PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrARESTIN® MICROSPHERES

Minocycline Hydrochloride Controlled-Release Microspheres
Minocycline 1 mg / cartridge
(As minocycline base per cartridge in controlled-release microspheres)

Antibacterial Periodontal Agent

Manufactured by:
OraPharma, Inc.
Bridgewater, New Jersey, USA

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ARESTIN MICROSPHERES (minocycline hydrochloride) is indicated:

- as an adjunct to scaling and root planning (SRP) procedures to decrease pocket depth (PD) in adult patients with chronic periodontitis.

ARESTIN MICROSPHERES is administered with SRP to help further reduce PD in the treatment of adult patients with moderate to advanced chronic periodontal disease.

ARESTIN MICROSPHERES may be used as part of a periodontal maintenance program which includes good oral hygiene and SRP.

ARESTIN MICROSPHERES should be administered under the supervision of a qualified health professional who is experienced in the management of adult periodontitis.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ARESTIN MICROSPHERES and other antibacterial drugs, ARESTIN MICROSPHERES should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): The mean age of subjects treated in pivotal trials was 49.1 (range 29 -76) years. Age did not affect ARESTIN MICROSPHERES efficacy (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to minocycline or tetracyclines or to any ingredient in the formulation or component of the container. For a complete listing, see the 6 DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Teeth may become permanently discoloured if exposed to minocycline during their development.
- ARESTIN MICROSPHERES should not be given during tooth development, to pregnant women or to nursing women.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

The recommended dose is one cartridge of ARESTIN MICROSPHERES, containing 1 mg minocycline and 3 mg of polymer carrier, administered sub-gingivally, per periodontal pocket greater than or equal to 5 mm as soon as possible after SRP. The total dose per patient varies with the number of pockets treated.

The maximum number of pockets treated in one visit during the clinical trials was 122 (122 ARESTIN MICROSPHERES cartridges, 122 mg minocycline). The mean dose administered, per visit, was 31 mg. In the two pivotal trials, probing depths were maintained for up to 9 months during which ARESTIN MICROSPHERES alone was reapplied twice; however, the trials did not provide evidence that reapplication of ARESTIN MICROSPHERES alone provided additional or incremental clinical benefit.

4.4 Administration

ARESTIN MICROSPHERES 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 healthcare professional removes the disposable dispenser from its pouch, removes a cartridge and connects it to the handle mechanism as shown in Figure 1 below.

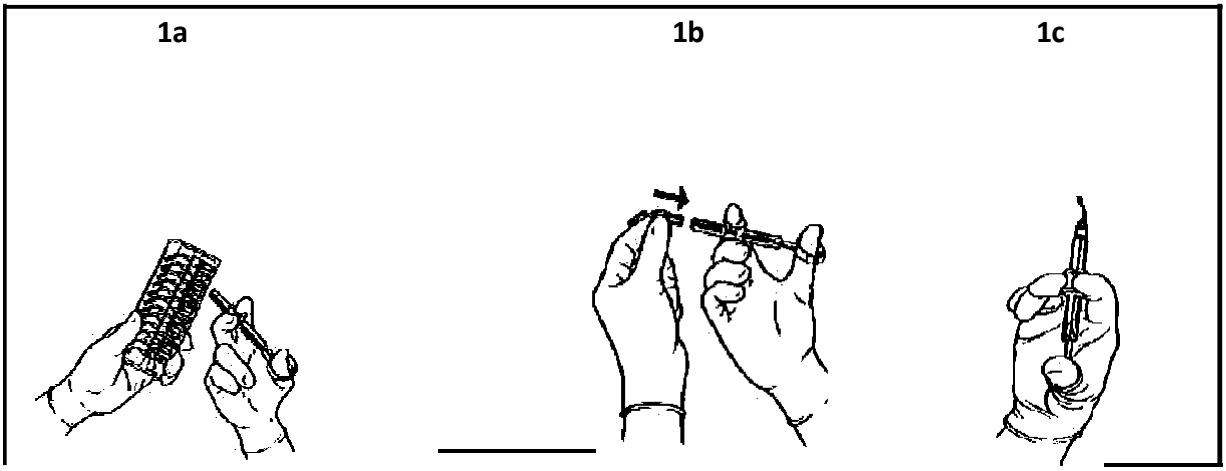


Figure 1: Removal of Cartridge from Package and Insertion onto Handle

The administration of ARESTIN MICROSPHERES does not require local anaesthesia. Professional subgingival administration is accomplished by inserting the tip of 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 MICROSPHERES does not have to be removed, as it is bioresorbable, nor is an adhesive or dressing required.

Patients should be cautioned about foods touching the site of ARESTIN MICROSPHERES insertion and the need to delay tooth brushing and cleaning following treatment (see 7

WARNINGS AND PRECAUTIONS).

5 OVERDOSAGE

There have been no reports of overdosage with the use of ARESTIN MICROSPHERES and such risks are limited due primarily to the method and route of its administration.

Overdose symptoms reported with oral use of minocycline hydrochloride include dizziness, nausea, vomiting, abdominal pain, intestinal haemorrhage, hypotension, lethargy, coma, acidosis, and azotemia without a concomitant rise in creatinine.

Treatment

Dilute well with water or milk due to the possibility of esophageal ulceration. Antacids may relieve nausea and abdominal pain (e.g., calcium carbonate or lactate, milk of magnesia, aluminum hydroxide). Measures to reduce absorption such as induction of emesis or use of cathartic may be beneficial in certain cases.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subgingival	Controlled-release microspheres, minocycline 1 mg as base	Poly (glycolide-co-dl-lactide)

Description

ARESTIN MICROSPHERES (minocycline hydrochloride) is a subgingival controlled-release product, containing the antibiotic minocycline hydrochloride incorporated into a bioresorbable polymer, poly (glycolide-co-dl-lactide) or PGLA, and it is intended for professional subgingival administration into periodontal pockets. Each unit dose cartridge delivers microspheres in powder form and contains minocycline hydrochloride equivalent to 1 mg minocycline free base in 3 mg of polymer.

ARESTIN MICROSPHERES is supplied in single dose cartridges equivalent to 1 mg (as minocycline base). 12 cartridges are packaged in one tray with desiccant in a heat-sealed foil laminate resealable pouch. Each cartridge contains 4 mg of powder made up of minocycline hydrochloride and poly (glycolide-co-DL-lactide), PGLA. There is one pouch (total of 12 units) or two pouches (total of 24 units) in each box. Each unit dose cartridge contains the product

identifier "OP-1".

7 WARNINGS AND PRECAUTIONS

General

ARESTIN MICROSPHERES has not been clinically tested in immunocompromised patients (such as those immunocompromised by diabetes, chemotherapy, radiation therapy, or infection with HIV).

ARESTIN MICROSPHERES should be used with caution in patients having a history or predisposition to oral candidiasis. The safety and effectiveness of ARESTIN MICROSPHERES have not been established for the treatment of periodontitis in patients with co-existent oral candidiasis.

Carcinogenesis and Mutagenesis

Dietary administration of minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumour 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 tumours).

Minocycline demonstrated no potential to cause genetic toxicity in a battery of *in vitro* and *in vivo* assays in animals.

The significance of these studies to human administration of ARESTIN MICROSPHERES is unknown.

Ear/nose/throat

The insertion of ARESTIN MICROSPHERES in periodontal pockets affected by acute abscess formation has not been studied and is not recommended.

