CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 50-781

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-781

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

Dear Mr. Herzig:

Please refer to your new drug application (NDA) dated February 16, 2000, received February 17, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arestin (minocycline hydrochloride) Microspheres, 1mg.

We acknowledge receipt of your submissions dated February16, 17, 29, March 13, April 4, 11 (2), 19, May 18, June 5, 16, 19 and 29, July 21, August 16, September 11, 27, October 9, November 3 (2), 6, 9, 16 and 20, December 1 and 7, 2000; and January 3, 9, 10, 11, 12, 25 and 30, 2001 and February 16, 2001 (3 facsimiles).

This new drug application provides for the use of Arestin (minocycline hydrochloride) Microspheres, 1mg, as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 50-781." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application, since the adult form of periodontitis is found almost exclusivity in adults.

We remind you of your commitment agreed to in your submission dated January 25, 2001, to provide method validation data for the particle size specification.

In addition, we remind you of your commitment, agreed to in your submission dated October 9, 2000, and your fax dated February 16, 2001 to: 1) treat all medication error reports, regardless of patient outcome between these two names as 15 day expedited reports and 2) agree to change the name of the product if post marketing reports are received of a patient receiving the wrong drug.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Kalyani Bhatt, Project Manager, at (301) 827-2020.

Sincerely,

/S/ 2/16/01

for Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

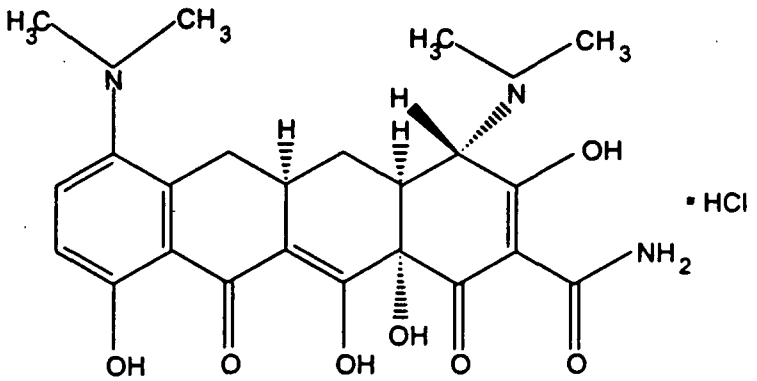
[redacted] Approved Label
[redacted] 7/01

ARESTIN ™ (minocycline hydrochloride)
Microspheres, 1 mg

DESCRIPTION

ARESTIN™ (minocycline hydrochlorhide) Microspheres is a subgingival sustained-release 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 cartridge delivers minocycline hydrochloride equivalent to 1 mg of minocycline free base.

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



CLINICAL PHARMACOLOGY
Microbiology

Minocycline, a member of the tetracycline class of antibiotics, has a broad spectrum of activity.[1] It is bacteriostatic and exerts its antimicrobial activity by inhibiting protein synthesis.[1] In vitro susceptibility testing has shown that the organisms *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Eikenella corrodens* and *Actinobacillus actinomycetemcomitans*, which are associated with periodontal disease, are susceptible to minocycline at concentrations of ≤ 8 μg/mL;[2] qualitative and quantitative changes in plaque microorganisms have not been demonstrated in patients with periodontitis, using this product.

The emergence of minocycline-resistant bacteria in single site plaque samples was studied in subjects before and after treatment with ARESTIN™ at two centers. There was a slight increase in the numbers of minocycline-resistant bacteria at the end of the 9-month study period, however the number of subjects studied was small and the clinical significance of these findings is unknown.

The emergence of minocycline-resistant bacteria and changes in the presence of *Candida albicans* and *Staphylococcus aureus* in the gastrointestinal tract were studied in subjects

treated with ARESTIN™ in one phase 3 study. No changes in the presence of minocycline-resistant bacteria or *C. albicans* or *S. aureus* were seen at the end of the 56-day study period.

