biopharmaceutic reviewer of your original NDA 50-781 Minocycline PTS 1 mg. Please send this as soon as possible so we may expedite the review process.

1.) Extraction procedure of Minocycline from human serum and saliva.

2.) Method of quantitations of Minocycline with proper documentation from human saliva at concentrations above 10 mcg/mL as the validation of the assay was done in the concentration range of ———

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

HFD-88C
Wang

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: ~~April 11, 2000~~ Sept. 20, 2000 Number of Pages 2

TO: Markus Herzig
COMPANY: ORAPHARMA INC
FAX #: 1-215-443-9531

Resent FAX
Again Sponsor did not submit information.

MESSAGE: Please see comments for NDA 50-781 Minocycline

FROM: Kalyani Bhatt
TITLE: Regulatory Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

CC:
NDA - 50781
~~DivFile~~
WANG - 880
BHATT - 540

Please see comments from the Biopharmaceutics Reviewer:

1. Full study report for these studies should be submitted if available. The sponsor only submitted the summary for Lederle study 15-16-1, 15-18-1 and 15-20-2.

2. Detailed description of drug product release rate (dissolution) testing and proposed product released rate (dissolution) and specification should be submitted.

MESSAGE CONFIRMATION

04/12/00 08:48

NO.	MODE	BOX	GROUP
912	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
04/12 08:47	00'28"	912154439531	002/002	OK		0000

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 11, 2000 Number of Pages 2

TO: Markus Herzig
COMPANY: ORAPHARMA INC
FAX #: 1-215-443-9531

MESSAGE: Please see comments for NDA 50-781 Minocycline

FROM: Kalyani Bhatt
TITLE: Regulatory Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

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

ORAPHARMA INC.

FAX COVER SHEET

To:	Ms. K.Bhatt	**From:**	Markus F. Herzig
Company:	FDA, HFD-540	**Date:**	08/16/00
Fax No.:	301-827-2075	**No. of pages w/cover:**	3
RE:	**Journal article**		

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

Dear Ms. Bhatt,

Attached are two documents from the publisher of the erroneous article. The first is a letter in which the editor-in-chief states that it was their mistake. The second is a press release from the publisher (montage media) again stating their error.

If you have any questions about this fax please call me at 215-956-2207.

Sincerely,

Markus F. Herzig

The Journal of
Practical Hygiene
Improving Communications Among Dental Professionals

August 15, 2000

Markus Herzig
Executive Director of Regulatory Affairs
OraPharma, Inc.
732 Louis Drive
Warminster, PA 18974

Dear Mr. Herzig:

This letter is to explain a misprint that appeared within the July/August, 2000 issue of the ***Journal of Practical Hygiene***. The "Hot Off The Press" department, on page 12 of that issue, erroneously stated that "OraPharma, Inc. has received FDA approval for its Minocycline Periodontal Therapeutic System (MPTS)." This statement should have read, "OraPharma, Inc. has received FDA acceptance for its submission of a New Drug Application (NDA) for its Minocycline Periodontal Therapeutic System (MPTS)." This erratum will appear in the next issue of the ***Journal of Practical Hygiene*** (September/October, 2000) on the "Editor's Message" page. I apologize for any inconvenience this error may have caused you.

Jill Rethman, RDH, BA
Editor-in-Chief
Journal of Practical Hygiene

cc: S. Clements
J. King
J. Wharton

Editorial Office: 1000 Wyckoff Avenue • Mahwah, NJ 07430 • 800-899-5350 • 201-891-3200
Fax: 201-891-2626 • **E-Mail:** jph@montagemedia.com

