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.
Periodontitis can be a serious chronic infection\(^2\)

- Periodontitis may be associated with an increased risk for other chronic conditions throughout the body, including coronary heart disease and cerebrovascular disease\(^3,4\)
- Systemic diseases and chronic conditions may influence periodontitis\(^5-6\)

The impact of periodontitis is significant

99% increase in global prevalence of periodontitis between 1990 and 2019\(^7\)

Prevalence in US risk groups is high

- 59.8% adults 65 years and older\(^8\)
- 42.2% adults 30 years and older\(^9\)
- 62.4% current smokers\(^8\)
- 44.4% obese individuals\(^8\)

Overgrowth of keystone pathogens can lead to dysbiosis and periodontitis\(^10-15\)

- Orange complex bacteria bridge earlier bacteria that appear on the tooth surface with red complex bacteria\(^16\)
- Red complex bacteria are the most common and destructive keystone pathogens\(^11,12\)

Keystone pathogens may be associated with other diseases\(^17,18\)

How concerned are you about keystone pathogens?
Periodontitis can be controlled, not cured

SRP ALONE HAS BEEN SHOWN TO BE EFFECTIVE IN ONLY ABOUT 4 OUT OF 10 CASES

- Periodontal sites treated with SRP alone are subject to recolonization with pathogens similar to those present before treatment
- Bacteremia has occurred as frequently as 44% of the time following SRP
- The diversity of periodontal pathogens increases as the disease continues to develop

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.
- 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.

Comprehensive treatment of periodontitis can include ARESTIN + SRP

ARESTIN is the only FDA-approved locally applied antibiotic for use with SRP as part of periodontal disease management.

Subgingival sustained-release product containing the antibiotic minocycline hydrochloride incorporated into a bioresorbable polymer

Each unit-dose cartridge delivers minocycline hydrochloride equivalent to 1 mg of minocycline free base

Bacteriostatic and exerts its antimicrobial activity by inhibiting protein synthesis

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Demonstrated statistically significant reduction in pocket depth (PD) at 9 months
Choose ARESTIN for sustained results
ARESTIN + SRP resulted in a greater percentage of pockets showing a change of ≥2 mm compared with SRP alone at 9 months
At 9 months, the reduction in mean PD was 1.08 mm for SRP alone, 1.00 mm for SRP + vehicle, and 1.32 mm for ARESTIN + SRP
40.5% of patients in the ARESTIN + SRP group achieved PD reduction at 9 months compared with 32.87% and 28.98% of patients treated with SRP alone and SRP + vehicle, respectively
In a subgroup of patients with more advanced disease (baseline mean PD ≥6 mm), reduction in bleeding on probing was 26.04% for ARESTIN + SRP compared with 19.80% for SRP alone and 18.11% for SRP + vehicle, respectively

Study Description
In 2 well-controlled, multicenter, investigator-blind, vehicle-controlled, parallel-design studies (3 arms) of 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 mm and 5.81 mm, respectively, were enrolled. 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 were combined, the mean PD reduction at 9 months was 1.18 mm, 1.10 mm, and 1.42 mm for SRP alone, SRP + vehicle, and ARESTIN + SRP, respectively.

Bacteriostatic effects remain active in the periodontal pockets for at least 14 days

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.
• 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.

Additional data from a novel study of individuals without comorbidities: ARESTIN + SRP produced a larger decrease in clinical markers of periodontitis than SRP alone

**3 keystone pathogens that were measured all decreased**

- **F. nucleatum, T. denticola, and T. forsythia decreased**
- **F. nucleatum is a prominent orange complex bacteria that is central to interactions between gram-positive and gram-negative bacteria**

**Cumulative salivary pathogens decreased**
However, larger decreases were observed in the SRP + MM (ARESTIN) group.

**Study Description**
ARSESTIN was studied in a randomized, open-label, controlled clinical trial comparing ARESTIN + SRP vs SRP alone. Subjects were 70 male and female adults ≥18 years old with a diagnosis of Stage II to Stage IV, Grade B periodontitis. Inclusion criteria were a minimum of 8 sites with a PD of ≥5 mm and 8 sites of BOP in any of the 4 quadrants. The primary outcome measure was an assessment of the adjunctive effects of ARESTIN on PD, CAL, BOP, and GI compared with SRP alone. The secondary outcome measure was a determination of the relative numbers of 11 periodontal pathogens in saliva after treatment with ARESTIN + SRP compared with SRP alone.

**Study Outcome**
ARESTIN was well tolerated, with no serious adverse events reported. Reduction in PD, CAL, BOP, and GI was observed in the ARESTIN + SRP group compared with SRP alone. Reduction in BOP was greater in the ARESTIN + SRP group compared with SRP alone. However, larger decreases were observed in the SRP + MM (ARESTIN) group.

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Adverse events in pivotal clinical studies

The most frequently reported nondental, treatment-emergent, adverse events in the 3 pivotal multicenter US trials were headache, infection, flu syndrome, and pain. 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>SRP Alone n=250</th>
<th>SRP + Vehicle n=249</th>
<th>SRP + ARESTIN n=423</th>
</tr>
</thead>
<tbody>
<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>26.1%</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>8.9%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>7.2%</td>
<td>8.9%</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>8.9%</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>5.8%</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</td>
<td>4.0%</td>
</tr>
<tr>
<td>Infection Dental</td>
<td>4.0%</td>
<td>3.6%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Mucous Membrane Disorder</td>
<td>2.4%</td>
<td>0.9%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

AE, adverse event.

IMPORTANT SAFETY INFORMATION (continued)

- In clinical trials, the most frequently reported nondental treatment-emergent adverse events were headache, infection, flu syndrome, and pain. 1

Meet each patient's unique needs with tailored options

Between ARESTIN Now and ARESTIN Rx Access, we've got you and your patients covered

This chart explains how and when to make the most of each solution

- ARESTIN NOW
  - Treat immediately and efficiently
  - Streamline periodontal maintenance
  - Overcome coverage gaps

- ARESTIN Rx ACCESS*
  - Treat comprehensively
  - Minimize financial barriers
  - May increase patient acceptance

With ARESTIN Rx Access, eligible commercially insured patients may be able to receive ARESTIN through their medical prescription benefits. Commercially insured patients may be eligible for a copay as low as $0 through the ARESTIN Copay Assistance Program. Contact the ARESTIN Rx Access Service Center at 1-855-684-7481 to find out which program may help your patient.

*Login required. Visit RxAccessPortal.com to create an account for the ARESTIN Rx Access Portal.

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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.

Please see accompanying full Prescribing Information in pocket.