

Harmful bacteria have infected your gums

How ARESTIN® can help treat
the infection—and tips for
getting the best results

Arestin® 
minocycline HCl 1mg
Microspheres

Fight infection right where it starts.

Periodontal bacteria have been infecting your foundation

Your gums are an important **foundation** for your teeth and provide stability for all of your dental work—so it's important to keep them healthy. However, your dental professional identified a **chronic bacterial infection** in your gums known as **periodontal disease** (gum disease).

Important facts about periodontal disease

- Periodontal disease is the #1 cause of adult tooth loss in the United States
- This silent infection occurs when harmful bacteria travel beneath the gum line and create “pockets”—spaces or gaps in the gums around the teeth
- If left untreated, periodontal bacteria can lead to bone and tooth loss that threatens your foundation
- Infected periodontal pockets are usually 4 or more millimeters (mm) in depth

Infected areas in your gums

One or more infected pockets inside your gums have been identified. These infected areas require treatment before periodontal disease causes further damage.



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

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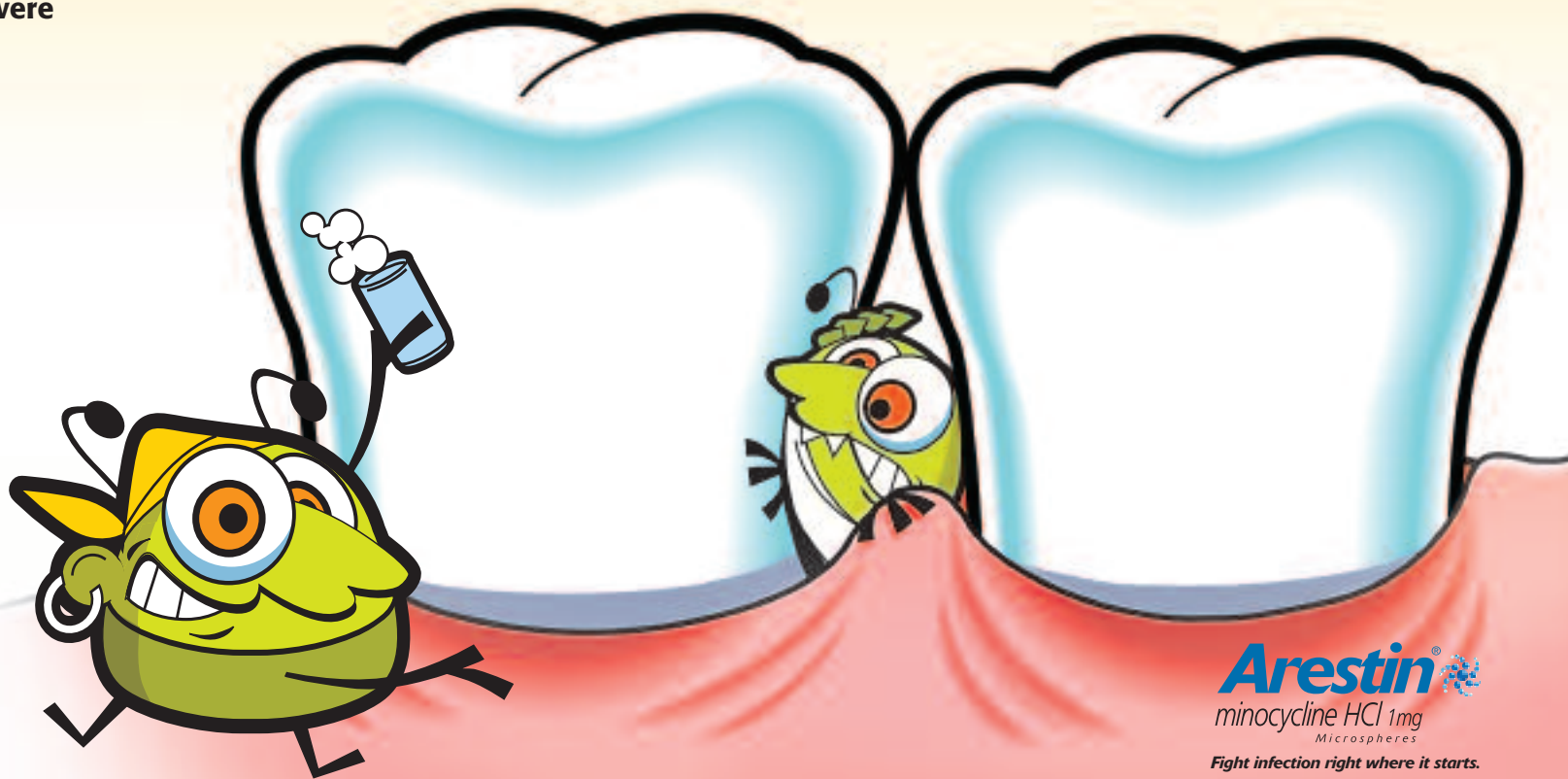
The role of your dental healthcare team