URGENT
FOR IMMEDIATE RELEASE

Contact: Jill Rethman
Editor-in-Chief
Montage Media Corporation
(201) 891-3200

Dental Professionals

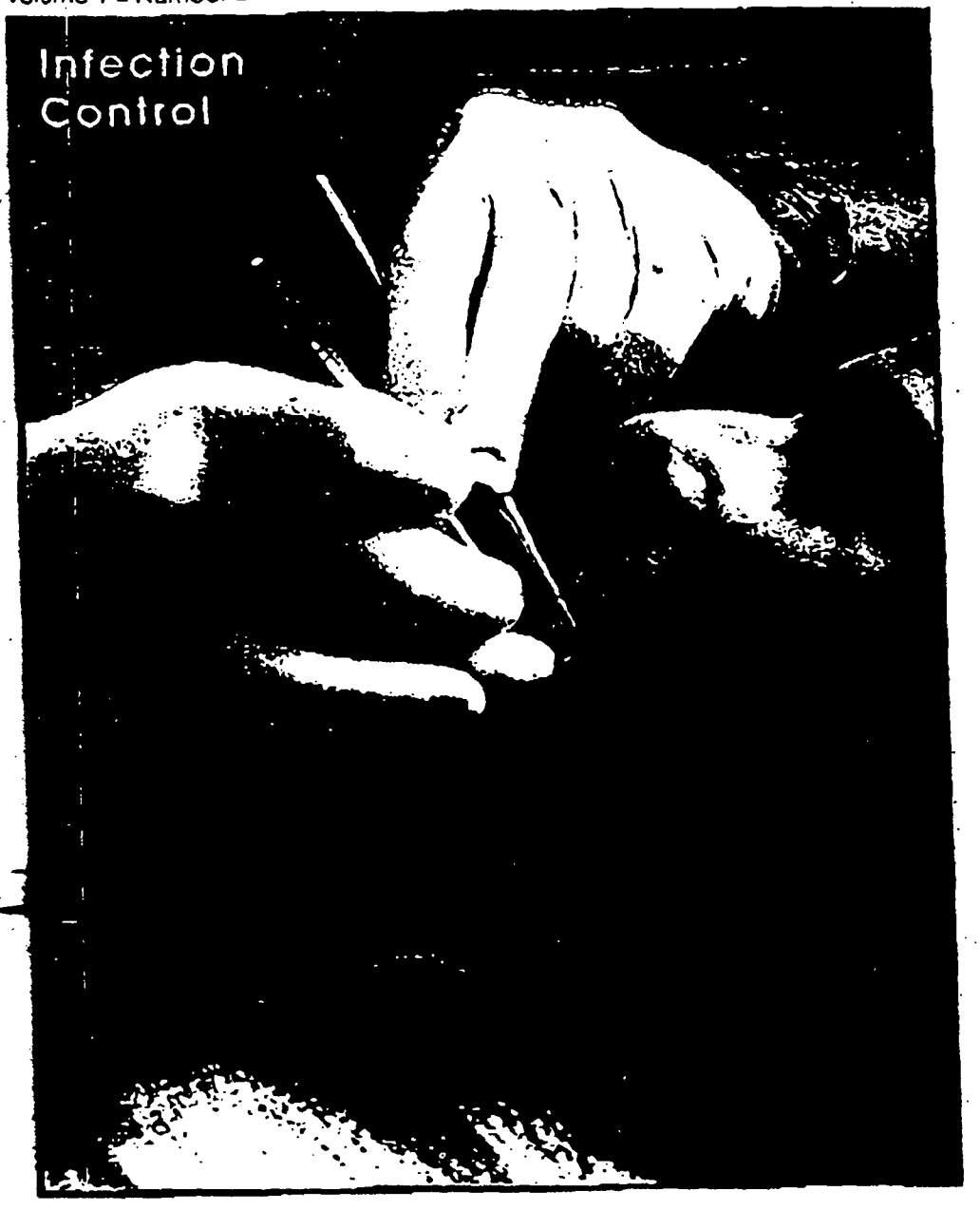
Please be advised that within the recent July/August issue of ***The Journal of Practical Hygiene***, in the "Hot Off the Press" section (page 12), an erroneous statement was made - "OraPharma, Inc. has received FDA approval for its Minocycline Periodontal Therapeutic System (MPTS)." This statement should have read, "OraPharma, Inc. has received FDA acceptance for its submission of a New Drug Application (NDA) for its Minocycline Periodontal Therapeutic System (MPTS)." While this erratum will appear within the next issue of ***The Journal of Practical Hygiene*** (September/ October 2000) we felt it was important to inform you of this error as soon as possible.

