INDICATION
ARESTIN® (minocycline HCl) Microspheres, 1mg 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 maintenance program, which includes good oral hygiene and SRP.

IMPORTANT SAFETY INFORMATION
• ARESTIN is contraindicated in any patient who has a known sensitivity to minocycline or tetracyclines. Hypersensitivity reactions and hypersensitivity syndrome that included, but were not limited to anaphylaxis, anaphylactoid reaction, angioneurotic edema, urticaria, rash, eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis may be present. Swelling of the face, pruritus, fever and lymphadenopathy 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, as well as acute photosensitivity reactions.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
Left untreated, periodontal disease can have serious and expensive consequences

AMONG ADULTS, IT’S THE #1 CAUSE OF TOOTH LOSS\(^1\)

About 64.7 million Americans have periodontal disease.\(^2\) Periodontal disease affects nearly half of people over 30 and nearly 3 of every 4 people over 65.\(^3,4\)

THE PROBLEM STARTS WITH BACTERIA\(^5\)

- **BIOFILM FORMATION BEGINS**
- **UNHEALTHY BALANCE OF BACTERIA**
- **ORAL INFECTION**
- **FORMATION OF PERIODONTAL POCKETS**

Harmful bacteria can spread, jeopardizing the gingiva, connective tissue, and alveolar bone.\(^5\)

TO STOP THE INFECTION FROM PROGRESSING, YOU NEED TO ACT QUICKLY

IMPORTANT SAFETY INFORMATION (continued)

- THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH, AND THEREFORE SHOULD NOT BE USED IN CHILDREN OR IN PREGNANT OR NURSING WOMEN.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
SRP is effective, however…

BACTERIA CAN HIDE OUT OF REACH

Without an antibiotic, baseline levels of bacteria may return in just a few days after SRP.\(^5\)

ARESTIN\(^\circledast\) (MINOCYCLINE HCl) MICROSPHERES, 1 MG CAN TARGET BACTERIA WHERE INSTRUMENTS CAN’T REACH–EVEN IN THE HANDS OF THE MOST SKILLED DENTAL PROFESSIONALS–LIKE NEAR THE\(^5\):\(^12\):

- **CEMENTO-ENAMEL JUNCTION**\(^13\)
- **DENTINAL TUBULES**\(^14\)
- **GINGIVAL EPITHELIUM**\(^16\)

**IMPORTANT SAFETY INFORMATION (continued)**

- Tetracyclines, including oral minocycline, have been associated with development of autoimmune syndromes including a lupus-like syndrome manifested by arthralgia, myalgia, rash, and swelling. Sporadic cases of serum sickness-like reaction have presented shortly after oral minocycline use, manifested by fever, rash, arthralgia, lymphadenopathy and malaise. In symptomatic patients, diagnostic tests should be performed and ARESTIN treatment discontinued.
The results speak for themselves

Adding ARESTIN® (minocycline HCl) Microspheres, 1 mg to SRP targets the active infection at the base of the pocket, helping disrupt the progression of periodontitis.\(^\text{16}\)

In a clinical trial, ARESTIN added to SRP provided better results than SRP alone after 30 days\(^\text{17}\):

- **REDUCED GUM POCKET DEPTH**
  - **ARESTIN + SRP**: Reduced pocket depth by 1.38 mm in deep sites
  - **SRP ALONE**: Reduced pocket depth by 1.01 mm in deep sites

- **REDUCED HARMFUL BACTERIA**
  - **ARESTIN + SRP**: Reduced mean red complex bacteria from \(18.9 \times 10^5\) to \(9.5 \times 10^5\)
  - **SRP ALONE**: Reduced mean red complex bacteria from \(19.3 \times 10^5\) to \(14.3 \times 10^5\)

- **REDUCED BLEEDING ON PROBING**
  - **ARESTIN + SRP**: Reduced bleeding on probing in deep sites by 25%
  - **SRP ALONE**: Reduced bleeding on probing in deep sites by 13.8%

 ALSO DECREASED THE NUMBER OF DEEP POCKETS MORE EFFECTIVELY\(^\text{†}\)

- **40% MORE**
- **2x MORE\(^\ddagger\)**
- **2x MORE EFFECTIVELY\(^\ddagger\)**

\(*\)Single-blind, randomized, parallel-group study of 127 patients with moderate-to-severe periodontitis who had at least 5 teeth with ≥5 mm pocket depths (PDs). Mean reductions in PD of deep sites were 1.38 mm in the minocycline microspheres (MM) + SRP group compared with 1.01 mm in the SRP alone group (\(P=0.00004\)).