ARESTIN MICROSPHERES 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.

Immune

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-like reaction have presented shortly after oral minocycline use, manifested by fever, rash, arthralgia, lymphadenopathy, and malaise.

Exacerbation of systemic lupus erythematosus has also occurred.

If any of the above effects should occur after ARESTIN MICROSPHERES treatment, no further treatment with ARESTIN MICROSPHERES should be administered to the patient. If autoimmune syndrome symptoms develop, liver function tests, ANA, CBC, and other appropriate tests should be performed to evaluate the patient.

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, polyarthralgia, 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 MICROSPHERES. 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. Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) including fatal cases have been reported with minocycline use. If this syndrome is recognized, the drug should be discontinued immediately.

The potential for local manifestations of hypersensitivity reactions also exists. Patients should be notified to inform their health care provider if itching, swelling, papules, reddening or other signs and symptoms of possible hypersensitivity occur.

Reproductive health: Female and male potential

Minocycline, like other tetracyclines, may decrease the effectiveness of oral contraceptives. Women of childbearing potential should use an effective method of contraception when treated with minocycline for 3 weeks after treatment.

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

Sensitivity/Resistance

Development of Drug-Resistant Bacteria

Prescribing ARESTIN MICROSPHERES in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of resistant drug-resistant bacteria.

Potential for Microbial Overgrowth

While no overgrowth by opportunistic microorganisms, such as yeast, were noted following single dosing in clinical studies, as with other antimicrobials, the use of ARESTIN MICROSPHERES may result in overgrowth of non-susceptible microorganisms including fungi.

If superinfection with resistant organisms is suspected, appropriate measures should be taken.

Skin

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. Further sun exposure is to be avoided should any form of cutaneous rash occur.

As with the systemic administration of minocycline, hypersensitivity reactions are possible with ARESTIN MICROSPHERES (see 7 WARNINGS and PRECAUTIONS, Hypersensitivity Reactions and Hypersensitivity Syndrome).

7.1 Special Populations

7.1.1 Pregnant Women

ARESTIN MICROSPHERES has not been clinically tested and is not recommended for use in pregnant women.

The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of eight years) may cause permanent discolouration 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.

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. Tetracyclines complex with calcium in bone-forming tissue. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

7.1.2 Breast-feeding

Minocycline like other tetracyclines is excreted in human milk. ARESTIN MICROSPHERES should not be administered to nursing women because of the potential for serious adverse reactions in nursing infants.

7.1.3 Pediatrics

Pediatrics (< 18 years of age)

Like other tetracyclines minocycline can stain growing teeth and affect growing bone in children. ARESTIN MICROSPHERES has not been studied and is not recommended for use in children. No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

7.1.4 Geriatrics

Geriatrics (> 65 years of age)

There are no specific monitoring requirements or hazards associated with the use of ARESTIN MICROSPHERES in geriatric patients (see 1.2 Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequently reported non-dental treatment emergent adverse events irrespective of causation in pivotal clinical trials with ARESTIN MICROSPHERES, were headache, infection, flu syndrome and pain.

The most frequently reported dental treatment-emergent adverse events which were reported in pivotal trials, irrespective of causation, were dental pain (toothache, pain associated with teeth and discomfort after dental procedures, periodontitis and gingivitis, tooth disorders (tooth fractures, problems with fillings and hot/cold sensitivity), tooth caries (root surface decay, recurrent decay, and dental caries), stomatitis, dental infections.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Three major studies were conducted in 922 subjects to evaluate the safety and efficacy of ARESTIN MICROSPHERES. At baseline all subjects received SRP and ARESTIN MICROSPHERES, vehicle, or nothing. ARESTIN MICROSPHERES or vehicle alone was re-administered twice during the 9-month observation period. Adverse events reported, irrespective of causation are presented in Table 2.

Table 2: Incidence of Adverse Events Reported by ≥ 1% of ARESTIN MICROSPHERES Subjects.

Protocols 103A, 103B, 104 Combined

Event	ARESTIN MICROSPHERES + SRP n = 423 (%)	Vehicle + SRP n = 249 (%)	SRP Alone n = 250 (%)
Body as a Whole			
Headache	10.4	13.7	9.2
Infection	8.0	10	8.4
Flu Syndrome	5.2	6.8	3.6

Pain	5.0	2.4	4
Accidental Injury	2.6	3.6	3.6
Mucous Membrane Disorder	3.5	1.6	2.4
Back Pain	2.8	2.8	0.8
Allergic Reaction	1.2	0.8	2.0
Abdominal Pain	1.2	0.8	0
Digestive			
Periodontitis	17	28.5	26.8
Tooth Disorder	13.0	16.5	13.2
Tooth Caries	12.1	13.3	10.4
Dental Pain	10.9	11.6	11.6
Gingivitis	10.6	10	8.4
Stomatitis	6.6	8	9.2
Infection Dental	4.3	4.4	4
Mouth Ulceration	5.9	3.6	1.6
Dyspepsia	4.0	0	2.4
Leukoplakia of Mouth	2.4	1.2	2
Periodontal Abscess	1.7	2	1.6
Tongue Discolouration	1.7	0.4	0.8
Diarrhea	1.4	1.2	0
Musculoskeletal			
Myalgia	1.9	1.2	0.8
Arthralgia	1.2	1.2	0.8
Nervous			
Hypertension	2.8	2.0	0.8
Respiratory			
Pharyngitis	5.2	1.6	3.6
Rhinitis	2.4	2.8	1.2
Bronchitis	1.4	2.4	1.2
Sinusitis	1.7	2.8	0.4
Skin & Appendages			
Rash	1.2	0	1.2

8.4 Abnormal laboratory findings: Hematologic, clinical chemistry and other quantitative data

No clinical laboratory safety evaluations were performed in the three Phase 3 studies.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of ARESTIN MICROSPHERES. Because these events were reported voluntarily from a population of

unknown size, frequencies cannot be estimated accurately.

- ***Skin and hypersensitivity reactions***: anaphylaxis, angioneurotic edema, acute febrile neutrophilic dermatosis (Sweet's syndrome), urticaria, rash, swelling of the face and pruritus.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Subgingival administration results in systemic blood levels which are 2 to 3 times lower than that found after oral administration. The potential for drug-drug interactions is considered low.

However, the possibility that interactions could occur should not be ignored.

Because tetracyclines can decrease plasma prothrombin activity, they may potentiate the effects of oral anticoagulants. The low plasma concentrations associated with ARESTIN MICROSPHERES (minocycline hydrochloride) treatment have not been assessed for these effects.

As for other tetracyclines, there is demonstrable antagonism *in vitro* between minocycline and either beta-lactam (e.g., penicillin, amoxicillin, cefaclor) or aminoglycoside (e.g., gentamycin, tobramycin) antibiotics. The clinical relevance of these findings to periodontal use of ARESTIN MICROSPHERES is unknown.

Concurrent use of methoxyflurane anaesthesia and tetracyclines has been reported to seriously impair renal function, leading in some cases to death.

Minocycline, like other tetracyclines, may decrease the effectiveness of oral contraceptives.

9.5 Drug-Food Interactions

Interactions with food have not been studied. Oral and other forms of minocycline, like other tetracyclines, can chelate with cations.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Minocycline hydrochloride is a semisynthetic derivative of tetracycline. It is bacteriostatic and exerts its antimicrobial activity by inhibiting bacterial protein synthesis. It has non-antibacterial, anti-inflammatory, and other properties.

