ARESTIN® Prescription Form

Phone: 1-855-684-7481 **Fax: 1-855-630-9783**

*Required Information

1 PATIENT INFORMATION

Last Name* First Name*

Primary Phone Number* Alternate Phone Number
( ) ( )

Home Address* City* State* Zip*

Primary Language:
English ☐ Spanish ☐ Other ☐

Drug Allergies*

Gender* **Patient Date of Birth***

2 PRACTICE INFORMATION

Practice Name* Prescriber Name*

Office Contact Name* Office Contact Email

(Check preferred method of communication)
☐ Phone Number*( ) ☐ Fax Number*( )

Deliver to Address*

City* State* Zip*

Prescriber NPI #* **Today's Date***

IMPORTANT SHIPPING INFORMATION: Please note that product will be delivered within 14 business days of the prescription submission date if all required information is obtained. Product will always be delivered to the prescriber, Tuesday through Friday, except on major holidays or the day following a major holiday.

3 INSURANCE INFORMATION

*Include a copy of front/back of both insurance cards**

Prescription Benefit Insurance*

Prescription Insurance: _____
Insured Name: _____
Drug Cardholder ID # : _____
Group # : _____
Bin #: _____
Rx PCN # : _____
Phone Number : _____

Primary Medical Insurance*

Medical Insurance : _____
Insured Name : _____
Policy #: _____
Group #: _____
Member Services Phone #: _____

☐ Check here to provide patient quote to purchase medication directly from the pharmacy in the event the patient's benefit design does not cover the medication.

4 PRESCRIPTION

The dental practitioner prescribing ARESTIN® will determine the appropriate course of therapy for the patient. Each prescription is a 30-day supply with no refills; a new prescription is required for each order. The prescription is for the patient listed on the prescription form and cannot be resold or used for any other patient.

COMPLETE THE FOLLOWING PRESCRIPTION PRIOR TO FAXING. The quantity dispensed represents no greater than a 30-day supply.
New York Prescribers may attach an official NY prescription.

PRESCRIPTION: ARESTIN® (minocycline hydrochloride) Microspheres, 1mg Cartridges

SIG*: For administration by the dental practitioner into the periodontal pocket only

Quantity*: _____cartridge(s)
(1 cartridge per site diagnosed)

X _____ X _____ _____

Prescriber Signature
Dispense as Written
Stamped signatures cannot be accepted

Prescriber Signature
Substitution Permissible
Stamped signatures cannot be accepted

Date

5 PRESCRIBER CONSENT

CHECK BOX BELOW TO CONFIRM AUTHORIZATION WAS OBTAINED

My signature indicates my authorization for BioSolutia Pharmaceutical Services, LLC (Business Associate or BA), as the operator of the ARESTIN® Rx Access Program, to obtain, use and disclose protected health information as defined in 45 CFR 160.103 (PHI) about my patients, to and from (i) patient's insurer, including eligibility and other benefit information, for my payment and/or healthcare operation purposes and (ii) healthcare providers, such as specialty pharmacies (SPs), for treatment purposes, including to forward the prescription and associated PHI to a valid SP and to track the status of medications dispensed by SPs for my patients for coordination of care and related purposes. BA may de-identify, use and disclose PHI of my patients to the extent allowed by 45 CFR 164.504, provided that the de-identification complies with the requirements of 45 CFR 164.514(b). BA shall maintain administrative, technical and physical safeguards to ensure the availability, integrity and confidentiality of PHI and shall notify me of any impermissible use or disclosure Security Incident and Breach of Unsecured PHI as required by law. This agreement incorporates and BA agrees to comply with requirements of 45 CFR 164.504 and 164.314(a)(2). This BA agreement shall terminate upon any material violation of this agreement by BA, upon the written request of physician, or two years after the signature date below. Upon termination, BA shall destroy PHI in its possession.

☐ ***(CHECK HERE)*** I have received oral authorization from my patient to act as his/her agent for the delivery receipt, storage, and administration of his/her ARESTIN® prescription medication.

_____ _____ _____

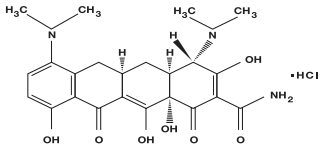
Prescriber Name* (Please Print) **Prescriber Signature* (Do Not Stamp)** **Signature Date***

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

Mechanism of Action

The mechanism of action of ARESTIN® as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis is unknown.

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 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, PGLA), 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 ± 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; SRP = scaling and root planing; PD = pocket depth.
Significantly different from SRP *($P \leq 0.05$); ** ($P \leq 0.001$).
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± 0.09 mm	n = 90 -0.98± 0.07 mm	n = 90 -1.24± 0.09 mm**
Nonsmokers	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**

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		
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

Hypersensitivity Reactions

Hypersensitivity reactions that included, but were not limited to anaphylaxis, angioneurotic edema, urticaria, rash, swelling of the face, and pruritus have been reported with the use of ARESTIN®. Some of these reactions were serious. Post-marketing cases of anaphylaxis and serious skin reactions such as Stevens-Johnson syndrome and erythema multiforme have been reported with oral minocycline.

Autoimmune Syndromes

Tetracyclines, including oral minocycline, have been associated with the development of autoimmune syndromes including a Lupus-like syndrome manifested by arthralgia, myalgia, rash, and swelling. Sporadic cases of serum sickness have presented shortly after oral minocycline use, manifested by fever, rash, arthralgia, and malaise. In symptomatic patients, liver function tests, ANA, CBC, and other appropriate tests should be performed to evaluate the patients. No further treatment with ARESTIN® should be administered to the patient.

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 chewing hard, crunchy, or sticky foods (e.g., carrots, taffy, and gum) with the treated teeth for 1 week, as well as avoid touching treated areas. Patients should also postpone the use of interproximal cleaning devices around the treated sites 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. Patients should be notified to inform the dentist if itching, swelling, rash, papules, reddening, difficulty breathing, or other signs and symptoms of possible hypersensitivity 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 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 ≥3% of the Combined Clinical Trial Population of 3 Multicenter US Trials by Treatment Group

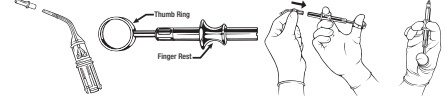
	SRP Alone N=250	SRP + Vehicle N=249	SRP + ARESTIN® N=423
Number (%) of Patients Treatment-emergent AEs	62.4%	71.9%	68.1%
Total Number of AEs	543	589	987
Periodontitis	25.6%	28.1%	16.3%
Tooth Disorder	12.0%	13.7%	12.3%
Tooth Caries	9.2%	11.2%	9.9%
Dental Pain	8.8%	8.8%	9.9%
Gingivitis	7.2%	8.8%	9.2%
Headache	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.

DOSAGE AND ADMINISTRATION

ARESTIN® is provided as a dry powder, packaged in a unit-dose cartridge with a deformable tip (see Figure 1), which is inserted into a spring-loaded cartridge handle mechanism (see Figure 2) 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 3-4). ARESTIN® is a variable dose product, dependent on the size, shape, and number of pockets being treated. In US clinical trials, up to 122 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.



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 as follows:

- 1 unit-dose cartridge with desiccant in a heat-sealed, foil-laminated pouch (NDC 65976-100-01).
- 12 unit-dose cartridges in 1 tray with desiccant in a heat-sealed, foil-laminated, resealable pouch (NDC 65976-100-24). 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.
5 Walnut Grove Drive
Horsham, PA 19044

For more information call 1-866-ARESTIN (1-866-273-7846)

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.

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7,699,609

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