Pharmacokinetics

In a pharmacokinetic study, 18 patients (10 men and 8 women) with moderate to advanced chronic periodontitis were treated with a mean dose of 46.2 mg (25-112 unit doses) of ARESTIN™. After fasting for at least 10 hours, patients received subgingival application of ARESTIN™ (1 mg per treatment site) following scaling and root planing at a minimum of 30 sites on at least eight teeth. Investigational drug was administered to all eligible sites ≥ 5mm in probing depth. Mean dose normalized saliva AUC and C_{max} were found to be approximately 125 and 1000 times higher than those of serum parameters were respectively.

Clinical Studies

In two well controlled, multicenter, investigator-blind, vehicle-controlled, parallel-design studies (three arms), 748 patients (study OPI-103A = 368, study OPI-103B = 380) with generalized moderate to advanced adult periodontitis characterized by a mean probing depth of 5.90 and 5.81 mm respectively were enrolled. Subjects received one of three treatments: (1) scaling and root planing, (2) scaling and root planing + vehicle (bioresorbable polymer, PGLA), and (3) scaling and root planing + ARESTIN™. To qualify for the study, patients were required to have four teeth with periodontal pockets of 6-9 mm that bled on probing. However, treatment was administered to all sites with mean probing depths of 5 mm or greater. Patients studied were in good general health. Patients with poor glycemic control or active infectious diseases were excluded from the studies. Retreatment occurred at 3 and 6 months after initial treatment, and any new site with PD ≥ 5 mm also received treatment. Patients treated with ARESTIN™ were found to have statistically significantly reduced probing pocket depth (PD) compared with those treated with S/RP alone or S/RP + vehicle at 9 months after initial treatment, as shown in Table 1.

Table 1: Probing Pocket Depth at Baseline and Change in Pocket Depth at 9 Months from Two Multicenter U.S. Clinical Trials

Time	Study OPI-103A N=368			Study OPI-103B N=380		
	S/RP Alone N=124	S/RP + Vehicle N=123	S/RP + ARESTIN N=121	S/RP Alone N=126	S/RP + Vehicle N=126	S/RP + ARESTIN N=128
PD (mm) at Baseline, mean ± SE	5.88 ± 0.04	5.91 ± 0.04	5.88 ± 0.04	5.79 ± 0.03	5.82 ± 0.04	5.81 ± 0.04
PD (mm) Change from Baseline at 9 months, mean ± SE	-1.04 ± 0.07	-0.90 ± 0.54	-1.20*** ± 0.07	-1.32 ± 0.07	-1.30 ± 0.07	-1.63**** ± 0.07

SE = standard error, S/RP = scaling and root planing, PD = pocket depth

Significantly different from S/RP *($p \leq 0.05$); ** ($p \leq 0.001$)
Significantly different from S/RP + Vehicle • ($p \leq 0.05$); •• ($p \leq 0.001$)

In these two studies an average of 29.5 (5-114), 31.7 (4-137) and 31 (5-108) sites were treated at baseline in the S/RP alone, S/RP + vehicle and S/RP + ARESTIN™ groups, respectively. When these studies are combined the mean pocket depth change at 9 months was -1.18 mm, -1.10 mm, and -1.42 mm for S/RP alone, S/RP + vehicle, and S/RP+ ARESTIN™ respectively.

Table 2: Numbers (percentage) of Pockets Showing a Change of Pocket Depth ≥ 2 mm at 9 months from Two Multicenter U.S. Clinical Trials

	Study OPI-103A			Study OPI-103B		
	S/RP Alone	S/RP + Vehicle	S/RP + ARESTIN™	S/RP Alone	S/RP + Vehicle	S/RP + ARESTIN™
Pockets ≥ 2mm (% of total)	1046 (31.1%)	927 (25.7%)	1326 (36.5%)	1692 (42.2%)	1710 (40.0%)	2082 (51.0%)
Pockets ≥ 3mm (% of total)	417 (12.4%)	315 (8.7%)	548 (15.1%)	553 (13.8%)	524 (12.3%)	704 (17.3%)

S/RP + ARESTIN™ resulted in a greater percentage of pockets showing a change of PD ≥2 mm and ≥3 mm compared to S/RP alone at 9 months, as shown in Table 2.