Periodontitis is a bacterial infection with immuno-inflammatory components which destroys supporting tooth structures. A wide variety of bacterial pathogens are implicated and in part include *Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola, Tannerella forsythia, Fusobacterium nucleatum, Eikenella corrodens* and *Aggregatibacter actinomycetemcomitans* among others. *In vitro* susceptibility testing has demonstrated minimum inhibitory concentrations against tetracyclines of ≤4 mcg/mL for species of *Bacteroides, Prevotella, Porphyromonas* and *Fusobacterium*. These MIC values increase significantly in bacterial biofilm.

In vivo the plaque biofilm environment is protective of bacteria necessitating higher inhibitory drug concentrations. Plaque breakup and debridement with SRP along with adjunctive ARESTIN MICROSPHERES are used to decrease PD.

Antimicrobial

Like other tetracyclines, minocycline inhibits bacterial protein synthesis by binding the 30S ribosomal subunit. The binding to the ribosome is reversible, explaining the bacteriostatic nature of these compounds. This binding blocks the association of the aminoacyl transfer RNA to the acceptor site on the messenger RNA-ribosome complex, thus preventing the addition of new amino acids into the growing peptide chain. Like other tetracyclines minocycline enters the outer membrane of gram-negative bacteria by passive diffusion through porin channels OmpF and OmpC, probably as positively charged molecules associated with magnesium. Once in the periplasmic space, the complex dissociates, and minocycline enters the inner membrane by diffusion (minocycline is lipophilic). Similarly, the lipophilic form enters the cytoplasmic space of gram-positive bacteria driven by a process dependent on the change in pH.

Non-antimicrobial

Periodontal disease is characterized by a breakdown of connective tissue and bone loss caused by resorption. Minocycline HCl and other tetracyclines have been shown to retard pathologic connective tissue breakdown, including bone loss, when administered either orally, or when applied directly to the molar teeth of rats. For example, minocycline HCl

(10 mg/kg/day, administered orally for 21 days) ameliorated the elevations of collagenase, gelatinase, elastase, and β-glucuronidase in the gingiva and skin of diabetic rats and in the gingiva of rats challenged with bacterial endotoxin, while 0.2% minocycline HCl significantly reduced root caries and bone loss when applied to the molar teeth of rats for nine weeks.

Minocycline, given orally in a dose of 20 mg daily for 21 days, also increased protein synthesis and secretions in periodontal ligament fibroblasts and increased collagen synthesis in osteoblasts of streptozotocin-induced diabetic rats. Minocycline HCl and other tetracyclines inhibit the breakdown of connective tissue because they inhibit the activity of matrix metalloproteinase (MMP) collagenase.

One study has explored the potential non-antimicrobial effects of ARESTIN MICROSPHERES on host biomarkers of tissue breakdown. Local levels of catabolic host markers in 48 chronic periodontitis patients treated with either ARESTIN MICROSPHERES + SRP or vehicle (PGLA) + SRP were monitored. The investigators also included 8 periodontally healthy subjects as negative controls. Accordingly, gingival crevicular fluid (i.e., a serum-like exudate that diffuses from the periodontal tissues and bathes the periodontal pocket) was sampled using absorbent paper strips (8 sites per patient) and analyzed using ELISA techniques for two host biomarkers. These were pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP)

which is a bone-specific collagen degradation product, and interleukin-1 beta (IL-l) which is a potent bone-resorptive cytokine.

The results indicated that gingival crevicular fluid levels of ICTP and IL-l are related to baseline clinical observations. Cross-sectionally, deep sites had significantly ($p<0.001$) higher ICTP and IL-1 levels as compared to shallow sites. In addition, healthy subjects had significantly lower levels ($p<0.001$) at baseline as compared to periodontitis subjects. Significant ($p<0.05$) reductions in ICTP and IL-l were observed at 1 month for periodontitis patients treated with ARESTIN MICROSPHERES + SRP as compared to patients treated with the adjunctive vehicle. In addition, the ARESTIN MICROSPHERES + SRP group had significantly ($p<0.02$) lower crevicular fluid levels of IL-l when compared to the vehicle + SRP group at 1 month. These data suggested that local delivery of minocycline via ARESTIN MICROSPHERES may inhibit local collagen breakdown and inflammatory responses in patients with chronic periodontitis.

Animal Pharmacology

Blood levels produced following oral dosing of minocycline hydrochloride to various animals' species were:

- 21 mg/L at steady state in monkeys administered 30 mg/kg.
- 6.5 mg/L at 3 hours post-dose in rats given a single 25 mg/kg dose.

Minocycline hydrochloride was extensively distributed to all tissues examined in 14C-labelled drug studies in dogs.

10.3 Pharmacokinetics

Pharmacokinetic parameters were derived from a study of 18 subjects with moderate to advanced chronic periodontitis who, following full-mouth SRP, were treated with ARESTIN MICROSPHERES at a minimum of 30 sites (unit dose of 1 mg minocycline per site) on at least 8 teeth with PD of ≥5 mm. The mean minocycline dose per patient was 46 mg, and the doses ranged from 25 to 112 mg. Serum and saliva data from this study normalized per unit 1 mg dose of minocycline are displayed in Table 3. The mean patient C_{max} irrespective of dose was 0.216 mcg/mL in serum and 254 mcg/mL in saliva.

Table 3: Pharmacokinetic Parameters of Minocycline after Subgingival Administration of ARESTIN MICROSPHERES*

PK Parameter	Biological Fluid Sampled	
	Serum Data Mean (%CV) (n=18)	Saliva Data Mean (%CV) (n=13)
$AUC_{0\rightarrow T}$ dose** (mcg·h/mL)	0.139 (40.0)	17.5 (45.3)
AUC_{∞}/dose (mcg·h/mL)	0.169 (40.0)	17.6 (44.7)
C_{max}/dose (mcg. mL)	0.00488 (38.2)	5.55 (47.9)
T_{max} (h)	4.83 (37.7)	0.748 (74.8)

k_{e1} (1/h)	0.0322 (33.2)	0.0181 (40.2)
Half-life (h)	23.8 (34.5)	44.7 (42.9)
CL/F(L/h)	7.12 (51.8)	Not calculated
V_{AREA}/F(L)	223 (38.7)	Not calculated

*One treatment with ARESTIN MICROSPHERES to each qualifying pocket (1 mg minocycline/pocket; mean number pockets treated per patient 46 (range 25-112).

**Values reported are not the observed values, but are dose adjusted (normalized) to a single dose, to account for the different number of pockets treated for each patient.

Serum data from the above study, dose adjusted (normalized) to a single 1 mg minocycline dose to account for the different number of pockets treated for each patient, was compared to serum data for a single oral minocycline dose of 100 mg and these results are shown in Table 4.

