

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



FAX COVER SHEET

To:	Ms. F. Beam	From:	Markus Herzig
Company:	FDA	Date:	06/26/00
Fax No.:	301-480-8173	No. of pages w/cover:	1
RE:	NDA-50-781		
CC:	Ms. K. Bhatt - 301-827-2075		

Urgent Reply ASAP Please comment Please review For your information

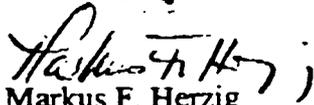
Dear Ms. Beam:

I want to thank you for calling me back on Friday, June 23, 2000 regarding OraPharma's pending "Arestin" tradename. I especially appreciated it, as I am under pressure from our Marketing Department to hear that the review will be concluded during the last week in June.

I will check with the Division's project manager, Ms. K. Bhatt later in the week as to the recommendation OPDRA provided to them.

Thank you again for your prompt return of my telephone inquiry.

Sincerely,


Markus F. Herzig
Executive Director Regulator Affairs

MFH:stk

cc: Ms. K. Bhatt, Project Manager
Division of Dermatologic & Dental Drug Production
(HFD-540)

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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

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 #: 301-827-2029
FAX #: 301-827-2075 2091

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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**).

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



FAX COVER SHEET

To:	Ms. Kalyani Bhatt, Project Manager	From:	Markus Herzig
Company:	Division of Dermatologic / Dental Drug Products	Date:	06/20/00
Fax No.:	301-827-2075	No. of pages w/cover:	5
RE:	NDA Amendment		

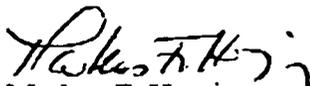
Urgent Reply ASAP Please comment Please review For your information

Ms. Bhatt:

Please replace the last page in the NDA Amendment dated June 19, 2000 (vol. 5.1) with the attached page. The number in the 30°C/60% RH - 9 mo data field still had an error in it - instead of —.

Sorry for the inconvenience.

Sincerely,


Markus F. Herzig

PS. I am sending you 4 duplicates for the review, archival and the two desk copies.

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WITHHOLD 1 PAGE (S)

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


ORAPHARMA INC.

FAX COVER SHEET

To:	Kalyani Bhatt	From:	Markus Herzig
Company:	Food and Drug Administration	Date:	05/18/00
Fax No.:	301-827-2075	No. of pages w/cover:	4
RE:	Response to fax dated May 11, 2000		

Urgent Reply ASAP Please comment Please review For your information

Dear Ms. Bhatt:

Attached is the response to the FDA fax of May 11, 2000. As discussed, I will submit as an official amendment with an extra desk copy.

Sincerely,


Markus F. Herzig
Executive Director Regulatory Affairs

This facsimile contains confidential information intended for the person(s) named above. If you have received this facsimile in error, please notify us immediately by telephone and destroy this transmission.

FDA Question of May 12, 2000:

Please indicate the volume and page number where the following can be located in the NDA submission:

- *The results for the subjects who had baseline pocket depths of 7-9 mm, including the mean pocket depth reduction as well as the proportion of subjects who achieved 1 mm in reduction, 1.5 mm in reduction and 2.0 mm in reduction.*

OraPharma Answer:

A complete answer to this question is not available by reference to a single table or listing in the NDA.

Two sources provide the information:

ISE Listing 5 - Electronic in file app87124.pdf.

Navigation to Listing 5:

Start at NDATAOC file, *select CLINICAL (clinstat), select INTEGRATED SUMMARY OF EFFICACY (clinstat\ise\isetoc.pdf), select PATIENT DATA LISTINGS (ise\app87124.pdf), select bookmark LISTING 5.*

ISE Table 8.7-G - Volume 1.91, Page 38

Post-Text Table 3.11.3 contains the much of the same information and can be found in Volume 1.91, Page 110, and is also provided electronically.

Navigation to Table 3.11.3:

Start at NDATAOC file, *select CLINICAL (clinstat), select INTEGRATED SUMMARY OF EFFICACY (clinstat\ise\isetoc.pdf), select TABLES REFERED TO BUT NOT INCLUDED IN THE TEXT (ise\app87121.pdf), select bookmark TABLE 3.11.3.*

Using Listing 5 and Table 8.7-G from the ISE, following table was constructed (TABLE 1). A total of 19 patients from the pivotal trials (103-A and 103-B) had an average pocket depth of ≥ 7 mm, ranging from 7.00 mm to 8.38 mm. TABLE 1 shows by treatment group, the patient identification with baseline pocket depth (PD), average change in PD at Month 9, and group mean of PD change.

TABLE 1: Patients with PD ≥ 7 mm

Treatment*	Study No.*	Patient ID*	Baseline PD (mm)*	Average PD (mm) change from baseline at Month 9*	Group Mean and Standard Deviation (SD) of PD (mm) change from baseline at Month 9**
Minocycline PTS (n=5)	103-A	1030248	7.11	-1.48	-2.88 [SD 0.83]
		1040449	7.20	-1.29	
		1091026	7.21	-2.96	
	103-B	2040361	7.00	-2.95	
		2060700	7.52	-2.73	
Vehicle (n=8)	103-A	1020207	7.44	-0.18	-0.70 [SD 0.76]
		1040363	7.54	0.33	
		1040424	7.71	-1.19	
		1040439	7.24	-0.81	
		1050565	7.08	-0.43	
	103-B	2040428	7.23	-1.82	
		2060666	7.80	-1.50	
		2070784	7.57	0.00	
S/RP Alone (n=6)	103-A	1040370	7.12	0.34	-1.3 [SD 0.87]
		1040425	7.36	-1.71	
		1050568	8.38	-1.63	
		1091028	7.08	-1.39	
	103-B	2050542	7.13	-2.19	
		2060692	7.03	-1.25	

* Source: Listing 5 from ISE provided electronically in file app87124.pdf.

Navigation to Listing 5: Start at NDATAOC file, select CLINICAL (clinstat), select INTEGRATED SUMMARY OF EFFICACY (clinstat\ise\isetoc.pdf), select PATIENT DATA LISTINGS (ise\app87124.pdf), select bookmark LISTING 5.