The good news is that there are effective treatments available for periodontal disease. Your dental healthcare team—which typically includes your **dentist**, your **hygienist**, and sometimes your **periodontist**—chooses the most effective method of treatment for your infection and is dedicated to helping you fight periodontal disease.

The treatment your dental healthcare team selects is designed to:

- **Reduce the bacteria causing your infection**
- **Shrink the size of your periodontal pockets**
- **Manage your infection to stop it from spreading or becoming more severe**

ARESTIN® contains minocycline, a tetracycline derivative, and therefore should not be used in children and in pregnant or nursing women. The use of drugs of the tetracycline class during tooth development may cause permanent discoloration of the teeth.



Treatment with scaling and root planing (SRP)

To treat periodontal disease, dental professionals use a common deep-cleaning procedure known as SRP.

- **Scaling** removes plaque, tartar, and stains from the surface of teeth
- **Planing** smooths the rough areas on the roots of teeth to promote healing

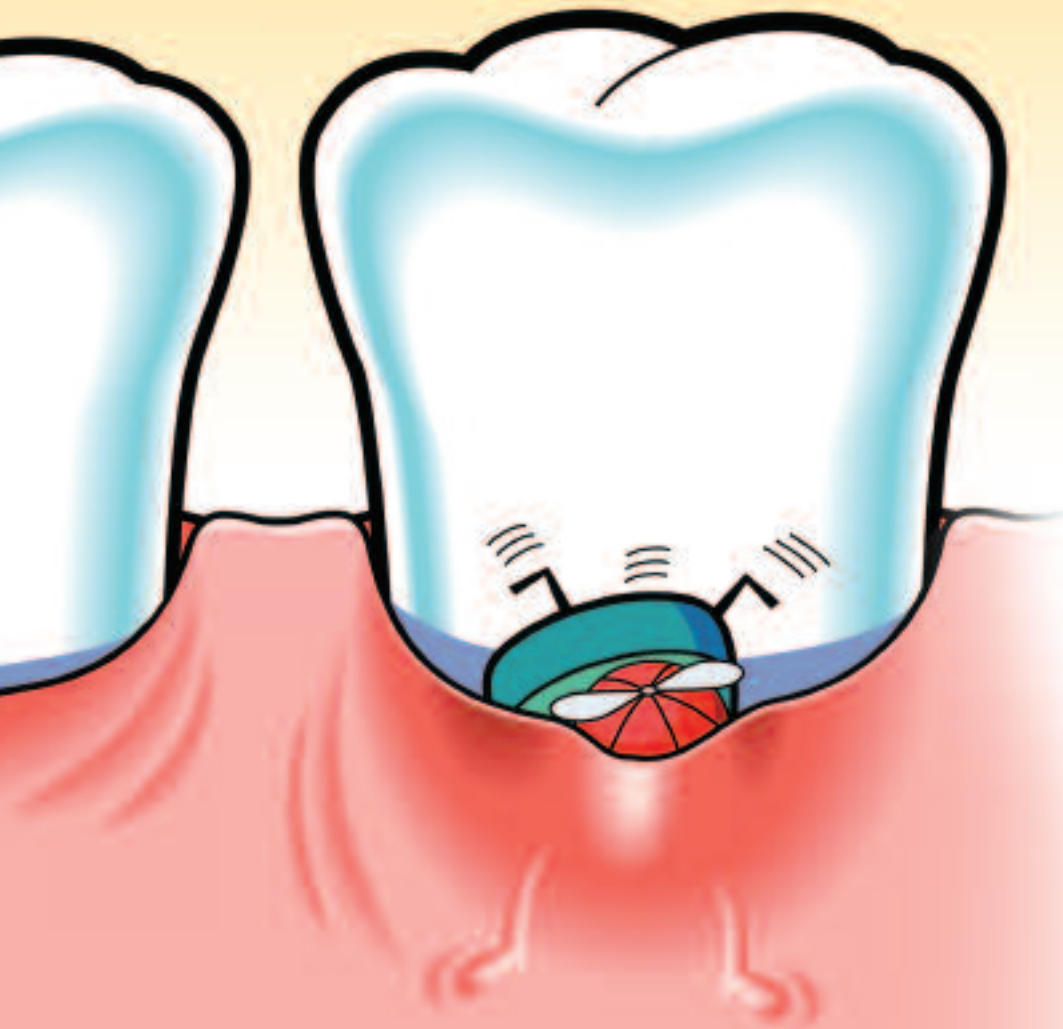
SRP is an effective way to remove the bacteria that form plaque and cause infection.