\(\dagger\)Mean red-complex bacteria (RCB) numbers at day 30 were reduced from \(18.9 \times 10^5\) to \(9.5 \times 10^5\) (50%) by ARESTIN + SRP (\(P=0.002\)) and from \(19.3 \times 10^5\) to \(14.3 \times 10^5\) (26%) by SRP alone (\(P=0.002\)).

\(\ddagger\)Mean reduction in bleeding on probing in sites initially deep at baseline was 25.2% in the MM + SRP group compared with only 13.8% in the SRP alone group, nearly a 2-fold difference (\(P=0.009\)).

IMPORTANT SAFETY INFORMATION (continued)
- The use of ARESTIN in an acutely abscessed periodontal pocket or for use in the regeneration of alveolar bone has not been studied.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
**ARESTIN® (minocycline HCl)**
Microspheres, 1 mg keeps working for the long term

When incorporated into a routine oral maintenance program along with SRP, ARESTIN\textsuperscript{11}:

<table>
<thead>
<tr>
<th>1 MONTH\textsuperscript{*}</th>
<th>Targeted periodontal bacteria to fight infection at 30 days\textsuperscript{18}</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 MONTHS\textsuperscript{†}</td>
<td>Provided significantly greater pocket depth reduction for up to 90 days vs SRP alone\textsuperscript{11}</td>
</tr>
<tr>
<td>9 MONTHS\textsuperscript{†}</td>
<td>Resulted in reduced pocket depth after 1 month and maintained at 9 months\textsuperscript{11}</td>
</tr>
</tbody>
</table>

The effects of ARESTIN on microorganism overgrowth have not been studied beyond 6 months.

\textsuperscript{*}Single-blind, randomized, parallel-group study of 127 patients with moderate-to-severe periodontitis who had at least 5 teeth with ≥5 mm pocket depths. Mean RCB numbers at day 30 were reduced from $18.9 \times 10^5$ to $9.50 \times 10^5$ (50%) by ARESTIN + SRP ($P<0.002$) and from $19.3 \times 10^5$ to $14.2 \times 10^5$ (26%) by SRP alone ($P=0.002$).

\textsuperscript{†}In 2 multicenter, investigator-blind, parallel-design studies of 748 patients with generalized moderate-to-advanced adult periodontitis characterized by a mean probing depth of 5.90 and 5.81 mm, subjects received 1 of 3 treatments: (1) SRP, (2) SRP + vehicle, and (3) SRP + ARESTIN. 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. ARESTIN vs SRP alone (n=250) $P<0.01$; ARESTIN vs vehicle + SRP (n=249) $P<0.001$; ARESTIN + SRP vs vehicle (n=249) $P<0.001$.

**IMPORTANT SAFETY INFORMATION (continued)**

- The safety and effectiveness of ARESTIN has not been established in immunocompromised patients or in those with coexistent oral candidiasis. Use with caution if there is a predisposition to oral candidiasis.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
How should we communicate with patients about periodontal disease?

Patients may not feel any discomfort or notice any symptoms. However, the longer they put off treatment, the greater the chance that they may potentially need:

- Painful oral surgery
- Expensive oral surgery
- To have teeth removed

FACTORS IN ACCEPTING TREATMENT

According to a survey conducted by OraPharma in 2017 (N=264), the most influential factors determining treatment acceptance were:

1. Trust of their DHCP
2. Understanding the consequences of NOT undergoing treatment
3. Understanding of the recommended treatment
4. Understanding of the diagnosis
5. Cost of the recommended treatment
6. Comfort of the treatment procedure
7. Length of time for treatment

Contrary to what you might expect, cost was not the top factor.