** Source: Table 8.7-G in ISE. Volume 1.91, Page 38

Post-Text Table 3.11.3 in ISE. Volume 1.91, Page 110, and is also provided electronically. Navigation to Table 3.11.3: Start at NDATAOC file, select CLINICAL (clinstat), select INTEGRATED SUMMARY OF EFFICACY (clinstat\ise\isetoc.pdf), select TABLES REFERRED TO BUT NOT INCLUDED IN THE TEXT (ise\app87121.pdf), select bookmark TABLE 3.11.3.

The tables in the original NDA submission show PD reduction in whole millimeter increments only. To answer what proportion of subjects achieved 1 mm, 1.5 mm and 2.0 mm in reduction in PD, a new table is constructed below (TABLE 2) to categorize PD reduction in one-half millimeter increments for patients who had a baseline PD of ≥ 7 . TABLE 2 is constructed from data contained in Listing 5.

TABLE 2: PD reduction in 0.5 mm increments in patients with baseline PD ≥ 7 mm.

Treatment	No change or Increase in PD	<0.5 mm reduction n (%)	>0.5 and ≤ 1 mm reduction n (%)	>1 and ≤ 1.5 mm reduction n (%)	>1.5 and ≤ 2 mm reduction n (%)	>2 and ≤ 2.5 mm reduction n (%)	>2.5 mm reduction n (%)
Minocycline PTS (n=5)	0	0	0	2 (40%)	0	0	3 (60%)
Vehicle (n=8)	2 (25%)	2 (25%)	1 (12.5%)	2 (25%)	1 (12.5%)	0	0
S/RP Alone (n=6)	1 (16.7%)	0	0	2 (33.3%)	2 (33.3%)	1 (16.7%)	0

Source: Listing 5



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: May 11, 2000

Number of Pages 1

TO: Markus F. Herzig

COMPANY: OraPharma Inc.

FAX #: 1-215-443-9531

MESSAGE: The following information is requested regarding NDA 50-781, Minocycline PTS from the dental officer.

- Please indicate the volume and page number where the following can be located in the NDA submission:
- The results for the subjects who had baseline pocket depths of 7 - 9 mm, including the mean pocket depth reduction as well as the proportion of subjects who achieved 1 mm in reduction, 1.5 mm in reduction, and 2.0 mm in reduction.

FROM: Kalyani Bhatt,

TITLE: Project Manager

PHONE #: 301-827-2049

FAX #: 301-827-2075/2091

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MESSAGE CONFIRMATION

05/11/00 12:11

NO.	MODE	BOX	GROUP
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DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
05/11 12:11	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: May 11, 2000

Number of Pages 1

TO: Markus F. Herzig
COMPANY: OraPharma Inc.
FAX #: 1-215-443-9531

MESSAGE: The following information is requested regarding NDA 50-781, Minocycline PTS from the dental officer.

- Please indicate the volume and page number where the following can be located in the NDA submission:
 - The results for the subjects who had baseline pocket depths of 7 - 9 mm, including the mean pocket depth reduction as well as the proportion of subjects who achieved 1 mm in reduction, 1.5 mm in reduction, and 2.0 mm in reduction.

FROM: Kalyani Bhatt,

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



FAX COVER SHEET

To:	Ms. Kalyani Bhatt, Project Manager	From:	Markus Herzig
Company:	FDA	Date:	04/12/00
Fax No.:	301-827-2075	No. of pages w/cover:	1
RE:	NDA-50-781		

Urgent Reply ASAP Please comment Please review For your information

Dear Ms. Bhatt:

Attached is our reply to the Biopharmaceutics Reviewer comment number 1. We will address comment 2 separately.

Sincerely,


Markus Herzig

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BIOPHARMACEUTICS REVIEWER COMMENT

Comment 1: Full sponsor 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.

Reply: The clinical Pharmacology section (8.3) in volume 1.20 does provide summaries of the Lederle Laboratories, Inc. conducted Phase 1 and 2 studies.

The completed (full) reports of these studies as received from Wyeth-Ayerst Research (who acquired Lederle Laboratories, Inc.) did not contain some appendix items. In the clinical data section in volume 1.21 on Page 1, a summary listing of the missing items is provided. Pages 2 through 6 contain correspondences from OraPharma, Inc. and Wyeth-Ayerst Research highlighting our efforts in getting complete documentation for these reports.

The full reports as they were made available to OraPharma, Inc. are included in the NDA. The study report for 15-16-1 can be found in volume 1.21; the study report for 15-18-1 is contained in volumes 1.23 - 1.25; and the study report for 15-20-2 is located in volumes 1.32 and 1.33.

I hope this clarifies the comment 1 in the FDA telefax dated April 11, 2000. A reply for comment 2 will be provided under separate cover.

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Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
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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

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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
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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



FAX COVER SHEET

To:	Ms. Kalyani Bhatt, Project Manager	From:	Markus Herzig
Company:	FDA	Date:	04/07/00
Fax No.:	301-827-2075	No. of pages w/cover:	1
RE:	NDA-50-781		

Urgent Reply ASAP Please comment Please review For your information

Kalyani:

Attached is the certificate of analysis ——— uses in the identification of raw materials for manufacturing the dispenser tips for our minocycline PTS product. ——— does no further testing on incoming raw materials.

Thank you,


Markus F. Herzig

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WITHHOLD 2 PAGE (S)

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 Dry Products (HFDT40)	Date:	03/01/00
Fax No.:	301-827-2075	No. of pages w/cover:	3
RE:	NDA 50-781 (formerly 21-206)		

Urgent Reply ASAP Please comment Please review For your information

Dear Dr. Bhatt:

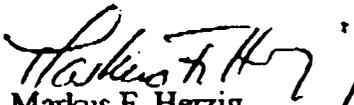
Attached is the information requested by Dr. M. Gautam-Basak during the telephone conversation held on March 1, 2000.

The information AAI provided is a complete corporate facility list on which I marked with a dot the addresses in our NDA.

Packaging Coordinates, Inc. (PCI), (DER 2530802) only has one location. The analytical laboratory (_____) identified on page 103 in vol. 1.1 is an independent laboratory, PCI will use for commercial product testing. This laboratory has not analyzed any material described in this NDA, but is planned to be used for commercial product testing.

I hope this clarifies the questions Dr. Gautam-Basak had.

