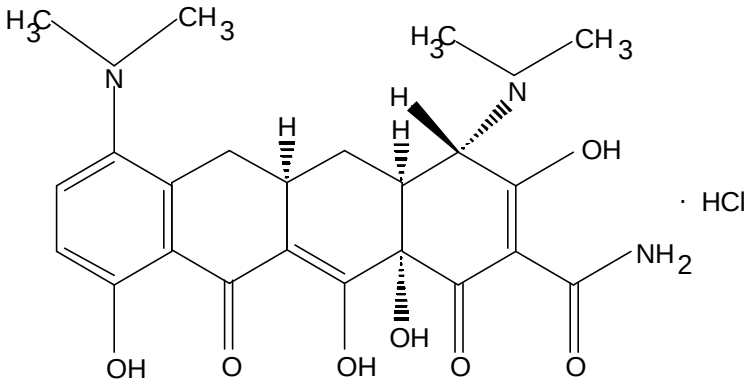
ARESTIN ™ (minocycline hydrochloride)
Microspheres, 1 mg

DESCRIPTION

ARESTIN™ (minocycline hydrochloride) 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 ³ 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≤ 0.05; ** S/RP v. S/RP + ARESTIN™ p ≤ 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 ³ 5 mm, ³ 6 mm and ³ 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 immunocompromised 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 tumorigenicity 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 toxicity in a battery of assays which included a bacterial reverse mutation assay (Ames test), an in *vitro* mammalian 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 3% of the Combined Clinical Trial Population of Three Multicenter US Trials by Treatment Group

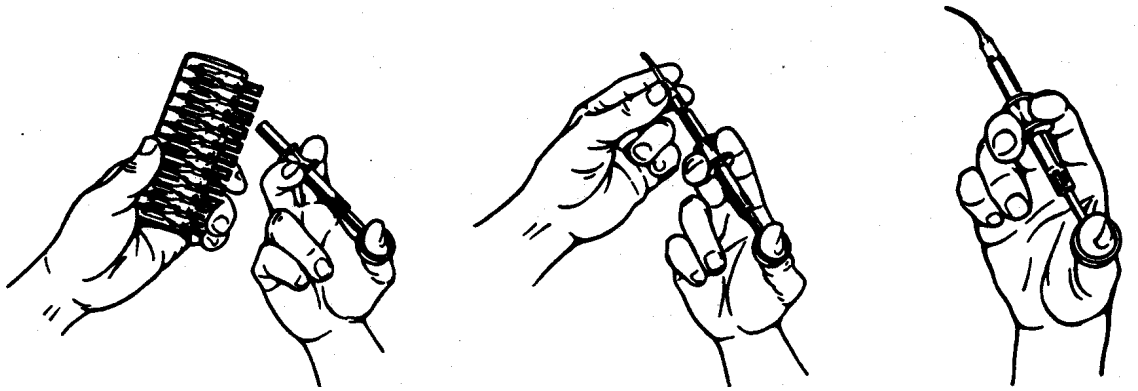
	S/RP Alone N=250	**S/RP + Vehicle** N=249	**S/RP + ARESTIN™** N=423
Number (%) of Patients Treatment Emergent AE	62.4%	71.9%	68.1%
Total Number of AEs	543	589	987
Periodontitis	25.6%	28.1%	16.3%
Tooth Disorder	12.0%	13.7%	12.3%
Tooth Caries	9.2%	11.2%	9.9%
Dental Pain	8.8%	8.8%	9.9%
Gingivitis	7.2%	8.8%	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.

Arestin™
minocycline HCl
Microspheres

MICROSPHERE DELIVERY SYSTEM

Arestin™
minocycline HCl
Microspheres

NDC 65976-100-24

2 resealable foil pouches
Each pouch contains
12 cartridges
Each cartridge contains
I mg of minocycline
For subgingival applicatio
Store at room temperatu
(20°C-25°C/68°F – 77°F).

Rx only

To order.
Call 1-866-ARESTIN **(273-784(**
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

FP0

Arestin™
minocycline HCl
Microspheres

PHARMAGRAPHICS #ORA MPT Q6441 Cartridge Box Client/Product: OraPharma Arestin

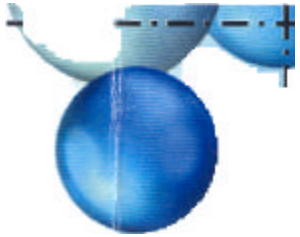
Dale Set 12/8/00
AD: Is

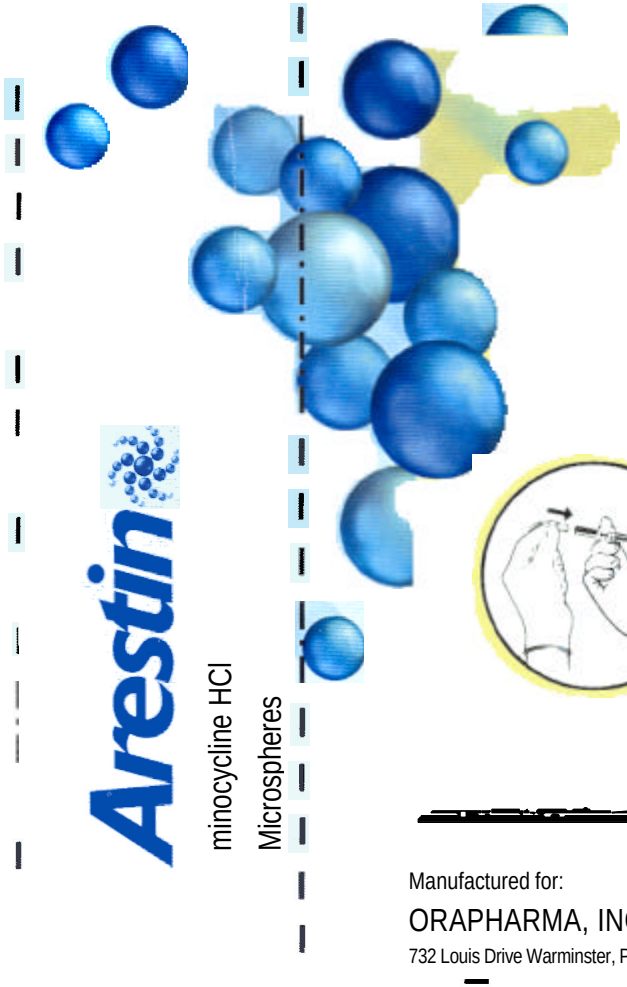
Proof #9 **Revise Date:** 12/29/00 **Op:** clt,md,lr,ah,af,md
Colors: 4/c process **Galley #** 1b of 1

Arestin™

minocycline HCl

Microsp*beres*





Arestin

minocycline HCl

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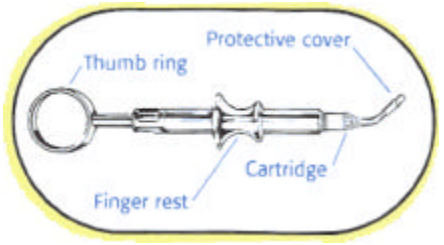
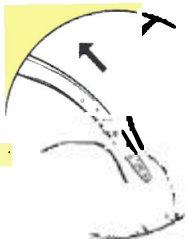


ARESTIN is provided as a dry powder, packaged in a specially designed unit-dose cartridge. Insert cartridge into handle and twist until it snaps into place. Remove protective cover.



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 thu ring to release the cartridge from the handle.

Manufactured for:

ORAPHARMA, INC

732 Louis Drive Warminster, PA 18974

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