Table 4: Mean Serum Pharmacokinetic Estimates: ARESTIN MICROSPHERES vs Minocycline 100 mg Orally

Parameter	Treatment with Minocycline	
	ARESTIN MICROSPHERES administered at various doses depending on the number of pockets (normalized to a single 1 mg dose)	**Minocycline single oral dose of 100 mg**
Reference	Study 105	Saivin & Houin Clin Pharmacokinetics 1988, 15:355
AUC_{∞}/dose (mcg·h/mL)	0.169	31.6
C_{max}/dose (mcg/mL)	0.00488	1.6
T_{max} (h)	4.83	1.9
Half-life (h)	23.8	18.4

Absorption

In the study summarized in Table 3, mean dose normalized saliva AUC_{∞} and C_{max} were found to be approximately 125 and 1000 times higher than those of serum parameters respectively. The rate and extent of absorption of minocycline from this study based on C_{max} and AUC_{∞} respectively are estimated to be 3 and 2 times lower than would be expected following an equivalent oral (systemic) minocycline dose.

Distribution

Minocycline's high degree of lipophilicity explains its wide distribution in all the body tissues. Plasma protein binding of minocycline ranges from 70% to 80%. The volume of distribution ranges from 80 L to 115 L.

Metabolism

Minocycline is subject to biotransformation in the liver. Three microbiologically inactive metabolites have been found in urine and faeces, the main metabolite being 9-hydroxy-minocycline, and the two others resulting from demethylation of the parent compound in the 4 or 9 positions.

Excretion

Elimination of unchanged minocycline in the urine represents 8 to 12% of the oral dose and corresponds to a renal clearance of 0.54 L/h. Faecal elimination of the parent compound represents 20 to 35% of the dose, the rest being eliminated as metabolites either in the urine or in the faeces. Total clearance of minocycline ranges from 33.6 L/h to 5.7 L/h. The elimination half-life of minocycline after oral dosing is reported to be between 13.5 and 18.4 hours and after IV dosing, between 12.6 and 16 hours.

Polymer and Gingival Crevicular Fluid (GCF) Concentration

The polymer microspheres are hydrophilic and coalesce within the pocket forming a honeycomb structure which slowly releases minocycline to the GCF. The polymer microspheres adhere to each other and to subgingival tissues when in contact with crevicular fluid. The polymer is bio-resorbed within a month converting to its lactic acid and glycolic acid components. High mean minocycline concentrations were recorded in GCF within periodontal pockets following single doses of ARESTIN MICROSPHERES in 10 patients (n=21-24 periodontal pockets; 1 mg minocycline per periodontal pocket) decreasing from 562 mcg/mL at 3 days to 7 mcg/mL by 2 weeks and 0.5 mcg/mL by 28 days.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C to 30°C. Avoid exposure to excessive heat.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions for this product.

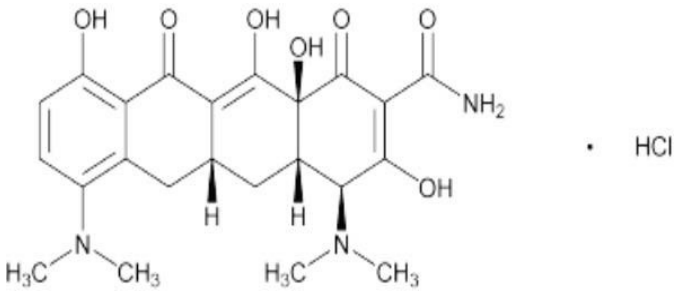
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Minocycline Hydrochloride
Chemical name:	7-dimethylamino-6-demethyl-6-deoxytetracycline hydrochloride 2-Naphthacenecarboxamide, 4,7-bis(dimethylamino) 1,4,4a,5,5a,6,11,12a-octahydro-3, 1 0,-12,12a-tetrahydroxy-1,11-dioxo-,monohydrochloride,[4S-(4α,4aα,5aα,12aα)]-4,7-Bis(dimethy1amlno)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11- dioxo-,2-naphthacene-carboxamide monohydrochloride
Molecular formula and molecular mass:	$C_{23}H_{27}N_3O_7HCl$ 493.94 g/mol

Structural formula:



Physicochemical properties:

Description:	Minocycline hydrochloride is a yellow crystalline powder that is essentially odourless and has a somewhat bitter taste. ARESTIN MICROSPHERES (minocycline hydrochloride) delivers a sustained release of minocycline for 14 days. *In vitro* studies have shown that approximately 90% of the polymer is hydrolyzed within 50 days of application. The polymer is bioresorbable so there is no need to remove the product.

Solubility: Minocycline hydrochloride is soluble in water and dissolves in aqueous solutions of alkali hydroxides and carbonates. Minocycline hydrochloride has the following solubilities in organic solvents:

Solvent	Minocycline Solubility (mg/mL at 25° C)
Methanol	14
Absolute Ethanol	42
1-Octanol	0.5
Acetone	0.6
Ethyl Acetate	0.3
Chloroform	0.13

pH: pH=3.9

pKa: pKa1=2.8 (tricarbonylmethane moiety)
pKa2=5.0 (7-dimethylammonium moiety)
pKa3=7.8 (phenolic diketone moiety)
pKa4=9.5 (4-dimethylammonium moiety)

Thermal properties: Minocycline hydrochloride loses its water of hydration between 75° to 150°C. Decomposition begins at approximately 177° to 181°C.

Hygroscopicity: Minocycline hydrochloride readily associates with two moles of water even at low relative humidity. However, once the dihydrate (6.8% water) is formed, further hydration at room temperature is negligible unless the material is exposed to conditions close to 100% RH.

Partition coefficient: 0.051 at pH 3.9 (octanol/aqueous buffer)
1.11 at pH 5.6 (octanol/aqueous buffer)
1.48 at pH 6.6 (octanol/aqueous buffer)
0.36 at pH 8.5 (octanol/aqueous buffer)

PLGA (poly (DL-lactide-co-glycolide))
ARESTIN MICROSPHERES (minocycline hydrochloride) releases minocycline continuously for 14 days. According to *in vitro* studies, around 90% of the polymer is hydrolyzed within 50 days of application. As the polymer is resorbed in the body, there is no need to remove it.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Adjunct to Scaling and Root Planning (SRP) Procedures to Decrease Pocket Depth (PD) in Adult Patients with Chronic Periodontitis

The efficacy of ARESTIN MICROSPHERES (minocycline hydrochloride) as an adjunct to SRP in reducing PD in adults with chronic moderate to advanced periodontitis (American Dental Association Class 3 and 4) was demonstrated principally in 3 clinical trials conducted in the US. Two were pivotal, controlled, 9-month trials (103A and 103B) with identical protocols. The third (104) was a single-arm, uncontrolled, open, 12-month study.

Study demographics and trial designs are summarized in Table 5.