Sincerely,


Markus F. Herzig
Executive Director Regulatory Affairs

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2320 Scientific Park Drive
Wilmington, NC 28405

Tel: 910.575.4AAI (4224) / 1.910.254.7000
Fax: 1.910.815.2100

COMPANY PROFILE INFORMATION Applied Analytical Industries, Inc. (AAI)

Brief Background/Profile of the Company

Applied Analytical Industries, Inc. (AAI) was established in 1979 as a contract laboratory primarily conducting stability analyses for pharmaceutical products. Over the years, it has grown considerably in the breadth and depth of services that it provides on a contractual basis to the pharmaceutical industry. Currently, AAI is a publicly traded (NASDAQ AAI) pharmaceutical research and development firm that provides the following services:

- formulation development,
- analytical development,
- method validation and testing,
- cell biology and biotechnology product testing,
- clinical supply and low volume marketed product manufacturing and packaging,
- stability storage and testing, and
- quality assurance and regulatory affairs consulting.

Besides these services, AAI provides clinical research services through our subsidiaries, AAI-Deutschland and MTRA (in Boston). Bioanalytical services are provided through our subsidiaries AAI-Deutschland and Kansas City Analytical Services (KCAS). These additional sites and services are not covered in this document.

AAI is comprised of seven buildings in the Wilmington, North Carolina area (which meet the requirements for being one site according to the November 1999 "Guidance for Industry: Changes to an Approved NDA or ANDA"), one site in Durham, North Carolina, and one site in North Brunswick, New Jersey. Site and building addresses, activities, Drug Establishment Registration (DER/CFN), and Drug Enforcement Administration registration are noted in the attached table. AAI certifies that it operates in conformance with Current Good Manufacturing Practice in accord with Parts 210 and 211 of 21 CFR and, when applicable, in conformance with Good Laboratory Practices in accord with Part 58 of 21 CFR. As a contract testing laboratory and manufacturer of U.S. Food and Drug Administration approved pharmaceutical products, the AAI facilities are registered with the FDA under the Drug Establishment Registration (DER) System under which AAI facilities are subject to routine FDA inspections. Additionally, since AAI analyzes and manufactures controlled substances, the facilities are registered with the Federal Drug Enforcement Administration and with the corresponding state agencies that regulate controlled substances.

Description of the Operations Carried out at AAI

Below is a table with a list of AAI sites and the operations performed at each building within the site.

Building	Operations	DER/CFN #	DEA (type) Registration #
Wilmington, North Carolina Site			
Corporate Headquarters and Mailing Address 2320 Scientific Park Drive Wilmington, NC	Executive Offices Purchasing & Financing Legal Regulatory Affairs Marketing & Sales Training Document Control Information Systems Warehousing Metrology Quality Assurance Physical Chemistry Testing	1049418	Lab B (analytical) RA0138518
Expn - Operations Headquarters Laboratory Site B 1206 North 23rd Street Wilmington, NC	Operations Headquarters Formulation Development Pilot Synthesis Analytical Development Analytical Testing Cell Biology Biotechnology Products Testing Warehousing	1049418	FDL (manufacturer) RF0202755 Lab B (analytical) RA0138518
Hall Drive Laboratory Laboratory Site A Route 6, Hall Drive Wilmington, NC	Analytical Development Analytical Testing Microbiological Testing Quality Control	1049418	Lab A (analytical) PA0200585
Manufacturing Plant 1726 North 23rd Street Wilmington, NC	Manufacturing Packaging & Labeling Warehousing QC Laboratory (Lab P) Quality Control	1049418	MSD (manufacturer) RA0139928 MSD (importer) RA0244474 Lab P (analytical) RA0230259
Clinical Distribution Specialists 1519 North 23rd Street Wilmington, NC	Clinical Supplies Distribution Cold Storage Controlled Substances Storage Solvent Storage Warehousing	1049418	CDS (distributor) RA0244462
Stability Services 3101 North Kerr Avenue Wilmington, NC	Stability Sample Storage Offices	1049418	Lab B (analytical) RA0138518
Beta Lactam Antibiotic Development Facility 1927 Trask Drive Wilmington, NC	Beta Lactam Antibiotic Formulation Development	not applicable (N/A)	N/A
Durham, North Carolina Site			
Durham Laboratory Laboratory Site C 6101 Quadrangle Drive Durham, NC	Analytical Development Analytical Testing	1058430	Lab C (analytical) RA0196596
New Jersey Site			
New Jersey Laboratory 3 Silver Line Drive Rt. 1 North Brunswick, NJ	Analytical Development/Testing Analytical Testing Biotechnology Products Testing Microbiological Testing Stability Storage	2249351	NJ Lab (analytical) RA0248927



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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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: February 10, 2000

Number of Pages 2
(Including cover sheet)

TO: Marcus Herzig
COMPANY: Orapharma Inc.
FAX #: 1-215-443-9531

MESSAGE: Please see comments regarding your submission dated November 8, 1999 for the proposed test method for microbial limits.

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

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MESSAGE CONFIRMATION

02/10/00 17:38

	BOX	GROUP

TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
00'37"	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

February 10, 2000

Number of Pages 2
(Including cover sheet)

Marcus Herzig

COMPANY: Orapharma Inc.

1-215-443-9531

MESSAGE: Please see comments regarding your submission dated November 8, 1999 for the proposed test method for microbial limits.

FROM: Kalyani Bhatt

TO: Project Manager

PHONE #: 301-827-2020

FAX #: 301-827-2075/2091

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

December 19, 2000

Issues for t-con with OraPharma (NDA 50-781)

1. Method validation package (Vol. 2.1) received on 4/12/2000 is incomplete. COAs for samples listed (i.e. Lot # 03868 for Minocycline hydrochloride DS and Lot #98336C for the finished drug product) should be provided.
2. Please ship the complete dispenser/delivery system ?
3. The packaging flow-chart (Vol. 1.3, page 26) and packaging directions in the batch documentation (Vol. 1.7, pages 133-152) are not consistent.
4. Also, on page 186 (Vol. 1.7) you have indicated that the % accountability should be between — % . The % Accountability for Batch No. 98214 was about — with overall yield = — . On page 154 you have included Deviation Form where it is indicated that "There will be no corrective measures at this time". Please explain.
5. What are the controls employed for checking fill weight?
6. Information on sampling procedure is needed. In the Batch documentation you have indicated that fill weight check is performed for every 50 dispenser/barrel unit being filled.
7. Release rate results (ug/mg/hour): Can results reported (as ug/mg/hour) at 4 hrs, 24 hours etc., can be translated into total or % release from the drug product.
8. We have not received your response to our CMC IR fax dated 11/27/00

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



FAX COVER SHEET

To:	Ms. Kalyani Bhatt, Project Manager	From:	Markus Herzig
Company:	FDA	Date:	04/07/00
Fax No.:	301-827-2075	No. of pages w/cover:	1
RE:	NDA-50-781		

Urgent Reply ASAP Please comment Please review For your information

Kalyani:

Attached is the summary of the teleconference conversation of April 7, 2000. If you have any questions, please don't hesitate to contact me.