Table 3: Mean Pocket Depth Changes (SE) in Subpopulations, Studies 103A and 103B Combined

	S/RP Alone	S/RP + Vehicle	S/RP + ARESTIN
Smokers	N = 91 -0.96±0.09 mm	N = 90 -0.98±0.07 mm	N = 90 -1.24±0.09 mm**
Non Smokers	N = 159 -1.31±0.06 mm	N = 159 -1.17±0.07 mm	N = 159 -1.53±0.06 mm**
Patients > 50 YOA	N = 21 -1.07±0.09 mm	N = 81 -0.92±0.08 mm	N = 107 -1.42±0.08 mm**
Patients ≤ 50 YOA	N = 167 -1.24±0.06 mm	N = 168 -1.19±0.06 mm	N = 142 -1.43±0.07 mm*
Patients with CV Disease	N = 36 -0.99±0.13 mm	N = 29 -1.06±0.14 mm	N = 36 -1.56±0.14 mm**
Patients w/o CV Disease	N = 214 -1.22±0.06 mm	N = 220 -1.11±0.05 mm	N = 213 -1.40±0.06 mm**

S/RP = scaling and root planing, YOA = Years of Age, CV = cardiovascular
* S/RP v. S/RP + ARESTIN™ $p \leq 0.05$; ** S/RP v. S/RP + ARESTIN™ $p \leq 0.001$

In both studies, the following patient subgroups were prospectively analyzed: smokers, patients over and under 50 years of age, and patients with a previous history of

cardiovascular disease. The results of the combined studies are presented in Table 3. In smokers, the mean reduction in pocket depth at nine months was less in all treatment groups than in non-smokers, but the reduction in mean pocket depth at 9 months with S/RP + ARESTIN™ was significantly greater than with S/RP + vehicle or S/RP alone.

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

Mean Baseline Pocket Depth	Study OPI-103A			Study OPI-103B		
	S/RP Alone	S/RP + Vehicle	S/RP + ARESTIN™	S/RP Alone	S/RP + Vehicle	S/RP + ARESTIN™
≥ 5mm (n)	-1.04mm (124)	-0.90mm (123)	-1.20mm* (121)	-1.32mm (126)	-1.30mm (126)	-1.32mm* (128)
≥ 6mm (n)	-0.91mm (34)	-0.77mm (46)	-1.40mm* (45)	-1.33mm (37)	-1.46mm (40)	-1.69mm* (25)
≥ 7mm (n)	-1.10mm (4)	-0.46mm (5)	-1.91mm (3)	-1.72mm (3)	-1.11mm (3)	-2.84mm (2)

*Statistically significant comparison between S/RP + ARESTIN™ and S/RP Alone

The combined data from these two studies also shows that for pockets 5mm to 7mm at baseline, greater reductions in pocket depth occurred in pockets that were deeper at baseline.

INDICATIONS AND USE

ARESTIN™ is indicated as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis. ARESTIN ™may be used as part of a periodontal maintenance program which includes good oral hygiene, and scaling and root planing.

CONTRADICTIONS

ARESTIN™ should not be used in any patient who has a known sensitivity to minocycline or tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF EIGHT YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH(YELLOW-GRAY BROWN). This adverse reaction is more common during long-term use of the drugs, but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, OR IN PREGNANT OR NURSING WOMEN, UNLESS THE POTENTIAL BENEFITS ARE CONSIDERED TO OUTWEIGH THE POTENTIAL RISKS. Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development).

Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. If any tetracyclines are used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

Precautions
The use of ARESTIN ™ in an acutely abscessed periodontal pocket has not been studied and is not recommended.

While no overgrowth by opportunistic microorganisms, such as yeast, were noted during clinical studies, as with other antimicrobials the use of ARESTIN™ may result in overgrowth of non-susceptible microorganisms including fungi. The effects of treatment for greater than six months has not been studied.

