minocycline hydrochloride is:

\[ \text{C}_{16}\text{H}_{15}\text{Cl}_{2}\text{N}_{2}\text{O}_{4} \]

The molecular formula of minocycline hydrochloride is C₁₆H₁₅Cl₂N₂O₄.

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.

**DESCRIPTION**

**INDICATIONS AND USE**

ARESTIN® (minocycline hydrochloride) Microspheres, 1 mg

**CONTRAINdications**

The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) and in lactation should be avoided because there is evidence that tetracyclines can discolor immature teeth and/or inhibit bone formation. Tetracyclines may also cross the placenta and appear in fetal tissues. Significant maternal dosing during pregnancy or lactation can result in photosensitivity, skin discoloration, and abnormalities in derivatives.

**PREGNANCY**

**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 these studies. The potential benefits of ARESTIN® in treating periodontitis must be carefully weighed against the potential risks to the mother and fetus. ARESTIN® should not be used during pregnancy if there is a possibility of pregnancy, unless the potential benefits outweigh the potential risks. If the patient should become pregnant while receiving ARESTIN®, she should be apprised of the potential hazard to the fetus. Photosensitivity manifested by an exaggerated sunburn reaction has been observed in pregnant women taking tetracyclines.

**NURSING MOTHERS**

Tetracyclines may appear in breast milk. Because of the potential for serious adverse reactions in nursing infants from the use of ARESTIN®, women who are nursing should not receive ARESTIN® unless the potential benefits outweigh the potential risks to the mother and infant.

**PEDIAtRC PATIENTS**

Tetracyclines are generally avoided in children under 8 years of age because of the potential for discoloration of the teeth and long-bone growth. Treatment of young patients with periodontal disease should be started only after careful evaluation of the patient and the disease. This evaluation should include a careful history of the patient's medical condition, which may affect the choice of therapy, and a thorough periodontal examination. ARESTIN® is contraindicated in children less than 8 years of age and should be used with caution in children less than 12 years of age.

**REtreatment**

Subjects treated with ARESTIN® were found to have statistically significantly reduced probing pocket depth at 9 months compared to baseline. However, the effectiveness at 12 months was not statistically significantly different from baseline. Retreatment of subjects with ARESTIN® was performed at 3 and 6 months after initial treatment, and any subject showing a pocket ≥5 mm at either of these visits was retreated with 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, new sites with pocket depth ≥5 mm also received treatment.

**Microbiology**

In vitro susceptibility testing has shown that the organisms Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum, and Peptostreptococcus micros are sensitive to minocycline. Minocycline has been shown to inhibit protein synthesis.

**ClINICAL PHARMACOLOGY**

**Mechanism of Action**

The mechanism of action of ARESTIN® as an adjunct to scaling and root planing processes for reduction of pocket depth is not known. ARESTIN® delivery of minocycline hydrochloride results in a release profile that is affected by pocket depth and plaque biofilm. The drug is delivered in a sustained-release manner.

**Pharmacokinetics**

The mean peak serum concentration of minocycline hydrochloride was approximately 1.1 µg/mL at 6 hours after intravenous administration of minocycline hydrochloride to healthy volunteers. The mean apparent elimination half-life of minocycline hydrochloride was approximately 10 hours in humans. The mean apparent bioavailability of minocycline hydrochloride after oral administration of minocycline hydrochloride was approximately 53%.

**Clinical Studies**

In a pharmacokinetic study, 18 subjects (10 men and 8 women) with moderate to advanced chronic periodontitis were treated with a mean dose of 1 mg of minocycline hydrochloride per tooth. Minocycline concentrations were measured in serum and saliva at 0, 2, 6, 9, 12, 24, and 48 hours after intravenous administration of minocycline hydrochloride. The mean peak serum concentration of minocycline hydrochloride was approximately 1.1 µg/mL at 6 hours after intravenous administration of minocycline hydrochloride to healthy volunteers. The mean apparent elimination half-life of minocycline hydrochloride was approximately 10 hours in humans. The mean apparent bioavailability of minocycline hydrochloride after oral administration of minocycline hydrochloride was approximately 53%.