Thank you,


Markus F. Herzig

This facsimile contains confidential information intended for the person(s) named above. If you have received this facsimile in error, please notify us immediately by telephone and destroy this transmission.

FDA Contact Report	Date: April 7, 2000
Project: Minocycline PTS	<input checked="" type="checkbox"/> FDA Initiated <input type="checkbox"/> OraPharma, Inc. Initiated
IND #	NDA #: 50-781
Contact Person:	Ms. K. Bhatt, Project Manager - 301-827-2023 Division of Dermatologic and Dental Drug Products
<p>Ms. Bhatt called me on April 7, 2000 at 10:30 AM with Dr. M. Gauteum-Basak (Chemistry Reviewer) and Dr. Riley (Microbiologist).</p> <p>This was a follow-up call to the March 13, 2000 teleconference with Ms. Bhatt and Dr. Gauteum-Basak.</p> <p>Dr. Gauteum-Basak wanted to provide OraPharma with additional information for the preparation of the "mini-micro-CMC" section. She asked Dr. Riley to provide the detail. Ms. Bhatt mentioned that Dr. Riley is addressing issues faxed to OraPharma on February 10, 2000.</p> <p>I did not recall the aforementioned fax and Ms. Bhatt will re-send it.</p> <p>Dr. Riley stated that he had a concern regarding our bioburden limits. Specifically, he stated that when calculating the limits on a per gram basis our limit specifications are very high. Dr. Riley requested that we also measure the bioburden on the bulk drug product and set a limit. I stated that I would inform our Pharmaceutical Development group of this request. Dr. Gauteum-Basak asked that when preparing this mini-micro section we should leave the original pagination and add the new information.</p> <p>I informed Dr. Gauteum-Basak that I just received the revised sample section and would be able to submit them shortly. I also stated that I have received the certification of analysis from _____ who uses them for identification of the raw materials used in producing the dispenser tips. Ms. Bhatt asked me to fax this information to her and include it in the formal submission.</p> <p>I also informed FDA that I would submit an Errata sheet, which identifies some inconsistencies found in the original submission as well as a revised methods validation volume.</p> <p>This concluded the teleconference and Ms. Bhatt asked me to fax the summary of this teleconference to her.</p>	
Signature: <i>Markus F. H. H.</i>	Date: 4/7/00

CC: Ron Lawter
April Einstein
Jan Lessem

Markus\fa contact report 19

WITHHOLD 1 PAGE (S)

Forward Planning Meeting Summary

Date: April 6, 2000

Participants from the FDA:

Jonathan Wilkin, M.D., Division Director, HFD-540

John Kelsey, D.D.S., M.B.A., Dental Team Leader, HFD-540

Clarence Gilkes, D.D.S., Dental Officer, HFD-540

Fred Hyman, D.D.S., Dental Officer, HFD-540

Wilson Decamp, Ph.D., Chemistry Team Leader, HFD-830

Mamta Gatuam-Basak, Ph.D., Chemistry Reviewer, HFD-830

Norman See, Ph.D., Pharm-Tox Reviewer, HFD-540

Dennis Bashaw, PharmD., Biopharmaceutic Team Leader, HFD-880

Dan Wang, PharmD., Biopharmaceutic Reviewer, HFD-880

Mohammed A. Osh, Biostatistics Team Leader, HFD-725

Shala Farr, Ph.D. Biostatistics Reviewer, HFD-725

Subject: NDA 50-781 ARESTIN, (minocycline hydrachloride) microspheres, 1 mg

Objective: To determine the fileability of NDA 50-781.

The meeting was convened to determine the adequacy of NDA 50-781 for filing. All sections of the New Drug Application (NDA) were evaluated in terms of the general content and format requirements. The application was deemed fileable. Biopharmaceutic reviewer stated that this NDA would be re-assigned.

/s/

Kalyani Bhatt, Project Manager

Mary Jean Kozma-Fornaro
Chief, Project Management Staff

10

PAGE(S) HAVE BEEN REDACTED IN
FULL FROM THIS DOCUMENT

REASON:

b(2) 'low'

b(4) CCI

b(4) TS

b(5) Deliberative Process; Attorney
Client and Attorney Work Product Privilege

b(6) Personal Privacy

b(7) Law Enforcement Records

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

EVALUATION OF CLINICAL INVESTIGATOR INSPECTIONS.

DATE: January 30, 2001

NDA 50-781

HFD 540

SPONSOR: OraPharma, Inc.

Product: Minocycline PTS (minocycline periodontal therapeutic system)

Indications: Adjunctive therapy to Scaling and Root planning procedures in patients with adult periodontitis.

Project
Manager: Kalyani Bhatt

Medical
Officer: Clarence Gilkes

I. Background:

These routine inspections were part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which NDA 50-781 approval may be based and to assure that the rights and welfare of the human subjects of those studies were protected. These inspections were conducted in accordance with CP 7348.811, Clinical Investigators, in addition to concentrate in comparing source documents, case report forms (CRFs), and data listings in regard to primary endpoints, adverse drug events reporting and discontinued subjects in these protocols. Sites selected in corroboration between HFD-540 Division medical officer, Dr. Gilkes and DSI reviewer, Dr. Jose Carreras.

