ARESTIN

התוויות ושימוש: מיועדת לשימוש בטיפול נלווה להסרת אבנית והחלקה של אזור כיס השן (שורש השן) במטרה להקטין כיסים פריודונטאליים אצל חולים אשר סובלים ממחלת חניכיים. ניתן להשתמש ב-Arestin כחלק מתוכנית טיפול מחזוקתית כוללת של היגינת פה טובה והסרת אבנית והחלקה של אזור כיס השן (שורש השן).

מינון ואופן השימוש: Arestin מסופקת כאבקה יבשה, כאשר היא ארוזה במנה אחת בתוך מחסנית המחוברת לידית מיוחדת בעת מתן הטיפול. המטפלת מציאה את מחסנית החד-פעמית מתוך השקית ומחברת אותה למנגנון הידית (ראו תמונות 3-1). כמות המנות של Arestin הניתנות בטיפול אחד מותנה בכמות, בגודל, ובצורת הכיסים המטופלים. בכיסים קלינים שבוצעו באר"ב החדרו עד 121 מחסניות (מנות) בביקור אחד של חולה, ועד שלושה טיפולים במרווחים של 3 חודשים, החודרו לתוך כיסים בעומקים של 5 מ"מ ומעלה.

תמונה 1

תמונה 2

תמונה 3

Arestin לא נדרשת הדמיה מקומית. החדרה תת-חניכית מקצועית של Arestin לטיפול ב- נעשית ע"י הכנסת קצה האפליקטור עד תחתית הכיס הפריודונטאלי, ואח"כ לחיצה על טבעת הידית עם האגודל בכדי לפזר את האבקה. תוך כדי הוצאת קצה האפליקטור באופן הדרגתי, מתחתית הכיס החוצה. יש לחסא את הידית לאחר כל שימוש, על מנת לשמור עליה סטרילית לטיפול הבא.

אחסנה: אחסן במקום קריר, מתחת ל- 25°C. יש להימנע מחשיפה לחום.

שים/י לב: בטרם השימוש במוצר יש לעיין בעלון לרופא במלואו.

ARESTIN®

(minocycline hydrochloride) Microspheres, 1 mg

AIS-INS-001

Physicians Prescribing Information

ARESTIN®

Minocycline Hydrochloride Microspheres (Soluble Powder)

The format and contents of this leaflet were determined, checked and approved by the Israeli Ministry of Health

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 $C_{23}H_{27}N_3O_7 \cdot HCl$, and the molecular weight is 493.94.

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 ≤8 µg/mmL 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 6-day study period.

Pharmacokinetics: In a pharmacokinetic study, 18 patients (110 men and 8 women) with moderate to advanced chronic periodontitis were treated with a mean dose of 46.22 mg (225 to 112 unit doses) of ARESTIN. After fasting for at least 10 hours, patients received subgingival application of ARESTIN (11 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 Cmax were found to be approximately 125 and 1,000 times higher than hose 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.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 ± 0.04	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 ≤0.05); **(P ≤0.001).
Significantly different from SRP + vehicle † (P ≤0.05); †† (P ≤0.001).

In these 2 studies, an average of 29.55 (55-114), 31.77 (44-137), and 31 (55-108) 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 -11.18 mm, -11.10 mm, and -11.42 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

Time	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=91 ; -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 ≤0.05*; *SRP vs SRP + ARESTIN *P ≤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

Time	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.

AIS-INS-001

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 kin erythema.

PRECAUTIONS: There is a potential for local hypersensitivity reactions to occur. Patients should be notified to inform the dentist if itching, swelling, papules, reddening or other signs and symptoms of possible hypersensitivity occur.
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, hemotherapy, radiation therapy, or infection with IV). 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 he treatment of failing implants.

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 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 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.

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/TTK+/- 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%	98.1%
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, 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

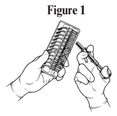

Figure 2

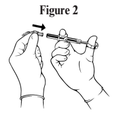

Figure 3

The administration of ARESTIN does not require local anesthesia. Professional sub-gingival 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.
- 12 unit-dose cartridges in 1 tray with desiccant in a heat-sealed, foil-laminated, resealable pouch. There is 1 pouch in each box.
- 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."
Other pack sizes might be available. Not all pack sizes are marketed.

Storage Conditions: Store below 25°C (below 77°F) / 60% RH. Avoid exposure to excessive heat.

Rx only

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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oraPHARMA, INC.

AIS-INS-001

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