Table 5: Summary of Patient Demographics for Clinical Trials in The Treatment of Acne Vulgaris in Patients 9 Years of Age and Older

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
103 A	Multicentre, randomized, single-blind, evaluator-blind, parallel, vehicle-controlled, 3-arm studies.	SRP to all teeth at baseline; subgingival adjunctive treatments at baseline and at 3 & 6 months to pockets ≥5 mm. Possible doses of 4-168 mg minocycline (ARESTIN MICROSPHERES) per treatment.	368 patients	48.1 (29-77)	203 M 165 F
103 B	Multicentre, randomized, single-blind, evaluator-blind, parallel, vehicle-controlled, 3-arm studies.	SRP to all teeth at baseline; subgingival adjunctive treatments at baseline and at 3 & 6 months to pockets ≥5 mm. Possible doses of 4-168 mg minocycline (ARESTIN MICROSPHERES) per treatment.	380 patients	47.9 (29-79)	207 M 173 F

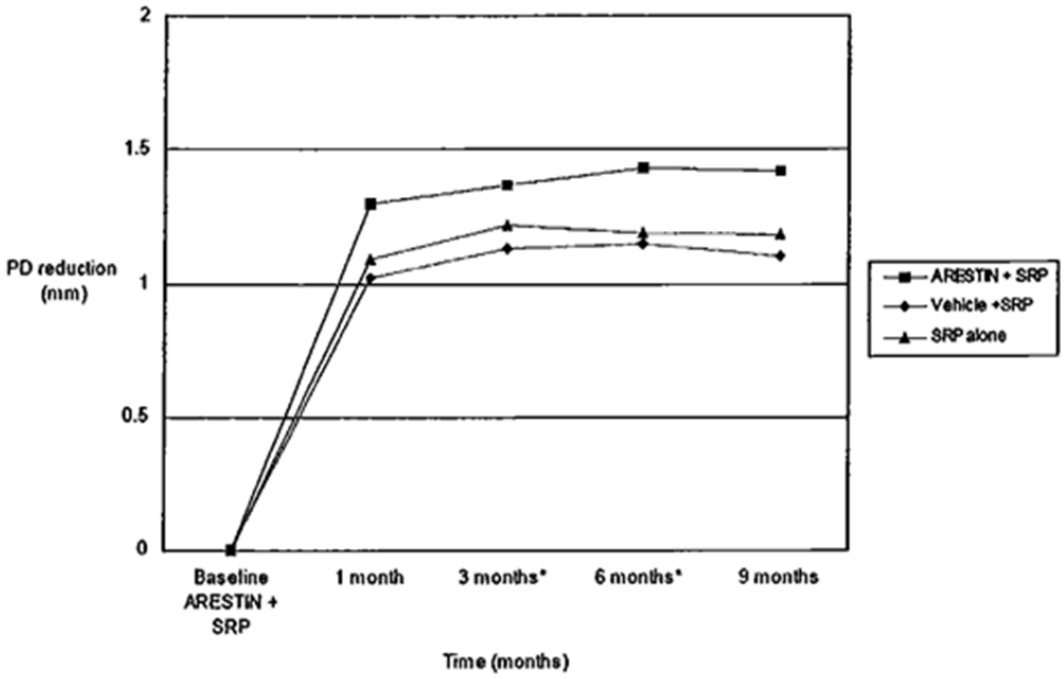
104	Multicentre, open label	SRP to all teeth at baseline; subgingival adjunctive treatments at baseline and at 3 & 6 months to pockets ≥5 mm. Possible doses of 4-168 mg minocycline (ARESTIN MICROSPHERES) per treatment.	173 patients	48.8 (29-78)	92 M 81 F

Severity of periodontal disease was moderate in 61% of patients and advanced in 39% of patients. Subjects in pivotal trials received at baseline one of three treatments: (1) ARESTIN MICROSPHERES + SRP, (2) Vehicle (bioresorbable polymer, PGLA) + SRP, and (3) SRP alone. Retreatment with ARESTIN MICROSPHERES or vehicle alone occurred at 3 and 6 months after initial treatment. Any new site with PD ≥5mm also received treatment but was assessed separately. To qualify for the study, patients were required to have four teeth with periodontal pockets of 6-9 mm that bled on probing. However, adjunctive treatment was administered to all sites with mean probing depths of 5 mm. Third molars were not included. Patients studied were in good general health.

Patients with poor glycemic control or active infectious diseases were excluded from the studies.

Table 6: Results of Study in Scaling and Root Planning (SRP) Procedures to Decrease Pocket Depth (PD) in Adult Patients with Chronic Periodontitis

Primary Endpoints	Associated value and statistical significance for Placebo or active control
The primary variable in the 2 pivotal trials was PD reduction. Their integrated results (averages of patient means) are expressed in Figure 2 and with more details in Table 7. Patients treated with ARESTIN MICROSPHERES were found to have statistically significantly greater probing PD reduction compared to those treated with SRP alone or with vehicle at all post baseline observation times.	In these two pivotal studies, an average of 31 (5-108), 31.7 (4-137) and 29.5 (5-114) sites were treated at baseline in the ARESTIN MICROSPHERES + SRP group, Vehicle + SRP group and SRP alone group, respectively. Table 7 details integrated data for the 2 pivotal trials from the 3 treatment groups over time.



*ARESTIN MICROSPHERES alone or vehicle alone re-administered at the 3 month and 6-month visits.

Figure 2: Integrated Mean Patient PD Reduction from Baseline in Pivotal Trials 103A & 103B

Table 7: Integrated Patient Mean PD Reduction Results from Baseline in 2 Pivotal Trials

Time after Baseline Treatment	ARESTIN MICROSPHERES + SRP (n=249)	Vehicle + SRP (n=249)	SRP Alone (n=250)
	ITT patients mean PD at baseline (min ± SD)		
	5.84 (0.43)	5.86 (0.51)	5.83 (0.44)
	ITT patients mean PD reduction from baseline (min ± SD)		
Month 1	1.30 (0.69)	1.02 (0.64)	1.09 (0.66)
Month 3	1.37 (0.73)	1.13 (0.66)	1.22 (0.72)
Month 6	1.43 (0.77)	1.15 (0.73)	1.19 (0.76)
Month 9	1.42 (0.82)	1.10 (0.78)	1.18 (0.81)

PD reduction from baseline (ITT analysis): ARESTIN MICROSPHERES + SRP versus vehicle + SRP or SRP alone was statistically significant at all-time points (ANOVA p≤0.01)

Table 8 shows the comparative PD changes for ARESTIN MICROSPHERES+ SRP versus SRP alone for all pockets treated at baseline in trials 103A and 103B. ARESTIN MICROSPHERES + SRP resulted in a greater percentage of pockets showing a change of PD ≥2 mm and ≥3 mm compared to SRP alone at 3, 6 and 9 months after baseline treatment.

Table 8: Percent of Periodontal Pockets by Level of PD Reductions in Pivotal Trials 103 A & B

PD Reduction	ARESTIN MICROSPHERES + SRP (n=7713)			SRP (n=7365)		
	3 months	6 months	9 months	3 months	6 months	9 months
<0 mm	6.1	6.7	7.7	6.8	7.9	9.4
≥0 and <1 mm	21.1	20.9	20.8	26.6	27.8	26.7
≥1 mm	72.8	72.4	71.5	66.6	64.4	64
≥2 mm	43	44.9	44.2	36.8	37.3	37.2
≥3mm	14	15.8	16.2	12.1	12.8	13.2

Table 9 shows that PD reduction tended to be greater the larger the PD at baseline and ARESTIN MICROSPHERES + SRP was superior to either vehicle + SRP or SRP alone 9 months following baseline.