Name	City	Protocol	CL
Jack G. Caton, D.D.S.	Rochester, New York	#OPI-103A/103B	VAI
Richard J. Oringer, D.D.S.	Stony Brook, New York	#OPI-103A/103B	NAI
Thomas E. Van Dyke, D.D.S.	Boston, Massachusetts	#OPI-103A/103B	VAI
David Cochran, D.D.S.	San Antonio, Texas	#OPI-103A/103B	VAI*

Key to Classifications

NAI = No deviation from regulations

VAI = Minor Deviation(s) from regulations

* Based on observations listed on Form FDA 483. EIR has not been reviewed.

Site #1

Jack G. Caton, D.D.S.

This investigator enrolled fifty-six subjects in the study. Fifty-one subjects completed. The field investigator examined 20 records in depth. Data audit did reveal multiple protocol violations. These violations were documented by the investigator and reported to the IRB sponsor and to the FDA. There were no discrepancies between the case report forms, the source documents and the data submitted to the NDA except for two adverse events that were not reported on the case report forms for two subjects (white ulcerated patch on oral exam at visit 3 for subject #0124 and an increase of greater than 3mm of pocket depth for subjects # 0124 on visit 6). In terms of the missing measurements, the statistical analysis using last observation carried forward (LOCF) was proposed by the sponsor. The data from this site is acceptable. Findings discussed with Dr. Jake Kelsey Team Leader, Dental Officer, HFD 540.

Site #2

Richard J. Oringer, D.D.S.

This investigator enrolled fifty-seven subjects in the study. Fifty-six subjects completed. The field investigator examined 16 records and 15 screen failures in depth. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appear acceptable.

Site #3

Thomas E. Van Dyke, D.D.S.

This investigator enrolled fifty-six subjects in the study. Fifty-three subjects completed. The field investigator examined 19 records. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appear acceptable.

Site #4

David Cochran, D.D.S.

Classification based on observations listed on Form FDA 483. EIR has not been reviewed.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS :

No objectionable conditions were found in the above sites which would preclude the use of their data submitted in support of pending NDA.

Jose A. Carreras, M.D.

cc:
NDA 50-781
Division File
HFD-47/Currier

February 16, 2001

Team Leader Memo re: Arestin (minocycline hydrochloride microspheres) 1 mg

There is no separate review of the 120-day Safety Update for Arestin (minocycline hydrochloride microspheres) 1 mg, but the information is included in the Integrated Summary of Safety in Dr. Gilkes' review. At the time the 120-day Safety Update was submitted, a one year observational extension of one site from Study OPI-103A (which was designated OPI-106) and the open label study (OPI-104) were ongoing. Patients did not receive drug during this period, but the Sponsor did report adverse events. These adverse events were incorporated into the ISS.

TSI
325
John V. Kelsey, D.D.S., M.B.A.

for DFS - 2/16/01

Original to NDA 50-781

HFD-540 Division File
HFD-540 Wilkin
HFD-540 Gilkes
HFD-540 Kelsey
HFD-540 Hyman
HFD-540 Bhatt
HFD-540 Jacobs
HFD-540 See
HFD-833 DeCamp
HFD-833 Gautam-Basak
HFD-725 Al-Osh
HFD-725 Rahman
HFD-880 Bashaw
HFD-880 Ghosh
HFD-520 Mersik

for 2/16/01 DFS ✓

FDA Pediatric Page
1-11-01

PEDIATRIC PAGE

NDA/PLA/PMA # 50-781 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade and generic names/dosage form: ARESTIN (minocycline hydrochloride) Action: AP AE NA

Applicant OraPharma, Inc. Therapeutic Class 3S

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate N/A

Proposed indication in this application Treatment as an adjunct to scaling and root planing procedures for reduction of pockets in patients with adult periodontitis.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___ Yes (Continue with questions) X No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply) N/A

- Neonates (Birth-1month)
- Infants (1month-2yrs)
- Children (2-12yrs)
- Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
- d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

X 5. If none of the above apply, attach an explanation, as necessary. Pediatric Waiver requested. See attached ~~Medical officer's review.~~

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes X No N/A
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from medical review.

Division Director/Jonathan K. Wilkins M.D.

Kalyani Bhat/RPM

Date

Date

cc: Archival NDA 50-781, HED-540 Div File, NDA/PLA Action Package, HFD-104/Peds/T.Crescenzi

2. Slots J, Rams TE. 1990. Antibiotics in periodontal therapy: advantages and disadvantages. J Clin Periodontol 17: 479-493.

Financial Disclosure:

The Sponsor has provided the required certification (Form FDA 3454) regarding financial interests and arrangements of clinical investigators. The Sponsor has certified that the value of compensation to the investigator was not influenced by the outcome of the study. One investigator has received a \$1000/ month consulting retainer since February 1997. Four other investigators had stock or stock options in OraPharma valued at over \$100,000 each, based on the stock price at the time of this review. The Biostatistics reviewer was asked to re-evaluate those sites to determine if there was anything unusual about the reported results and to assess the impact of those sites on the overall studies. In one instance, _____, the mean baseline pocket depth for the active arm was the highest among all sites in the study and the mean baseline pocket depth for the S/RP arm was the lowest among all sites. Since we know that the deeper the pocket at baseline, the better the response is expected to be, the situation described would likely favor the active arm. In fact, the delta between the active and S/RP arms at that site was the second highest among all sites in that study. If that site is dropped from the analysis, the p-value for the comparison goes from .047 to .237. This site did enroll a large number of subjects, so dropping it would be expected to have some effect on the p-value, but it seems unlikely that the change would be so dramatic based on the number of subjects alone. Based on the unusual nature of the data and the fact that the investigator received substantial compensation, the Division has asked the Division of Scientific Investigations (DSI) to audit the site prior to making a final decision about the approvability of this NDA.

Pediatric Waiver:

Adult periodontitis, as its name indicates, affects only adults, so no studies in children are indicated. *

Recommendation:

NDA 50-781 for ARESTIN™ (minocycline hydrochloride), Microspheres, 1 mg is approvable with the labeling changes recommended above, contingent upon the DSI audit of the _____ site not resulting in the disqualification of the data from that site.

Clarence C. Gilkes, D.D.S.

Clarence C. Gilkes, D.D.S. 12-18-00

for DFS 12/18/00

Parent's Request For Pediatric Waiver

04-04-00

2000

NDA ORIG AMENDMENT



NC

NEW COPY

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
201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 50-781
Amendment: FDA Requested Information

Dear Dr. Wilkin:

Reference is made to a telephone conversation between Ms. K. Bhatt in your Division and undersigned during which Ms. Bhatt requested the attached pages for the above referenced NDA.