ARESTIN™ should be used with caution in patients having a history of predisposition to oral candidiasis. The safety and effectiveness of ARESTIN™ has not been established for the treatment of periodontitis in patients with co-existent oral candidiasis.

ARESTN™ has not been clinically tested in immunocompromised patients (such as those immunocommpromised by diabetes, chemotherapy, radiation therapy, or infection with HIV).

If superinfection is suspected, appropriate measures should be taken.

ARESTIN™ has not been clinically tested in pregnant women.

ARESTIN™ has not been clinically tested for use in the regeneration of alveolar bone, either in preparation for or in conjunction with the placement of endosseous (dental) implants or in the treatment of failing implants.

Information for Patients
After treatment patients should avoid eating hard, crunchy or sticky foods for one week and postpone brushing for a 12-hour period, as well as avoid touching treated areas. Patients should also postpone the use of interproximal cleaning devices for 10 days after administration of ARESTIN™. Patients should be advised that although some mild to moderate sensitivity is expected during the first week after S/RP and administration of ARESTIN™, they should notify the dentist promptly if pain, swelling or other problems occur.

Carcinogenicity, Mutagenicity, Impairment of Fertility
Dietary administration of minocycline in long term tumorigencity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasia in rats and dogs. In addition, there has been evidence of oncogenic

activity in rats in studies with a related antibiotic, oxytetracycline (i.e., adrenal and pituitary tumors). Minocycline demonstrated no potential to cause genetic toxticity in a battery of assays which included a bacterial reverse mutation assay (Ames test), an in *vitro* mammmalian cell gene mutation test (L5178Y/TK$^{+/-}$ mouse lymphoma assay), an in *vitro* mammalian chromosome aberration test, and an in *vivo* micronucleus assay conducted in ICR mice.

Fertility and general reproduction studies have provided evidence that minocycline impairs fertility in male rats.

Teratogenic Effects: Pregnancy Category D: (See **WARNINGS**)

Labor and Delivery
The effects of tetracyclines on labor and delivery are unknown.

Nursing Mothers
Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (See **WARNINGS**).

Pediatric Use
Since adult periodontitis does not affect children, the safety and effectiveness of ARESTIN™ in pediatric patients can not be established.

ADVERSE REACTIONS
The most frequently reported non-dental treatment emergent adverse events in the two three multicenter U.S. trials were headache, infection, flu syndrome and pain.

Table 4: Adverse Events Reported in ≥ 3% of the Combined Clinical Trial Population of Three Multicenter US Trials by Treatment Group

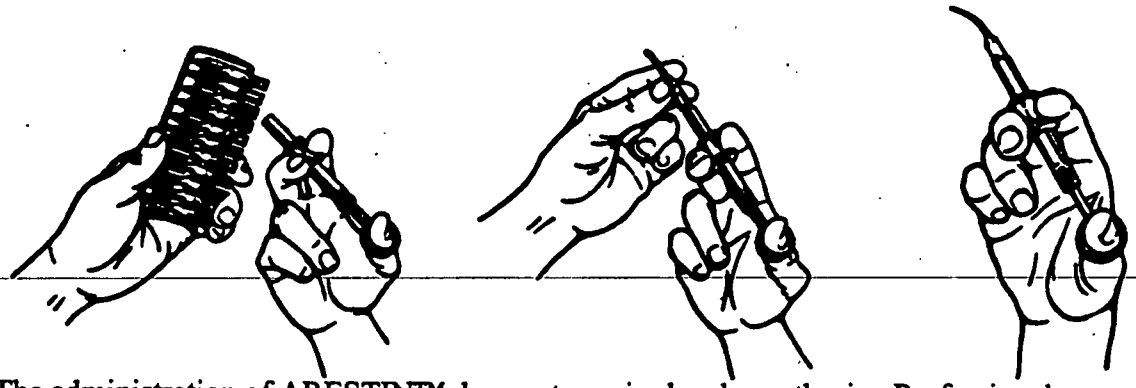
	S/RP Alone N=250	S/RP + Vehicle N=249	S/RP + ARESTIN™ N=423
Number (%) of Patients Treatment Emergent AE	62.4%	71.9%	68.1%
Total Number of AEs	543	589	987
Periodontitis	25.6%	28.1%	16.3%
Tooth Disorder	12.0%	13.7%	12.3%
Tooth Caries	9.2%	11.2%	9.9%
Dental Pain	8.8%	8.8%	9.9%
Gingivitis	7.2%	8.8%	9.2%
Headache	7.2%	11.6%	9.0%
Infection	8.0%	9.6%	7.6%
Stomatitis	8.4%	6.8%	6.4%
Mouth Ulceration	1.6%	3.2%	5.0%
Flu Syndrome	3.2%	6.4%	5.0%
Pharyngitis	3.2%	1.6%	4.3%
Pain	4.0%	1.2%	4.3%
Dyspepsia	2.0%	0	4.0%
Infection Dental	4.0%	3.6%	3.8%
Mucous Membrane Disorder	2.4%	0.8%	3.3%