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Give your gums a fighting chance

Even though SRP removes a great deal of the bacteria that cause periodontal infection, the instruments used during this mechanical procedure can't always reach the bacteria that hide in the bottom of pockets or in difficult-to-reach areas.

That's why a dental healthcare team often decides to add a locally administered antibiotic (LAA) such as ARESTIN®.

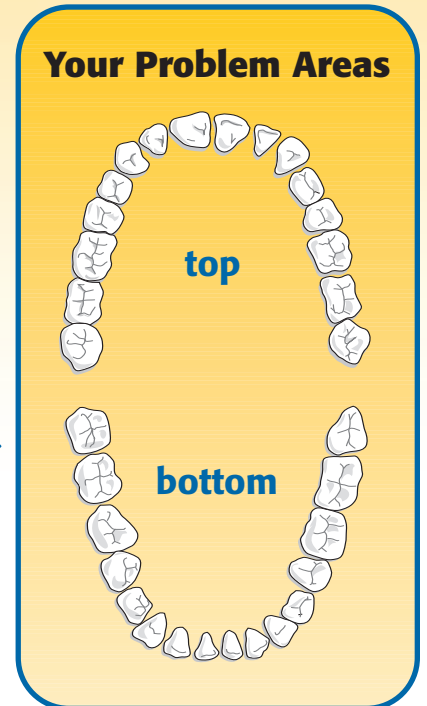


Adding ARESTIN® (minocycline hydrochloride) Microspheres, 1 mg

ARESTIN® is a small amount of antibiotic powder that is easily applied by a dental professional.

- **Clinical studies show that ARESTIN® + SRP is more effective at shrinking the size of infected periodontal pockets than SRP alone**
- **ARESTIN® remains in the pocket for at least 14 days—to help ensure continued treatment**
- **ARESTIN® is safe and easy for your dental professional to administer**

Ask your dental professional to use this chart to highlight the areas of infection inside your gums.



The most common treatment-emergent adverse events were headache (9.0%), infection (7.6%), flu syndrome (5.0%), and pain (4.3%). These occurred at a similar rate to SRP and SRP + placebo.

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minocycline HCl 1mg
Microspheres

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6 tips to remember after treatment with ARESTIN®

To help make sure you get the maximum results from your treatment, you should follow a few simple steps after your treatment with ARESTIN®.

1 Don't touch. Avoid touching areas of your gums that your dentist has treated.

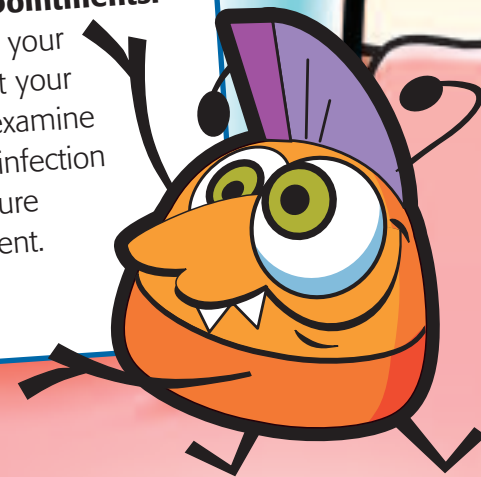
2 Wait to brush. Wait 12 hours after your treatment with ARESTIN® before brushing your teeth.