One page contains our request for the waiver to conduct pediatric studies and the second page identifies the location of the GCP statements in our clinical reports.

If you have any questions, I can be reached at (215) 956-2207.

Sincerely,

Markus F. Herzig

Markus F. Herzig
Executive Director, Regulatory Affairs

MFH:stk

ORIGINAL

Attachments

Form FDA 356h
Submitted in Duplicate

OraPharma, Inc.
minocycline (PTS)
NDA 50-781

NEW DRUG APPLICATION
- 20.0 Pediatric Use

20 PEDIATRIC USE

The intended use of minocycline PTS, 1 mg is as an adjunct to periodontal therapy involving scaling and root planing (SRP). Local administration on minocycline PTS, an antibiotic specific for periodontal pathogens combined with the sustained release properties of the medication, will improve the treatment of moderate to severe adult periodontitis.

Periodontal disease is not a disease of childhood and therefore OraPharma, Inc. has no plans to conduct trials in a pediatric population

WAIVER REQUEST:

We therefore request a waiver to conduct pediatric trials.

8 Clinical Data Section

GCP Statement:

The Phase 3 trial reports conducted by OraPharma contain the statement:

The investigator agreed that the study would be conducted according to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. The investigator conducted all aspects of this study in accordance with all national, state and local laws of the pertinent regulatory authorities.

These statements can be found in:

Volume 34, page 22 for study OPI-103A

Volume 40, page 19 for study OPI-103B

Volume 46, page 15 for Study OPI-104

And

Also, the PK-study OPI-105 has a statement on page 13 (volume 12)

20 PEDIATRIC USE

The intended use of minocycline PTS, 1 mg, is as an adjunct to periodontal therapy involving scaling and root planing (S/RP). Local administration of minocycline PTS, an antibiotic specific for periodontal pathogens combined with the sustained release properties of the medication, will improve the treatment of moderate to severe adult periodontitis.

Periodontal disease is not a disease of childhood and therefore OraPharma, Inc. has no plans to conduct trials in a pediatric population.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Director's Office):

Pete Cooney MFD-160

FROM:

Kalyani Bhatt, Project Manager MFD-540

DATE

4-18-00

IND NO.

NDA NO.

50-781

TYPE OF DOCUMENT

NEW NDA

DATE OF DOCUMENT

2-16-00

NAME OF DRUG

Minoxidil PTS

PRIORITY CONSIDERATION

3s

CLASSIFICATION OF DRUG

Antibiotic

DESIRED COMPLETION DATE

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY

- PRE-NDA MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT

- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

CMC Microbiology Consult

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review this NDA submission for CMC microbiology consult. Attached is a copy of 1.1. You will receive a separate CMC volume from the sponsor.

Thanks,

Kalyani Bhatt 827-2049

SIGNATURE OF REQUESTER

/S/

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):

ALSHEDON HFD-520

FROM:

Kalyani Bhatt, HFD-540-P.M.

DATE
2-25-00

IND NO.

NDA NO.

TYPE OF DOCUMENT

DATE OF DOCUMENT

NDA Submission

NAME OF DRUG

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE

Mincycline

Tetracycline

12-17-00

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY

- PRE-NDA MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA **electronic**
- CONTROL SUPPLEMENT

- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):
Micro Review.

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

One copy of 1.1 volume is for Team Leads + Reviewers.

SIGNATURE OF REQUESTER

/S/ D-540

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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



FAX COVER SHEET

To:	Ms. Kalyani Bhatt, Project Manager	From:	Markus Herzig
Company:	FDA	Date:	04/13/00
Fax No.:	301-827-2075	No. of pages w/cover:	1
RE:	NDA-50-781		

Urgent Reply ASAP Please comment Please review For your information

Dear Ms. Bhatt:

Attached is the information Dr. Gautam-Basak requested in our April 2, 2000 teleconference.

It contains the detailed composition of the investigational formulations manufactured at AAI.

Sincerely,


Markus F. Herzig
Executive Director Regulatory Affairs

This facsimile contains confidential information intended for the person(s) named above. If you have received this facsimile in error, please notify us immediately by telephone and destroy this transmission.

CMC - Information

Dr. Gautam-Basak requested detailed composition information on the batches of minocycline PTS produced at AAI. The batch numbers for these clinical batches are 98155 and 98214.

The following is the batch information for these two batches:

Table 3.4.2.1-B Composition of Minocycline PTS microspheres

Component	Quality (%)	Quantity per Batch (grams)*
Minocycline Hydrochloride USP	—	—
Poly(glycolide-co-dl-lactide) G.A. Initiated	—	—

The composition of all batches manufactured at AAI are identical. These batches were used for all the clinical trials and also the NDA stability studies.

The detailed composition can be found in the original NDA Vol. 1.1 page 102 and Vol. 1.2 page 59.

This facsimile contains confidential information intended for the person(s) named above. If you have received this facsimile in error, please notify us immediately by telephone and destroy this transmission.

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-MAR-2000				GAUTAMBASA
SUBMITTED TO DO	07-MAR-2000	10D			EGASM
INSPECTION PERFORMED	13-MAR-2000		08-MAR-2000		EGASM
EI DID NOT COVER THIS PRODUCT SPECIFICALLY					
DO RECOMMENDATION	06-JUN-2000			ACCEPTABLE INSPECTION	EGASM
OC RECOMMENDATION	06-JUN-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: _____

DMF No: _____

AADA: _____

Responsibilities: _____

Profile: CTL

OAI Status: NONE

Etab. Comment: _____

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-MAR-2000				GAUTAMBASA
SUBMITTED TO DO	07-MAR-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	19-APR-2000	PS			DPAGANO
INSPECTION SCHEDULED	12-MAY-2000				DPAGANO
INSPECTION PERFORMED	18-MAY-2000		16-MAY-2000		DPAGANO
DO RECOMMENDATION	18-MAY-2000			WITHHOLD	DPAGANO
OC RECOMMENDATION	22-MAY-2000			WITHHOLD FIRM NOT READY	DAMBROGIOJ
ASSIGNED INSPECTION	25-AUG-2000	PS			DPAGANO
INSPECTION SCHEDULED	18-SEP-2000				DPAGANO
INSPECTION PERFORMED	02-OCT-2000		27-SEP-2000		DPAGANO
DO RECOMMENDATION	02-OCT-2000			WITHHOLD	DPAGANO