The change in clinical attachment levels was similar across all study arms, suggesting that neither the vehicle nor ARESTIN™ compromise clinical attachment.

DOSAGE AND ADMINISTRATION

ARESTIN™ is provided as a dry powder, packaged in a unit dose cartridge, which is inserted into a cartridge handle to administer the product. The oral healthcare professional removes the disposable dispenser from its pouch and connects the cartridge to the handle mechanism (see Fig. 1-3). ARESTIN™ is a variable dose product, dependent on the size, shape and number of pockets being treated. In the US clinical trials up to 121 unit dose tips were used in a single visit and up to three treatments, at three month intervals, were administered in pockets with PD of 5 mm or greater.

Figure 1 Figure 2 Figure 3



The administration of ARESTIN™ does not require local anesthesia. Professional subgingival administration is accomplished by inserting the unit dose cartridge to the base of the periodontal pocket and then pressing the thumb ring in the handle mechanism to expel the powder while gradually withdrawing the tip from the base of the pocket. The handle mechanism should be sterilized between patients. ARESTIN ™ does not have to be removed, as it is bioresorbable, nor is an adhesive or dressing required.

HOW SUPPLIED

ARESTIN™ (minocycline hydrochloride) Microspheres, 1mg is supplied in unit doses of 12 cartridges in one tray (NDC number) packaged with desiccant in a heat-sealed foil laminate resealable pouch. There are two pouches in each box. Each unit dose cartridge contains the product identifier "OP-1".

Storage Conditions

Store at 20-25°C (68-77°F)/60%RH; excursions permitted to 15-30°(59-86°F).
Avoid exposure to excessive heat.

Rx only

Manufactured for OraPharma, Inc.

Distributed by: OraPharma, Inc.
732 Louis Drive
Westminster, PA 18974

REFERENCES

1. Stratton CW, Lorian V. Mechanisms of action of antimicrobial agents: general principles and mechanisms for selected classes of antibiotics. In Antibiotics in Laboratory Medicine, 4th edition, Williams and Wilkins, Baltimore, MD, 1996.

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

FRONT CARTON

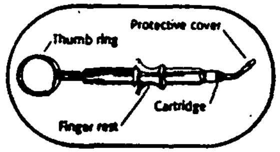
NDC 65976-100-24

2 resealable foil pouches
Each pouch contains
12 cartridges
Each cartridge contains
1 mg of minocycline
For subgingival application
Store at room temperature

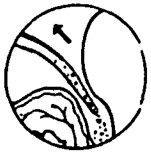
MICROSPHERE DELIVERY SYSTEM

Arestin
minocycline HCl
Microspheres

Arestin™
minocycline HCl
Microspheres



ARESTIN is provided as a dry powder, packaged in a specially designed unit-dose cartridge. Insert cartridge into handle and twist until it snaps into place. Remove protective cover.