Table 9: Mean Patient PD Reduction from BL at Month 9 for Patients with Mean BL PD ≥ 5 mm, ≥ 6 mm and ≥ 7 mm - Pivotal Studies (ITT)

Patient's Mean BL PD	Change from BL at Month 9	Treatment Group			Treatment Comparison *p* values[1] ARESTIN MICROSPHERES + SRP vs	
		ARESTIN MICROSPHERES + SRP	Vehicle + SRP	SRP Alone	Vehicle + SRP	SRP Alone
≥5 mm	N	249	249	250	<0.001	<0.001
	Mean (SD)	1.42 (0.82)	1.10 (0.78)	1.18 (0.81)		
≥6 mm	N	82	86	59	<0.001	0.002
	Mean (SD)	1.53 (0.89)	1.09 (0.88)	1.09 (0.86)		
≥7 mm	N	5	8	6		

	Mean (SD)	2.28 (0.83)	0.70 (0.76)	1.30 (0.87)	0.024	0.060

1 P-value from ANCOVA for testing the null hypothesis that the response is equal between the two treatment groups. Note: Baseline (BL) treatment sites are those sites that first qualified for treatment at the BL visit, prior to randomization. Missing responses were imputed using LOCF or WOCF rules.

Smoking status, age or history of cardiac disease did not impact on the ability of ARESTIN MICROSPHERES + SRP to provide greater PD reduction than Vehicle + SRP or SRP alone. Table 10 shows results at 9 months. No differences were observed relating to gender or race.

Table 10: Mean Patient PD Reduction ± SE (mm) in Subpopulations, Studies 103A and 103B Combined

Population	ARESTIN MICROSPHERES + SRP	Vehicle + SRP	SRP Alone
Smokers	N=90 1.24±0.09**	N=90 0.98±0.07	N=91 0.96±0.09
Non-smokers	N=159 1.53±0.06**	N=159 1.17±0.07	N=159 1.31±0.06
>50 Years Old	N=107 1.42±0.08**	N=81 0.92±0.08	N=83 1.07±0.09
≤50 Years Old	N=142 1.43±0.07*	N=168 1.19±0.06	N=167 1.24±0.06
Patients with CV Disease	N=36 1.56±0.14**	N=29 1.06±0.14	N=36 0.99±0.13
Patients without CV Disease	N=213 1.40±0.06**	N=220 1.11±0.05	N=214 1.22±0.06

*ARESTIN MICROSPHERES + SRP versus SRP alone p≤0.05; **ARESTIN MICROSPHERES + SRP versus SRP alone p≤0.001

Table 11 demonstrates a consistently higher incidence of PD reduction of ≥2 mm at individual sites within all subjects including smokers at 1 and 3 and 9 months following a single ARESTIN MICROSPHERES administration with SRP. These data demonstrate a higher likelihood or incidence for clinically relevant changes in PD ≥2 mm with adjunctive ARESTIN MICROSPHERES treatment relative to SRP alone. The early intergroup PD reduction differences observed at 1 and/or 3 months with adjunctive ARESTIN MICROSPHERES + SRP versus SRP alone are used as a basis to support clinical relevance of the findings.

The pivotal trials did not provide evidence that re-administration of ARESTIN MICROSPHERES alone at 3 and 6 months provided additional benefits compared to controls. Qualitative or quantitative changes in plaque microorganisms were not demonstrated in periodontitis patients in pivotal trials. Other conventional clinical measures of treatment success in addition to PD reduction were also evaluated in the pivotal trials. Bleeding on

probing was reduced and clinical attachment levels were increased following baseline treatments, but no consistent intergroup differences were noted.

Table 11: Percent of Periodontal Pockets with PD Reduction ≥ 2 mm at 1, 3 and 9 Months: ARESTIN MICROSPHERES + SRP versus SRP Alone

Patient Group	Baseline PD ≥5 mm		Baseline PD ≥6 mm	
	ARESTIN MICROSPHERES + SRP	SRP Alone	ARESTIN MICROSPHERES + SRP	SRP Alone
Month 1				
All Patients (%)	2981/7713 (39%)	2308/7365 (31%)	1624/3869 (42%)	1239/3571 (35%)
Smokers (%)	1057/3310 (32%)	797/3054 (26%)	534/1557 (34%)	392/1411 (28%)
	P=0.0004		P=0.0037	
Month 3				
All Patients (%)	3317/7713 (43%)	2713/7365 (37%)	1825/3869 (47%)	1508/3571 (42%)
Smokers (%)	1182/3310 (36%)	932/3054 (31%)	608/1557 (39%)	487/1411 (35%)
	P=0.0228		P=0.0714	
Month 9				
All Patients (%)	3408/7713 (44%)	2738/7365 (37%)	1943/3869 (50%)	1537/3571 (43%)
Smokers (%)	1172/3310 (35%)	882/3054 (29%)	647/1557 (42%)	480/1411 (34%)
	P=0.0014		P=0.0019	

Statistical comparisons are based upon sequential multivariate logistic regression models for correlated data (periodontal pockets within patient), where p-values represent treatment effect after adjustment for smoking status, baseline probing depth, and age. P-value refers to comparison between ARESTIN MICROSPHERES + SRP versus SRP alone.

Supportive Study

A third, uncontrolled study was conducted over an observation period of 12 months. The results of this study are consistent with the results of the 2 pivotal trials described above. In the non- comparative study, at 12 months, the mean PD reduction for ARESTIN MICROSPHERES + SRP was 1.79 mm.

15 MICROBIOLOGY

In Vitro Antimicrobial Activity

Periodontitis is a bacterial infection caused mainly by the growth of anaerobes or fastidious bacteria. These include *Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola, Tannerella forsythia, Fusobacterium nucleatum, Eikenella corrodens* and *Aggregatibacter actinomycetemcomitans* among others.

Minocycline is capable of inhibiting dental pathogens. The following are reported MIC90 ranges (mcg/mL) of minocycline against common dental pathogens:

- Porphyromonas gingivalis (n=13) 0.31-1.58
- Prevotella intermedia (n=10) 0.31-0.79
- Treponema denticola (n=2) 0.063-0.125
- Fusobacterium nucleatum (n=19) 0.31-0.79
- Eikenella corrodens (n=2) 1.58
- Aggregatibacter actinomycetemcomitans (n=16) 0.125-3.11

The *in vivo* biofilm environment, such as that of dental plaque, is highly protective of bacteria and 1000-1500-fold MIC increases have been reported *in vitro*. In addition, after SRP alone, *Porphyromonas gingivalis, Treponema denticola,* and *Tannerella forsythia*, labelled as "red complex organisms", have been reported to be significantly decreased relative to many other organisms amongst the 40 common bacterial species evaluated in dental plaque samples taken from the subgingival periodontal pockets of subjects with periodontal disease. These microbial changes due to SRP alone were accompanied by a significant decrease in full mouth mean PD and attachment level.

Antimicrobial Resistance

The emergence of minocycline-resistant bacteria in single site plaque and gastrointestinal samples was studied in subjects before and after treatment with ARESTIN MICROSPHERES. There was a slight increase in the numbers of minocycline-resistant bacteria at plaque site at the end of the 9-month study period, and gastrointestinal tract at the end of 56-day period. An overgrowth of Candida albicans or Staphylococcus aureus was also seen in the gastrointestinal samples. However, the number of subjects studied was small, and the clinical significance of these findings is not known.

In Vivo Antimicrobial Activity

In a multicentre, single-blinded, randomized, 30-day clinical trial, the effect of adjunctive treatment with ARESTIN MICROSPHERES on the subgingival flora in patients with moderate to advanced periodontitis was compared with the control of SRP alone. Five non-adjacent, interproximal, periodontal pockets with probing depth of ≥5 mm at baseline were sampled from each patient. Microbiological assessment was made by DNA probe technique.