If you have any questions regarding this oversight, please contact Jill Rethman, Editor-in-Chief of ***The Journal of Practical Hygiene***, at (201) 891-3200.

###

The Journal of
Practical Hygiene
Improving Communications Among Dental Professionals

Volume 9 ■ Number 4 July/August 2000



Post-it® Fax Note 7671 | Date 8/15/00 | # of pages ▶ 4
To Mr. K. Bhatt | From M. Herzig
Co./Dept. FDA HFD-345 | Co. Oral Pharmaceuticals Inc.
Phone # 301 827-2020 | Phone # 215 976-2207
Fax # 301 827-2075 | Fax # 215 443-9531

FEATURED PRODUCTS SUPPLEMENT:

aestheticproducts

A Montage Media Publication

ORAPHARMA INC.

FOR IMMEDIATE RELEASE

Contact:
Michael Kishbauch
James A. Ratigan
OraPharma, Inc.
215/956-2200

Juliane Snowden (investors), 212/510-9286
Michael Su (investors), 212/510-9346
Karina Byrne (media), 212/510-9266
Thomson Financial Investor Relations

FDA ACCEPTS ORAPHARMA'S NEW DRUG APPLICATION FOR MPTS IN ADULT PERIODONTITIS

WARMINSTER, PA – April 26, 2000 – OraPharma, Inc. (Nasdaq: OPHM), a company in the emerging field of oral care medicine, today announced the U.S. Food and Drug Administration (FDA) has accepted the Company's February 17, 2000 submission of a New Drug Application (NDA) for MPTS (Minocycline Periodontal Therapeutic System). Phase 3 clinical data, announced on November 29, 1999, demonstrated MPTS, when used as an adjunct to scaling and root planing, significantly reduced pocket depth versus scaling and root planing alone for the treatment of adult periodontitis.

"We are very pleased the FDA has accepted our NDA and is now in the process of reviewing the application. This marks yet another milestone for OraPharma. We have worked very closely with the Agency on the design and conduct of the MPTS trials, as well as the preparation of the NDA, and we will continue to do so through the review and approval process," said Mike Kishbauch, President and Chief Executive Officer of OraPharma. "The Phase 3 MPTS study was the largest periodontal therapeutic study ever conducted, and the results showed a clear benefit in patients using MPTS in conjunction with scaling and root planing, the standard therapy for the treatment of periodontitis. Additionally, in patients with more severe disease and patients at higher risk, the benefit appears to be particulariy striking."

MPTS, the broad-spectrum antibiotic minocycline encapsulated in bioresorbable microspheres, is delivered as a dry powder via a specially designed unit-dose dispenser into periodontal pockets. The drug is released over an extended time period as the microspheres dissolve, providing the patient with long-term site-specific therapy for adult periodontitis. OraPharma is seeking marketing approval for MPTS as an adjunctive treatment to scaling and root planing.

OraPharma conducted its Phase 3 clinical trials at 23 centers across the United States and tested MPTS in over 900 patients with moderate to severe adult periodontitis. The patients were enrolled in

one of three arms: MPTS with scaling and root planing, scaling and root planing with a placebo, and scaling and root planing alone.

While periodontal disease affects more than 50 million people in the U.S., less than a quarter of them are currently receiving treatment. In addition to being a major cause of tooth loss in adults, periodontal disease is believed to be a potential complicating factor in coronary heart disease, diabetes, and premature birth, as well as low infant birth weight. Providing more effective and convenient periodontal treatment to more people is one of OraPharma's major goals.