In the same survey, patients diagnosed with periodontal disease were willing to pay $633 to avoid losing a tooth.
Stock up and save with ARESTIN NOW and the ARESTIN ELITE Program

**arestin Now**

The next time your patient is in the chair, be ready to treat them right away. By stocking ARESTIN® (minocycline HCl) Microspheres, 1 mg at your practice, you can:

- **Treat as many indicated sites as needed, same day**
- **Treat your patient even when prescription coverage is not an option**
- **Prepare for both initial SRP and periodontal maintenance cases**

**arestin Elite Program**

Earn discounts whether you’re purchasing multiple boxes or one box at a time.

- Buy only what you need and efficiently manage your cash flow
- Lock in discounted pricing
- Manage inventory according to demand

**Ask your sales representative how much your practice can save**

**Arestin Rx Access® Program**

With Arestin Rx Access®, patients may be able to receive Arestin through their medical prescription benefits. They may be eligible for a copay as low as $0 through the Arestin Copay Assistance Program.*

*Please see Offer Restrictions and Eligibility Requirements on the Patient Eligibility Form at ArestinProfessional.com.

**Important Safety Information** (continued)

- In clinical trials, the most frequently reported nondental treatment-emergent adverse events were headache, infection, flu syndrome, and pain.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Call your ARESTIN sales representative for details
Or, simply place your order as you always do

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ARESTIN® (minocycline HCl) Microspheres, 1mg 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 maintenance program, which includes good oral hygiene and SRP.

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• The use of ARESTIN in an acutely abscessed periodontal pocket or for use in the regeneration of alveolar bone has not been studied.

• The safety and effectiveness of ARESTIN has not been established in immunocompromised patients or in those with coexistent oral candidiasis. Use with caution if there is a predisposition to oral candidiasis.

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Please see accompanying full Prescribing Information.

**ARESTIN®**
(minocycline hydrochloride) microspheres, 1 mg

**Rx only**

**DESCRIPTION**
ARESTIN (minocycline hydrochloride) microspheres, 1 mg is a subgingival sustained-release product containing the antibiotic minocycline hydrochloride incorporated into a bioreabsorbable 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_{3}O_{7}·HCl, and the molecular weight is 493.94. The structural formula of minocycline hydrochloride is:

![Molecular Structure of Minocycline Hydrochloride](image)

**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. It is bacteriostatic and exerts its antimicrobial activity by inhibiting protein synthesis. 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 mcg/mL; qualitative and quantitative changes in plaque microorganisms have not been demonstrated in subjects 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 Candida albicans or Staphylococcus aureus were seen at the end of the 56-day study period.

**Pharmacokinetics**
In a pharmacokinetic study, 18 subjects (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, subjects received subgingival application of ARESTIN (1 mg per treatment site) following scaling and root planing at a minimum of ARESTIN. After fasting for at least 10 hours, subjects received subgingival application of ARESTIN (1 mg per treatment site) following scaling and root planing at a minimum of ARESTIN.

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.

**Clinical Studies**
In 2 well-controlled, multicenter, investigator-blind, vehicle-controlled, parallel-design studies (3 arms), 748 subjects (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 (SRP), (2) SRP + vehicle (bioreabsorbable polymer, PGLA), and (3) SRP + ARESTIN. To qualify for the study, subjects 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. Subjects studied were in good general health. Subjects 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. Subjects 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>
<thead>
<tr>
<th>Time</th>
<th>Study OPI-103A</th>
<th>Study OPI-103B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=368</td>
<td>N=380</td>
</tr>
<tr>
<td></td>
<td>SRP Alone</td>
<td>SRP + Vehicle</td>
</tr>
<tr>
<td></td>
<td>n=124</td>
<td>n=123</td>
</tr>
<tr>
<td>PD (mm) at Baseline</td>
<td>5.88 ± 0.04</td>
<td>5.91 ± 0.04</td>
</tr>
<tr>
<td>[Mean ± SE]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD (mm) Change from Baseline at 9 Months</td>
<td>-1.04 ± 0.07</td>
<td>-0.90 ± 0.04</td>
</tr>
<tr>
<td>[Mean ± SE]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SE = standard error; SRP = scaling and root planing; PD = pocket depth
Significantly different from SRP: * (P <0.05); ** (P <0.001)
Significantly different from SRP + vehicle: † (P <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 1: Probing Pocket Depth at Baseline and Change in Pocket Depth at 9 Months from 2 Multicenter US Clinical Trials**