Care is needed in interpreting such data since DNA analysis techniques measure DNA content and do not differentiate between dead or living bacteria. In addition, the number of bacteria may be influenced by plaque sampling methodology. Tables 12 and 13 show the results for the

sum of the three red complex bacteria.

Table 12: Red Complex Bacteria Numbers; Reduction from Baseline

Treatment Group	N	Baseline Value (X10[1] Bacteria)	Mean Change (X10[1] Bacteria)	*p*-value
ARESTIN MICROSPHERES + SRP	62	18.9	9.4	0.002[1]
SRP Alone	65	19.3	5.1	

N is the number of subjects with observations at both Baseline and 30 days.

[1]ARESTIN MICROSPHERES + SRP versus SRP Alone by ANCOVA Log10 transformed red complex bacteria numbers. Bacterial number: Sum of numbers of red complex bacteria.

Table 13: Red Complex Bacteria Proportion; Reduction from Baseline

Treatment Group	N	Baseline Value (%)	Mean Change	*p*-value
ARESTIN MICROSPHERES + SRP	62	13.45	6.49	0.0005[1]
SRP Alone	65	15.11	5.03	

N is the number of subjects with observations at both Baseline and 30 days.

[1]ARESTIN MICROSPHERES + SRP versus SRP Alone by ANCOVA of Log10 transformed red complex bacteria proportions. Bacterial Proportion: Sum of red complex bacteria as a percentage of the total140 common dental bacteria analyzed.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Minocycline hydrochloride has been tested in acute experiments in mice and rats, sub-chronic and chronic experiments in rats and dogs following oral and parenteral routes of administration.

The LD of intravenous and intraperitoneal injections of minocycline in mice was 95 mg/kg and 280 mg/kg, respectively. The oral LD_{50} in mice was 3100 mg/kg.

Minocycline hydrochloride has been given orally each day to dogs for 6 months at doses of 0, 4, 20 and 60 mg/kg/day (100/mg/kg/day for the first month) equally divided each day. At 20 mg/kg/day, there were no apparent drug-related findings except yellow discolouration of the skeleton and teeth in some animals, occasional emesis, and black discolouration of the thyroid gland. At a dose of 4 mg/kg/day, there were no drug-related findings during the 6-month period, with the exception of discolouration of the thyroid gland and possibly some yellowing of the bones. Peak serum drug concentrations ranging from 8.5 to 100 mg/L were obtained with 60 and 100 mg/kg/day doses, 2.1 to 9.7 mg/L with the 20 mg/kg/day dose and 0.4 to 1.5 mg/L

with the 4 mg/kg/day dose.

Minocycline hydrochloride was also given intravenously to dogs at doses of 5, 10, 20 and 40 mg/kg/day, a very similar dose range to that of the oral study but administered for 1 month. Untoward findings such as body weight loss, reduced food consumption, erythema of the skin and of visible mucous membranes of varying duration, intensity, and incidence, were associated primarily with the high dose (40 mg/kg/day). These findings were similar, except for erythema, to those obtained after the same dose of tetracycline. These drug-related findings with minocycline hydrochloride were associated with serum concentrations of 95 mg/L, three times those found with tetracycline (31 mg/L). Dogs that received 5, 10 and 20 mg/kg/day intravenously gave serum concentrations of 4, 12 and 38 mg/L, respectively, and were found essentially to be without toxicity. These serum values are in considerable excess of those necessary for therapeutic effectiveness in man. In these experiments, minocycline hydrochloride appeared to be tolerated as well intravenously as it was orally.

Similar results were found following chronic oral administration of minocycline hydrochloride to rats for one year.

These animals were given a drug diet containing 0.008, 0.04, 0.2 and 1.0% minocycline hydrochloride, which corresponded to ranges of 4.4 to 8.5, 21.3 to 44.0, 108 to 122 and 593 to 812 mg/kg/day drug intake; these doses gave early morning plasma drug concentrations of 0.07 to 0.16, 0.36 to 0.51, 2.9 to 6.5 and 17 to 50 mg/L respectively. With the exception of the discolouration of the teeth (dose 0.04% drug diet or greater), femur and thyroid gland, there were no significant drug-related signs of toxicity at doses less than 1% drug diet.

As with other tetracyclines, minocycline hydrochloride has been found to produce discolouration of the thyroid gland in the rat, dog, monkey and human but not in the mouse. There was no evidence, however, from these investigations that thyroid function or bone growth was affected. A 23-month carcinogenicity study in the rat has shown that minocycline hydrochloride was not carcinogenic and that the black pigment in the thyroid gland did not cause neoplastic changes.

Biopsy specimens of thyroid tissue following the administration of minocycline and tetracyclines to man revealed an intraepithelial lipofuscin deposition of both drugs, considered to be within normal variation. Thyroid function studies in man displayed a decrease within the normal range of thyroxine, indicating a tendency toward relative hypothyroidism.

Other than the tooth and bone discolouration that also occurs with other tetracyclines and the thyroid pigmentation seen in rats, dogs and monkeys, toxic effects of minocycline hydrochloride were observed only where serum concentrations were in excess of the therapeutic concentrations. It is concluded from the chronic safety evaluation studies that minocycline hydrochloride has a good margin of safety between therapeutic blood concentrations and concentrations producing toxic effects.

Reproductive and Developmental Toxicology

Reproduction studies performed in rats, rabbits and dogs have shown, as with other tetracyclines in animal studies, that minocycline crosses the placenta, is found in fetal tissues, and can produce toxic effects on the developing embryo, fetus or neonate when present in sufficient amounts.

The effects observed on the conceptus in rats and rabbits ranged from a low incidence of slight retardation of ossification and slight angulation of ribs at oral doses of 70 mg/kg/day in rats and 25 mg/kg/day in rabbits during pregnancy, to more extensive retardation of ossification and

generalized morphologic changes and death at doses of 150 mg/kg/day and higher in the rat fetus. On other experiments, no deleterious effects were reported in rats or rabbits with oral doses as high as 100 and 75 mg/kg/day respectively. No adverse effects due to minocycline hydrochloride were seen in the newborn of 2 dogs given 20 mg/kg in 2 equally divided daily doses from days 35 to 62 of pregnancy.

Table 14 summarizes other recent toxicology studies conducted to confirm the safety of ARESTIN MICROSPHERES (minocycline hydrochloride).

Table 14: Overview of Toxicity Studies

Study	Species: Strain	Route and Dose/Concentration (mg/kg)	Result (Dose in mg/kg)
Special Toxicity (ARESTIN MICROSPHERES)			
Dermal Sensitization	Guinea Pig Hartley	Topical 25% (minocycline free base) used for induction, booster, and challenge doses	No contact sensitization at 4 or 48 hours
Local Tolerance	Dog	Topical application to gingiva • 37.5 mg/site (minocycline free base) • Two sites/dog, one abraded, one intact • Application to each site daily for 5 days	• No difference between healing time in abraded and intact sites • No differences in gingival reaction among control, abraded and intact sites

Genotoxicity (minocycline)			
AA13KR502.BTL Bacterial Reverse Mutation Assay	*Salmonella typhimurium strains* TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2uvrA	*In vitro* *0.025-7.5 mcg/plate*	• Cytotoxicity at ≥2.5 mcg per plate • No dose-dependent increase in revertant colony counts with or without • Activation
AA13KR704.BIL *In Vitro* Mammalian Cell Gene Mutation Test	L5178Y cells Clone 3.7.2C	*In vitro* 5-40 mcg/plate	• Cytotoxicity at ≥15 mcg per plate No dose-dependent changes in mutations with or without activation
AA13KR331.BTL *In Vitro* Mammalian Chromosome Aberration Test	CHO-K1, cells	*In vitro* 75-750 mcg/plate	• Cytotoxicity at ≥1500 mcg/mL non-activated, 4 hr; 500 mcg/mL activated, 4 hr; 50 mcg/mL non-activated, 20 hr No dose-dependent increase in aberrations
AA13KR123.BTL Mammalian Erythrocyte Micronucleus Test	ICR Mouse	IP 32-125	• Mortality in males and females ≥250 No dose-dependent increases in micronucleated polychromatic erythrocytes

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrARESTIN® MICROSPHERES
Minocycline Hydrochloride Controlled-release Microspheres

Read this carefully before you start receiving **ARESTIN MICROSPHERES** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ARESTIN MICROSPHERES**.