Founded in 1996, OraPharma, Inc., is dedicated to the research, development and marketing of pharmaceutical products for oral healthcare. MPTS represents a promising therapeutic advance for periodontal disease. The Company's other current technological initiatives are focused on the areas of bone and tissue regeneration, oral mucositis secondary to cancer therapy, and pain/trauma management. OraPharma successfully completed an initial public offering on March 9, 2000, and is listed on the Nasdaq National Market under the symbol "OPHM."

Statements included in this press release that are not historical in nature are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These statements include statements regarding the benefits of MPTS. The Company cautions readers that forward-looking statements are subject to certain risks and uncertainties, which could cause actual results to differ materially, due to the risks and factors identified from time to time in the Company's reports filed with the U.S. Securities and Exchange Commission, including its Form S-1 and amendments. We claim the protection of the Safe Harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

###

HOT off the PRESS

Stay educated, informed, and aware **of the latest trends in the medical profession. This up-to-date information is published periodically, and features valuable resources gathered from medical journals, consumer publications, company newsletters, and websites.**

Periodontally Healthy Mothers = Healthy Babies

An ongoing study of more than 2000 women, led by Dr. Marjorie Jeffcoat, has found that periodontal diseases may be significant risk factors in the birth of preterm low birth weight babies. To create awareness of this problem, Optiva Corporation has teamed up with the National Healthy Mothers, Healthy Babies Coalition (HMHB), to develop a program called "Brush For Two," an organization that delivers important public health information regarding the link between gum diseases and preterm low birth weight babies. For more information, contact 877-BRUSH-4-2.

Looking for the Latest Information on Women's Health Issues?

The National Women's Health Report, published by the National Women's Health Resource Center, provides up-to-date information on women's health issues. A recent issue reviewed oral health across the lifespan, diabetes, and medication use. Call 1-877-98NWHRC for subscription information, or visit their website at www.healthywomen.org. Another excellent resource: The Harvard Women's Health Watch. Contact them at 800-829-5921 or health.harvard.edu.

A New Slow-Release Drug on the Horizon...

A new slow-release product to treat periodontitis will soon join the ranks of Actisite®, PerioChip®, and Atridox™. OraPharma, Inc. has received FDA approval for its Minocycline Periodontal Therapeutic System (MPTS). When used as an adjunct to scaling & root planing, it was shown to significantly reduce pocket depths in adult periodontitis patients. MPTS contains the broad-spectrum antibiotic minocycline encapsulated in bioresorbable microspheres. It is delivered as a dry powder via a specially designed unit-dose dispenser. For further information, contact OraPharma at 215-956-2200.

Are Herbal Medications Safe?

In 1994, Congress deregulated the herbal medicine industry by passing the Dietary Supplements Health and Education Act. The law assumes that herbal remedies are natural and pose few risks. Recent reports of side effects and interactions with prescription medicines, however, question the safety of herbal medicine. Be sure to ask patients if they are using any alternative therapies and keep abreast of current concerns. Resources include: The National Center for Complementary and Alternative Medicine (888-644-6226), The Food & Drug Administration (800-FDA-1088, www.fda.gov/medwatch), and The American Botanical Council (800-373-7105, www.herbalgram.org).

Patients Won't Floss? It Could Help Them Live Longer!

Dr. Michael Rotzen, a Chicago Internist and Anesthesiologist, is having a positive impact on millions of consumers' attitudes toward flossing and oral health care in general. In his book, "RealAge: Are You as Young as You Can Be?" he states that flossing can actually help your patients live longer and younger...up to 6.4 years younger! The RealAge program is based on cutting-edge research composed of 25,000 medical studies that have been scientifically analyzed to determine behaviors that could delay the effects of aging. Other positive behaviors include having a pet, exercising, and drinking one glass of red wine a day. For more information, see Dr. Rotzen's website, www.RealAge.com, or the John O. Butler Company's website, www.LivingYounger.com.