3 Wait to floss. Do not floss or use toothpicks or any other devices that clean between your teeth for at least 10 days.

4 Avoid eating hard, crunchy, or sticky foods for 1 week after treatment.

5 Always follow up. Because the bacteria that cause periodontal disease are persistent, the infection can return. Please be sure to make follow-up appointments with your dental professional to maintain healthy gums and teeth.

6 Keep your scheduled appointments. It is important to keep all of your dental appointments so that your dental professional can re-examine your gums, make sure the infection is under control, and measure the success of your treatment.



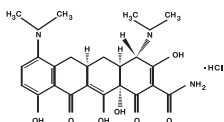
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ARESTIN®
(minocycline hydrochloride) Microspheres, 1 mg

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 PLGA, 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 $C_{23}H_{27}N_3O_7 \cdot HCl$, 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 $\leq 8 \mu\text{g/mL}$; 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 2 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 to 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 8 teeth. Investigational drug was administered to all eligible sites ≥ 5 mm 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, respectively.

Clinical Studies

In 2 well-controlled, multicenter, investigator-blind, vehicle-controlled, parallel-design studies (3 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 1 of 3 treatments: (1) scaling and root planing, (2) scaling and root planing + vehicle (bioresorbable polymer, PLGA), and (3) scaling and root planing + ARESTIN. To qualify for the study, patients were required to have 4 teeth with periodontal pockets of 6 to 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 pocket depth ≥ 5 mm also received treatment. Patients treated with ARESTIN were found to have statistically significantly reduced probing pocket depth compared with those treated with SRP alone or SRP + 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 2 Multicenter US Clinical Trials

Time	Study OPI-103A N=368			Study OPI-103B N=380		
	SRP Alone n=124	SRP + Vehicle n=123	SRP + ARESTIN n=121	SRP Alone n=126	SRP + Vehicle n=126	SRP + ARESTIN n=128
PD (mm) at Baseline, Mean \pm SE	5.88 \pm 0.04	5.91 \pm 0.04	5.88 \pm 0.04	5.79 \pm 0.03	5.82 \pm 0.04	5.81 \pm 0.04
PD (mm) Change From Baseline at 9 Months, Mean \pm SE	-1.04 \pm 0.07	-0.90 \pm 0.05	-1.20** \pm 0.07	-1.32 \pm 0.07	-1.30 \pm 0.07	-1.63*** \pm 0.07

SE = standard error; SRP = scaling and root planing; PD = pocket depth. Significantly different from SRP *($P \leq 0.05$); **($P \leq 0.01$).

Significantly different from SRP + vehicle †($P \leq 0.05$); ††($P \leq 0.001$).

In these 2 studies, an average of 29.5 (5-114), 31.7 (4-137), and 31 (5-108) sites were treated at baseline in the SRP alone, SRP + vehicle, and SRP + 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 SRP alone, SRP + vehicle, and SRP + ARESTIN, respectively.

Table 2: Numbers (percentage) of Pockets Showing a Change of Pocket Depth ≥ 2 mm at 9 Months From 2 Multicenter US Clinical Trials

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

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

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

	SRP Alone	SRP + Vehicle	SRP + ARESTIN
Smokers	n = 91 -0.96 \pm 0.09 mm	n = 90 -0.98 \pm 0.07 mm	n = 90 -1.24 \pm 0.09 mm**
Nonsmokers	n = 159 -1.31 \pm 0.06 mm	n = 159 -1.17 \pm 0.07 mm	n = 159 -1.53 \pm 0.06 mm**
Patients >50 YOA	n = 21 -1.07 \pm 0.09 mm	n = 81 -0.92 \pm 0.08 mm	n = 107 -1.42 \pm 0.08 mm**
Patients ≤ 50 YOA	n = 167 -1.24 \pm 0.06 mm	n = 168 -1.19 \pm 0.06 mm	n = 142 -1.43 \pm 0.07 mm*
Patients With CV Disease	n = 36 -0.99 \pm 0.13 mm	n = 29 -1.06 \pm 0.14 mm	n = 36 -1.56 \pm 0.14 mm**
Patients W/O CV Disease	n = 214 -1.22 \pm 0.06 mm	n = 220 -1.11 \pm 0.05 mm	n = 213 -1.40 \pm 0.06 mm**

SRP = scaling and root planing; YOA = years of age; CV = cardiovascular.