Professional subgingival administration is accomplished by inserting the cartridge tip to the base of the periodontal pocket and then pressing down on the handle thumb ring to expel the powder, while gradually withdrawing the cartridge tip from the base of the pocket.

After administration, pull back on the thumb ring to release the cartridge from the handle.

Manufactured for:
ORAPHARMA, INC.

To order: Call 1-866-ARESTIN (273-7846)
or visit our Web site at www.arestin.com.

Please see accompanying complete Prescribing Information.

Arestin™
minocycline HCl
Microspheres

BACK CARTON

Arestin™
minocycline HCl
Microspheres

MICROSPHERE DELIVERY SYSTEM

NDC 65976-100-24

2 resealable foil pouches
Each pouch contains 12 cartridges
Each cartridge contains 1 mg of minocycline

For subgingival application

Store at room temperature (20°C–25°C/68°F–77°F).

Rx only

To order:
Call 1-866-ARESTIN (273-7846)
or visit our Web site at
www.arestin.com.

ORAPHARMA, INC.

To order: Call 1-866-ARESTIN (273-7846) or visit our Web site at www.arestin.com.

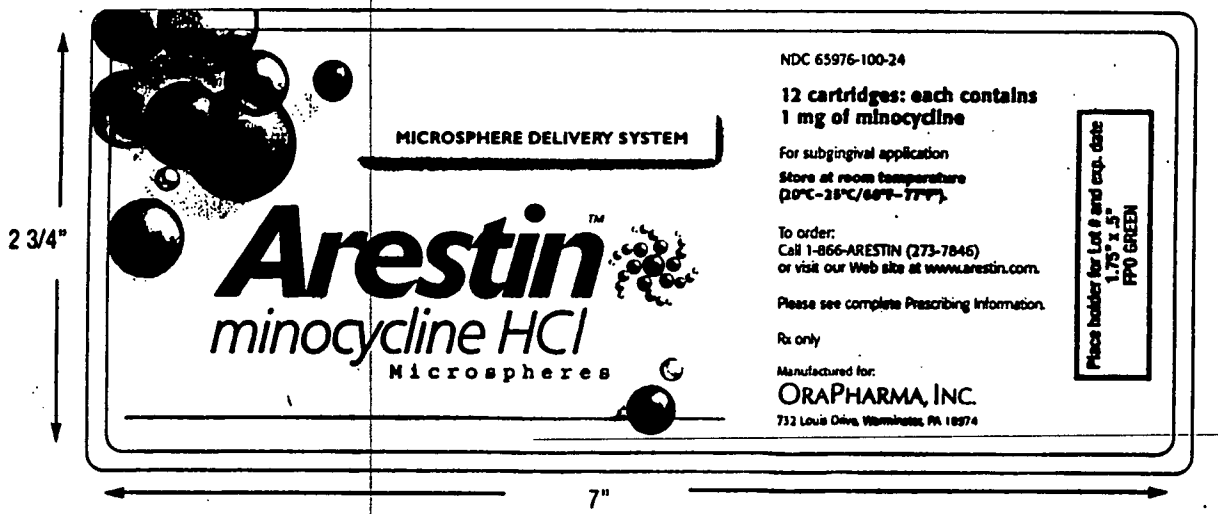
Lot: 00 0000 000 00
Exp: 00 00 00

FPO

Arestin
minocycline HCl
Microspheres

PHARMAGRAPHICS # ORA MPT 08441 Dispenser Box Date Set: 12/8/00 Proof #9 Revise Date: 12/29/00 Op: ck,md,lr,sh,al,md
Client/Product: OraPharma/Arestin Alt: la Colors: 4c process Galley # 1b of 1

Pouch



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

PHARMAGRAPHICS # ORA MPT 08441 Pouch Label	Date Set: 12/14/00	Proof # 7	Revise Date: 12/29/00	Op: ct,md,lr,ah,pgk,al,md
Client/Product: OraPharma/Arrestin	AD: la	Colors: 4/c process		Galley # 1 of 1