EIR RECEIVED BY OC 20-NOV-2000
OC RECOMMENDATION 01-DEC-2000

HARTMANB
HARTMANB
WITHHOLD
EIR REVIEW-CONCUR
W/DISTRICT

ASSIGNED INSPECTION 07-DEC-2000 PS
INSPECTION SCHEDULED 12-DEC-2000
INSPECTION PERFORMED 13-DEC-2000 12-DEC-2000
DO RECOMMENDATION 13-DEC-2000

DPAGANO
DPAGANO
DPAGANO
DPAGANO
ACCEPTABLE
INSPECTION

CORRECTIVE ACTION TO THE FDA-483 OBSERVATIONS RELATED TO THIS PRODUCT WAS
VERIFIED ON 12/12/00.

OC RECOMMENDATION 13-DEC-2000 ACCEPTABLE FERGUSONS

Establishment:

DMF No: _____ AADA:
Responsibilities: _____
Profile: CSN OAI Status: NONE
Etab. Comment: _____

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-MAR-2000				GAUTAMBASA
SUBMITTED TO DO	07-MAR-2000	GMP			EGASM
DO RECOMMENDATION	09-MAR-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
	BASED ON EI OF 4/2/98				
OC RECOMMENDATION	13-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment:

ORAPHARMA INC
732 LEWIS DRIVE
WARMINSTER, PA 18974

DMF No: _____ AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: POW OAI Status: NONE
Etab. Comment: APPLICANT MADE CHANGES TO FILLING EQUIPMENT AT PACKAGING SITE
WITHOUT SUBMITTING AN AMENDMENT. (on 03-NOV-2000 by S. FERGUSON
(HFD-324) 301-827-0062)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-NOV-2000				FERGUSONS
SUBMITTED TO DO	03-NOV-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	03-NOV-2000	PS			DPAGANO
ASSIGNED INSPECTION	03-NOV-2000	PS			DPAGANO
INSPECTION SCHEDULED	03-NOV-2000		02-NOV-2000		DPAGANO
INSPECTION PERFORMED	03-NOV-2000		02-NOV-2000		DPAGANO
DO RECOMMENDATION	03-NOV-2000			WITHHOLD INSUFFICIENT DEVELOPMENT DATA	DPAGANO

THE ORAPHARMA _____ HAS BEEN REDESIGNED SUBSEQUENT THE FILLING OF CLINICAL AND STABILITY BATCHES IN SUPPORT OF NDA 50-781. THERE IS NO COMPARABILITY REPORT BETWEEN THE ORIGINAL DESIGN, WHICH FILLED (LOTS 98155, 98212, 98214 & 98336) TO THE NEW DESIGN. THE NEW DESIGN ALLOWS APPROXIMATELY _____ OF MINOCYCLINE TO BE

IN ADDITION, AN EVALUATION OF WHAT EFFECTS THE NEW DESIGN MAY HAVE ON THE PRODUCT HAS NOT BEEN CONDUCTED.

DO RECOMMENDATION 14-DEC-2000

WITHHOLD

DPAGANO

INADEQUATE FIRM RESPONSE

PHI-DO RECEIVED VIA FAX - CORRECTIVE ACTION TO THE FDA-483 OBSERVATION ON 12/13 AND 12/14/00. IN ADDITION, TELEPHONE CONVERSATIONS BETWEEN THE FIRM AND DEBRA L. PAGANO WERE HELD ON 12/13 & 12/14. PHI-DO LEARNED THAT THE NEW FILLING EQUIPMENT CUSTOM DESIGNED BY THE APPLICANT IS NOT CAPABLE OF PROVIDING THE EXPECTED YIELD OF UNIT DOSE APPLICATORS. THE YIELD CURRENTLY IS ABOUT _____ THE FIRM IS RELYING ON WEIGHT CHECKS OF THE UNIT DOSE APPLICATOR AND ACCORDING TO THE FIRM OUT OF SPECIFICATION WEIGHT CHECKS OCCURS AROUND _____ OF THE BATCH. THE FIRM CONTENDS THAT THEY ARE BEING CONSERVATIVE IN THAT THEY ARE DISCONTINUING FILLING OF THE UNIT DOSE APPLICATORS ONCE THEY HAVE AN OUT OF WEIGHT CHECK AND THEY THEN DISCARD THE REMAINDER OF THE FILLING BATCH. PLEASE READ PREVIOUS COMMENTS ON PRIOR WITHHOLD RECOMMENDATION.

EIR RECEIVED BY OC 15-DEC-2000

HARTMANB

OC RECOMMENDATION 31-JAN-2001

WITHHOLD

HARTMANB

EIR REVIEW-CONCUR

W/DISTRICT

ACCEPTABLE

HARTMANB

OC RECOMMENDATION 31-JAN-2001

ORIGINAL WITHHOLD BASED ON REVIEW ISSUES. THESE ISSUES HAVE BEEN RESOLVED WITH THE FIRM AS OUTLINED IN A 1/30/01 MEMO FROM BONNIE DUNN, DNDCIII. THE OC RECOMMENDATION FOR ORAPHARMA IS CHANGED TO ACCEPTABLE.

Establishment:

DMF No: _____

Responsibilities

Profile:

Estab. Comment:

PACKAGING OF THIS PRODUCT WILL BE NEW TECHNOLOGY FOR _____
 _____ THE EQUIPMENT THAT WILL BE UTILIZED WILL BE
 DEDICATED TO THIS PRODUCT. THE EQUIPMENT WAS DESIGNED BY THE
 APPLICANT SPECIFICALLY FOR THE UNIQUE PACKAGING OPERATIONS.

PLEASE COMPLETE PAGE TWO OF THIS ASSIGNMENT AT THE COMPLETION OF
 THE INSPECTION AND FORWARD TO THE PRE-APPROVAL OFFICE AS WELL AS A
 COPY TO COMPLIANCE BRANCH.