*SRP vs SRP + ARESTIN $P \leq 0.05$; **SRP vs SRP + 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 9 months was less in all treatment groups than in nonsmokers, but the reduction in mean pocket depth at 9 months with SRP + ARESTIN® was significantly greater than with SRP + vehicle or SRP alone.

Table 4: Mean Pocket Depth Change in Patients With Mean Baseline PD ≥ 5 mm, ≥ 6 mm, and ≥ 7 mm at 9 Months From 2 Multicenter US Clinical Trials

	Study OPI-103A			Study OPI-103B		
	SRP Alone	SRP + Vehicle	SRP + ARESTIN	SRP Alone	SRP + Vehicle	SRP + ARESTIN
Mean Baseline Pocket Depth	SRP Alone	SRP + Vehicle	SRP + ARESTIN	SRP Alone	SRP + Vehicle	SRP + ARESTIN
≥ 5 mm (n)	-1.04 mm (124)	-0.90 mm (123)	-1.20 mm* (121)	-1.32 mm (126)	-1.30 mm (126)	-1.63 mm* (128)
≥ 6 mm (n)	-0.91 mm (34)	-0.77 mm (46)	-1.40 mm* (45)	-1.33 mm (37)	-1.46 mm (40)	-1.69 mm* (25)
≥ 7 mm (n)	-1.10 mm (4)	-0.46 mm (5)	-1.91 mm (3)	-1.72 mm (3)	-1.11 mm (3)	-2.84 mm (2)

*Statistically significant comparison between SRP + ARESTIN and SRP alone.

The combined data from these 2 studies also show that for pockets 5 mm to 7 mm 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.

CONTRAINDICATIONS

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 8 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 nonsusceptible microorganisms including fungi. The effects of treatment for greater than 6 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 coexistent oral candidiasis.

ARESTIN 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 1 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 SRP 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 (ie, 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 cannot be established.

ADVERSE REACTIONS

The most frequently reported nondental treatment-emergent adverse events in the 3 multicenter US trials were headache, infection, flu syndrome, and pain.

Table 5: Adverse Events (AEs) Reported in $\geq 3\%$ of the Combined Clinical Trial Population of 3 Multicenter US Trials by Treatment Group

	SRP Alone N=250	SRP + Vehicle N=249	SRP + ARESTIN N=423
Number (%) of Patients Treatment-emergent AEs	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.

DOSE 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 health care professional removes the disposable cartridge from its pouch and connects the cartridge to the handle mechanism (see Figures 1-3). ARESTIN is a variable dose product, dependent on the size, shape, and number of pockets being treated. In US clinical trials, up to 121 unit-dose cartridges were used in a single visit and up to 3 treatments, at 3-month intervals, were administered in pockets with pocket depth 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, 1 mg is supplied in unit doses of 12 cartridges in one tray (NDC 65976-100-24) packaged with desiccant in a heat-sealed foil-laminated resealable pouch. There are 2 pouches in each box. Each unit-dose cartridge contains the product identifier "OP-1."

Storage Conditions

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

Rx only

Manufactured for OraPharma, Inc.

Distributed by: Cord Logistics, Inc.
15 Ingram Boulevard
La Vergne, TN 37086

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 ed. Baltimore, Md: Williams and Wilkins; 1996. 2. Slots J, Rams TE. Antibiotics in periodontal therapy: advantages and disadvantages. *J Clin Periodontol*. 1990;17:479-493.



ORAPHARMA, INC.

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for a healthy smile!**

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**If you have additional
questions about how ARESTIN®
works to help reduce the bacteria that
cause periodontal disease, please ask a member of your
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