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

<table>
<thead>
<tr>
<th>Pockets ≥2 mm (% of Total)</th>
<th>Study OPI-103A</th>
<th>Study OPI-103B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SRP Alone</td>
<td>SRP + Vehicle</td>
</tr>
<tr>
<td></td>
<td>n=927</td>
<td>n=1326</td>
</tr>
<tr>
<td></td>
<td>(25.7%)</td>
<td>(36.6%)</td>
</tr>
<tr>
<td></td>
<td>9 Months</td>
<td>SRP Alone</td>
</tr>
<tr>
<td></td>
<td>n=992</td>
<td>n=1306</td>
</tr>
<tr>
<td></td>
<td>(28.0%)</td>
<td>(36.6%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Subjects</th>
<th>SRP Alone</th>
<th>SRP + Vehicle</th>
<th>SRP + ARESTIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>n=90</td>
<td>n=90</td>
<td>n=90</td>
</tr>
<tr>
<td></td>
<td>-0.96 ± (0.09) mm</td>
<td>-0.98 ± (0.07) mm</td>
<td>-1.24 ± (0.09) mm**</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>n=159</td>
<td>n=159</td>
<td>n=159</td>
</tr>
<tr>
<td></td>
<td>-1.31 ± (0.06) mm</td>
<td>-1.17 ± (0.07) mm</td>
<td>-1.53 ± (0.06) mm**</td>
</tr>
<tr>
<td>Subjects</td>
<td>n=21</td>
<td>n=81</td>
<td>n=107</td>
</tr>
<tr>
<td>&gt;50 YOA</td>
<td>n=167</td>
<td>n=168</td>
<td>n=142</td>
</tr>
<tr>
<td></td>
<td>-1.24 ± (0.06) mm</td>
<td>-1.19 ± (0.06) mm</td>
<td>-1.43 ± (0.07) mm*</td>
</tr>
<tr>
<td>Subjects with CV Disease</td>
<td>n=36</td>
<td>n=29</td>
<td>n=36</td>
</tr>
<tr>
<td></td>
<td>-0.99 ± (0.13) mm</td>
<td>-1.06 ± (0.14) mm</td>
<td>-1.56 ± (0.14) mm**</td>
</tr>
<tr>
<td>Subjects without CV Disease</td>
<td>n=214</td>
<td>n=220</td>
<td>n=213</td>
</tr>
<tr>
<td></td>
<td>-1.22 ± (0.06) mm</td>
<td>-1.11 ± (0.05) mm</td>
<td>-1.40 ± (0.06) mm**</td>
</tr>
</tbody>
</table>

SRP = scaling and root planing; YOA = years of age; CV = cardiovascular
*SRP vs SRP + ARESTIN P ≤0.05; **SRP vs SRP + ARESTIN P ≤0.001

In both studies, the following patient subgroups were prospectively analyzed: smokers, subjects over and under 50 years of age, and subjects 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.
The combined data from these 2 studies also show that for pockets 5 mm to 7 mm treatment of periodontitis in patients with coexistent oral candidiasis.

While no overgrowth by opportunistic microorganisms, such as yeast, was noted during clinical studies, as with other antimicrobials, the use of ARESTIN may result in overgrowth 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 planning.

**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 OUTWEIGHT 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 becomes accentuated during the first year of treatment. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this 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 and Hypersensitivity Syndrome

The following adverse events have been reported with minocycline products when taken orally. Hypersensitivity reactions and hypersensitivity syndrome that included, but were not limited to anaphylaxis, anaphylactoid reaction, angioneurotic edema, urticaria, rash, eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis may be present. Swelling of the face, pruritus, 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 oncogetic activity in rats in studies with a related antibiotic, oxytetracycline (i.e., adenal 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 (LS178Y/k/– mouse lymphoma assay), an in vitro mammalian chromosome aberration test, and an in vivo micronucleus assay conducted in ICR mice.