Serious Warnings and Precautions

Teeth may become permanently discoloured if ARESTIN MICROSPHERES is used on teeth that are developing. ARESTIN MICROSPHERES should not be used:

- in pregnant or nursing women;
- on teeth that are developing.

What is ARESTIN MICROSPHERES used for?

- Scaling and root planning (SRP) procedures are deep cleaning procedures done by your dental professional. Scaling removes plaque, tartar and stains from the surface of the teeth. Planning smooths the rough areas on the root of teeth to promote healing. ARESTIN MICROSPHERES is used alongside SRP to reduce pocket depth (the space between your teeth and gums) in adults with:
  - Chronic periodontitis
  - Moderate to advance chronic periodontal disease
- ARESTIN MICROSPHERES is also used in adults, as part of periodontal maintenance program which includes good oral hygiene and SRP.
- Antibacterial drugs like ARESTIN MICROSPHERES treat only bacterial infections. They do not treat viral infections. Although you may feel better early in your treatment, ARESTIN MICROSPHERES should be used exactly as directed. Misuse or overuse of ARESTIN MICROSPHERES could lead to the growth of bacteria that will not be killed by ARESTIN MICROSPHERES (resistance). This means that ARESTIN MICROSPHERES may not work for you in the future. Do not share your medicine.

How does ARESTIN MICROSPHERES work?

Harmful bacteria can infect the gums and form spaces or gaps around the teeth. These gaps are called periodontal pockets. While SRP has been shown to remove many of the bacteria, the instruments used during SRP sometimes can’t reach stubborn bacteria that hide in the bottom of pockets. ARESTIN MICROSPHERES is placed by your healthcare professional into the periodontal pockets. ARESTIN MICROSPHERES contain minocycline hydrochloride, a tetracycline antibiotic. It stops the growth of bacteria. ARESTIN MICROSPHERES will reduce the amount of bacteria in these pockets and helps reduce the depth of pockets around your

teeth.

What are the ingredients in ARESTIN MICROSPHERES?

Medicinal ingredients: Minocycline Hydrochloride

Non-medicinal ingredients: Poly (glycolide-co-dl-lactide) or PGLA.

ARESTIN MICROSPHERES comes in the following dosage forms:

- Powder (microspheres); 1 mg per cartridge

Do not use ARESTIN MICROSPHERES if:

- You are allergic to minocycline hydrochloride or any of the other ingredients in ARESTIN MICROSPHERES.
- You are sensitive to tetracycline, doxycycline, minocycline, or any other tetracycline drug.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive ARESTIN MICROSPHERES. Talk about any health conditions or problems you may have, including if you:

- are taking oral contraceptives. Antibiotics may decrease the effectiveness of your birth control pills.
- are pregnant or planning on becoming pregnant.
- are breastfeeding or planning to breastfeed.
- are taking penicillin or other antibiotics.
- have a history of thrush (a yeast infection in your mouth).
- have diabetes or HIV infection.
- are receiving chemotherapy or radiation treatment.
- have systemic lupus erythematosus.
- have acute abscess (pocket of pus caused by a bacterial infection) in the periodontal pocket.
- have dental implants or are going to be getting dental implants.

Other warnings you should know about:

Minocycline can cause the development of autoimmune syndromes. Symptoms can include fever, rash, joint stiffness, swollen lymph nodes and restlessness. If you have any of these symptoms, tell your healthcare professional immediately.

ARESTIN MICROSPHERES can cause swelling of the face, fever, itching and swelling of the lymph nodes. This may be a sign of hypersensitivity reactions. If you have any of these symptoms, tell your healthcare professional immediately.

Sun Sensitivity

ARESTIN MICROSPHERES can cause your skin to become sensitive to the sun and UV light. While taking ARESTIN MICROSPHERES, use sunscreen and protective clothing if you are going to be in direct sunlight. Avoid tanning beds and other sources of UV light. If you notice skin redness after being in the sun, avoid further sun exposure.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

It is unlikely drugs may interact with ARESTIN MICROSPHERES since it is placed in small pockets around your teeth from which small amounts of antibiotic are released over several weeks.

The following may interact with ARESTIN MICROSPHERES:

- Anticoagulants (medicine used to thin the blood and prevent blood clots).
- Beta-lactam antibiotics (such as penicillin, amoxicillin, cefaclor) and aminoglycoside antibiotics (such as gentamycin, and tobramycin).
- Hormonal birth control.
- Methoxyflurane anesthesia (medicine to control pain in emergency settings).

How to take ARESTIN MICROSPHERES:

- Your healthcare professional will administer ARESTIN MICROSPHERES.
- After you leave your dentist's or periodontist's office, don't brush your teeth for 12 hours.
- Don't touch the parts of your mouth where they put the medicine for 1 week.
- Don't eat hard, crunchy, or sticky foods, such as apples, raw carrots, and caramel candy for 1 week.
- Don't use dental floss, dental tape, or toothpicks around the area where they put the medicine for 10 days.
- It is important for you to continue with a good oral hygiene regimen as recommended by your dentist.

Overdose:

If you think you, or a person you are caring for, have been given too much ARESTIN MICROSPHERES, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using ARESTIN MICROSPHERES?

These are not all the possible side effects you may have when taking ARESTIN MICROSPHERES. If you experience any side effects not listed here, tell your healthcare professional.

- gum discomfort / pain / soreness, gum swelling
- bleeding gums
- mouth sores and Mouth pain
- toothache
- tooth and tongue discoloration
- upset stomach
- headache
- infection
- flu-like symptoms
- pain
- diarrhea
- inflammation of the sinuses (sinusitis), trachea and bronchi (bronchitis), back of the throat (pharyngitis)
- muscle pain
- joint stiffness

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY RARE			
Angioedema and Serious Allergic Reactions (including local allergic reactions): swelling of the face, eyes, lips, tongue or throat, trouble breathing or swallowing, itching, hives, small raised red pimples, or rash (papules), redness, rash, fever, abdominal cramps			√
UNKNOWN			
Acute febrile neutrophilic dermatosis (Sweet's syndrome): painful bumps or small blisters filled with pus on the face, neck, arms, or legs, skin and mouth sores, skin discoloration, fever, muscle and joint pain, headache, and fatigue			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store between 15°C to 30°C.
- Avoid exposure to excessive heat.
- Keep out of reach and sight of children.

If you want more information about ARESTIN MICROSPHERES:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling 1-866-ARESTIN (273-7846).

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