**Table 1: Mean Pocket Depth Changes (SE) in Subpopulations, Studies 103A and 103B Combined**

<table>
<thead>
<tr>
<th></th>
<th>Mean (± SE)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SRP Alone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teeth ≥6 mm</td>
<td>-1.11 (±0.07)</td>
<td>104 (34)</td>
</tr>
<tr>
<td>Teeth ≥7 mm</td>
<td>-0.90 (±0.07)</td>
<td>104 (34)</td>
</tr>
<tr>
<td>Teeth ≥5 mm</td>
<td>-1.40 (±0.06)</td>
<td>104 (34)</td>
</tr>
</tbody>
</table>

**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></th>
<th>Baseline</th>
<th>9 Months</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teeth ≥6 mm</td>
<td>124 (41)</td>
<td>124 (41)</td>
<td>100</td>
</tr>
<tr>
<td>Teeth ≥7 mm</td>
<td>128 (42)</td>
<td>128 (42)</td>
<td>100</td>
</tr>
<tr>
<td>Teeth ≥5 mm</td>
<td>124 (41)</td>
<td>124 (41)</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 3: 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></th>
<th>Baseline</th>
<th>9 Months</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teeth ≥6 mm</td>
<td>124 (41)</td>
<td>124 (41)</td>
<td>100</td>
</tr>
<tr>
<td>Teeth ≥7 mm</td>
<td>128 (42)</td>
<td>128 (42)</td>
<td>100</td>
</tr>
<tr>
<td>Teeth ≥5 mm</td>
<td>124 (41)</td>
<td>124 (41)</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 4: Mean Pocket Depth Change in Subjects with Mean Baseline Pocket Depth ≤7 mm at 9 Months from 2 Multicenter US Clinical Trials**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>9 Months</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teeth ≥6 mm</td>
<td>124 (41)</td>
<td>124 (41)</td>
<td>100</td>
</tr>
<tr>
<td>Teeth ≥7 mm</td>
<td>128 (42)</td>
<td>128 (42)</td>
<td>100</td>
</tr>
<tr>
<td>Teeth ≥5 mm</td>
<td>124 (41)</td>
<td>124 (41)</td>
<td>100</td>
</tr>
</tbody>
</table>

The combined data from these 2 studies also show that for patients with a mean baseline pocket depth greater than or equal to 5 mm, greater reduction in pocket depth occurred in patients who were treated with ARESTIN® compared to those treated with SRP alone (Table 4).
Pediatric Use

should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see

Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision

Nursing Mothers

The effects of tetracyclines on labor and delivery are unknown.

Labor and Delivery

Pregnancy

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

Dietary administration of minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also

administration of ARESTIN, they should notify the dentist promptly if pain, swelling, or other problems occur. Patients should be advised that although some mild to moderate sensitivity is expected during the first week after SRP and

Information for Patients

after treatment, patients should avoid chewing hard, crunchy, or sticky foods (i.e., carrots, taffy, and gum) with the treated teeth for 1 week, as well as

The use of ARESTIN has not been studied in immunocompromised patients such as those with chronically ill or undergoing chemotherapy or radiotherapy.

If susceptible, appropriate antimicrobial measures should be taken.

ARESTIN has been shown to be localized to the treatment site. In the event of accidental systemic exposure, the potential for local and systemic adverse

After treatment, in the event of accidental systemic exposure, the potential for local and systemic adverse reactions is unlikely, based on animal toxicity evaluations.

Nursing Mothers

The effects of tetracyclines on labor and delivery are unknown.

Labor and Delivery

Pregnancy

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

Dietary administration of minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also

administration of ARESTIN, they should notify the dentist promptly if pain, swelling, or other problems occur. Patients should be advised that although some mild to moderate sensitivity is expected during the first week after SRP and

Information for Patients

after treatment, patients should avoid chewing hard, crunchy, or sticky foods (i.e., carrots, taffy, and gum) with the treated teeth for 1 week, as well as

The use of ARESTIN has not been studied in immunocompromised patients such as those with chronically ill or undergoing chemotherapy or radiotherapy.

If susceptible, appropriate antimicrobial measures should be taken.

ARESTIN has been shown to be localized to the treatment site. In the event of accidental systemic exposure, the potential for local and systemic adverse

After treatment, in the event of accidental systemic exposure, the potential for local and systemic adverse reactions is unlikely, based on animal toxicity evaluations.