Maternity

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

**Pregnancy**

Teratogenic Effects: (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 non-dental, 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**

<table>
<thead>
<tr>
<th></th>
<th>SRP Alone N=250</th>
<th>SRP + Vehicle N=249</th>
<th>SRP + ARESTIN® N=423</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number (%) of Subjects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Number of AEs</td>
<td>543</td>
<td>589</td>
<td>987</td>
</tr>
<tr>
<td>Periodontitis</td>
<td>25.6%</td>
<td>28.1%</td>
<td>16.3%</td>
</tr>
<tr>
<td>Tooth Disorder</td>
<td>12.0%</td>
<td>13.7%</td>
<td>12.3%</td>
</tr>
<tr>
<td>Tooth Caries</td>
<td>9.2%</td>
<td>11.2%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Dental Pain</td>
<td>8.8%</td>
<td>8.8%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>7.2%</td>
<td>8.8%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>7.2%</td>
<td>11.6%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Infection</td>
<td>8.0%</td>
<td>9.6%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8.4%</td>
<td>6.8%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Mouth Ulceration</td>
<td>1.6%</td>
<td>3.2%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>3.2%</td>
<td>6.4%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3.2%</td>
<td>1.6%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Pain</td>
<td>4.0%</td>
<td>1.2%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2.0%</td>
<td>0.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Infection Dental</td>
<td>4.0%</td>
<td>3.6%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Mucous Membrane Disorder</td>
<td>2.4%</td>
<td>0.8%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

**Table 4: Mean Pocket Depth Change in Subjects with Mean Baseline PD ≥5 mm, ≥6 mm, and ≥7 mm at 9 Months from 2 Multicenter US Clinical Trials**

<table>
<thead>
<tr>
<th>Mean BaselinePocket Depth</th>
<th>SRP Alone</th>
<th>SRP + Vehicle</th>
<th>SRP + ARESTIN</th>
<th>SRP Alone</th>
<th>SRP + Vehicle</th>
<th>SRP + ARESTIN</th>
<th>SRP Alone</th>
<th>SRP + Vehicle</th>
<th>SRP + ARESTIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5 mm (n)</td>
<td>-1.04 mm</td>
<td>-0.90 mm (123)</td>
<td>-1.20 mm (121)</td>
<td>-1.32 mm (126)</td>
<td>-1.30 mm (126)</td>
<td>-1.63 mm (128)</td>
<td>-0.46 mm</td>
<td>-1.33 mm (45)</td>
<td>-1.46 mm (40)</td>
</tr>
<tr>
<td>≥6 mm (n)</td>
<td>-0.91 mm</td>
<td>-0.77 mm (46)</td>
<td>-1.40 mm* (45)</td>
<td>-1.33 mm (37)</td>
<td>-1.46 mm (33)</td>
<td>-1.91 mm</td>
<td>-1.11 mm</td>
<td>-1.72 mm (3)</td>
<td>-1.11 mm (3)</td>
</tr>
<tr>
<td>≥7 mm (n)</td>
<td>-1.10 mm</td>
<td>-0.46 mm (5)</td>
<td>-1.91 mm (3)</td>
<td>-1.72 mm (3)</td>
<td>-1.11 mm (3)</td>
<td>-2.84 mm</td>
<td>-1.11 mm</td>
<td>-1.11 mm (3)</td>
<td>-1.11 mm (3)</td>
</tr>
</tbody>
</table>

*Statistically significant comparison between SRP + ARESTIN and SRP alone.
The change in clinical attachment levels was similar across all study arms, suggesting that neither the vehicle nor ARESTIN compromise clinical attachment.

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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 biodegradable, nor is an adhesive or dressing required.

HOW SUPPLIED
ARESTIN® (minocycline hydrochloride) microspheres, 1 mg is supplied as follows:
NDC 65976-100-01 1 unit-dose cartridge with desiccant in a heat-sealed, foil-laminated pouch
NDC 65976-100-24 12 unit-dose cartridges in 1 tray 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.

Manufactured for:
OraPharma, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA
U.S. Patent Numbers: 6,682,348 and 7,699,609
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