_____ IS THE CONTACT FOR _____ AND SHE CAN BE REACHED AT _____
 _____ THE DUE DATE FOR THIS INSPECTION IS AUGUST 18, 2000.

(on 16-JUN-2000 by D. PAGANO (HFR-CE100) 215-597-4390)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-MAR-2000				GAUTAMBASA-
SUBMITTED TO DO	07-MAR-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	16-JUN-2000	PS			DPAGANO
INSPECTION SCHEDULED	05-OCT-2000				DPAGANO
INSPECTION PERFORMED	16-OCT-2000		12-OCT-2000		DPAGANO
DO RECOMMENDATION	16-OCT-2000			ACCEPTABLE INSPECTION	DPAGANO

NOTE: A RECOMMENDATION FOR _____ IS ACCEPTABLE HOWEVER INFORMATION DISCLOSED
 DURING THE _____ INSPECTION REVEALED THAT FOLLOW UP IS MANDATORY AT THE
 APPLICANT SITE - SEE BELOW -----

INVESTIGATOR ROBERT MAFFEI AND PAI MANAGER DEBRA L. PAGANO CONDUCTED THE
 INSPECTION. _____ IS ACCEPTABLE FROM A GMP PERSPECTIVE.

THERE ARE ISSUES WITH THE FILLING EQUIPMENT HOWEVER THE ISSUES NEED TO BE
 ADDRESSED WITH THE APPLICANT. THE FILLING EQUIPMENT HAS BEEN REDESIGNED.
 DURING THE INSPECTION, A REPRESENTATIVE FROM ORAPHARMA WAS PRESENT AND WE
 LEARNED THAT THIS INFORMATION HAS NOT BEEN AMENDED TO THE APPLICATION. ONE
 OF THE FEATURES OF THE NEW DESIGN IS THE ABILITY FOR _____

[] THERE HAS BEEN NO
 COMPARABILITY REPORT REGARDING THE MATERIAL PROCESSED WITH THE NEW DESIGN
 VERSUS WHAT THE MATERIAL LOOKED LIKE FOR THE CLINICAL AND STABILITY STUDIES.
 OC RECOMMENDATION 16-OCT-2000 ACCEPTABLE DAMBROGIOJ
 DISTRICT RECOMMENDATION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Bnc-t

Food and Drug Administration
Rockville MD 20857

OCT - 6 2000

Jack G. Caton, M.D.
University of Rochester
Eastman Department of Dentistry
625 Elmwood Avenue
Rochester, New York 14620

Dear Dr. Caton:

Between July 24 and August 7, 2000, Mr. Joseph A. Famiglietti, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #OPI-103A/103B) of the investigational drug Minocycline PTS (minocycline periodontal therapeutic system) performed for ORAPHARMA, INC. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report and your August 24, 2000, written response to the items listed on the Form FDA 483, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Famiglietti presented and discussed with you his inspectional observations. The discussion included: 1) failure to perform the study according to the relevant protocol; and 2) failure to maintain adequate and accurate records. We note your responses and your promise to make corrections/changes in your procedures to ensure that similar violations are not repeated in any ongoing or future studies.

We appreciate the cooperation shown investigator Famiglietti during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

WITHHOLD 1 PAGE (S)

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

EVALUATION OF CLINICAL INVESTIGATOR INSPECTIONS.

DATE: September 22, 2000

NDA 50-781

HFD 540

SPONSOR: OraPharma, Inc

Product: Minocycline PTS (minocycline periodontal therapeutic system)

Indications: Adjunctive therapy to Scaling and Root planning procedures in patients with adult periodontitis.

Project
Manager: Kalyani Bhatt

Medical
Officer: Clarence Gilkes

I. Background:

These routine inspections were part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which NDA 50-781 approval may be based and to assure that the rights and welfare of the human subjects of those studies were protected. These inspections were conducted in accordance with CP 7348.811, Clinical Investigators, in addition to concentrate in comparing source documents, case report forms (CRFs), and data listings in regard to primary endpoints, adverse drug events reporting and discontinued subjects in these protocols. Sites selected in corroboration between HFD-540 Division medical officer, Dr. Gilkes and DSI reviewer, Dr. Jose Carreras.

Name	City	Protocol	CL
Jack G. Caton, M.D.	Rochester, New York	#OPI-103A/103B)	VAI
Richard J. Oringer, D.D.S.	Stony Brook, New York	#OPI-103A/103B)	NAI

Key to Classifications

NAI = No deviation from regulations

VAI = Minor Deviation(s) from regulations

Site #1

Jack G. Caton, M.D.

This investigator enrolled fifty-six subjects in the study. Fifty-one subjects completed. The field investigator examined 20 records in depth. Data audit did reveal multiple protocol violations. These violations were documented by the investigator and reported to the IRB sponsor and to the FDA. There were no discrepancies between the case report forms, the source documents and the data submitted to the NDA except for two adverse events that were not reported on the case report forms for two subjects (white ulcerated patch on oral exam at visit 3 for subject #0124 and an increase of greater than 3mm of pocket depth for subject # 0124 on visit 6). In terms of the missing measurements, the statistical analysis using last observation carried forward (LOCF) was proposed by the sponsor. The data from this site is acceptable. Findings discussed with Dr. Jake Kelsey Team Leader, Dental Officer, HFD 540.

Site #2

Richard J. Oringer, D.D.S.

This investigator enrolled fifty-seven subjects in the study. Fifty-six subjects completed. The field investigator examined 16 records and 15 screen failures in depth. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appear acceptable.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS :

No objectionable conditions were found in the above sites which would preclude the use of their data submitted in support of pending NDA.

Jose A. Carreras, M.D.

cc:
NDA 50-781
Division File
HFD-47/Currier



HFD-540
Blatt

Food and Drug Administration
Rockville, MD 20857

SEP 13 2000

Richard J. Oringer, D.D.S., D.M.Sc.
SUNY Stony Brook
School of Dental Medicine
Department of Periodontics
Stony Brook, New York 11794-8703

Dear Dr. Oringer:

Between August 9 and 14, 2000, Mr. Thomas Hansen, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #OPI-103A/103B) of the investigational drug Minocycline PTS (minocycline therapeutic system), performed for ORAPHARMA, INC. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects

We appreciate the cooperation shown Investigator Hansen during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

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