

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 50-744

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Chemistry Review(s)	X			
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Statistical Review(s)	X			
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Clinical Pharmacology Biopharmaceutics Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50-744

Trade Name: PERIOSTAT CAPSULES, 20 MG

Generic Name:(doxycycline hyclate USP)

Sponsor: CollaGenex Pharmaceuticals, Inc.

Approval Date: September 30, 1998

INDICATION: Provides for the use of Periostat (doxycycline hyclate USP) Capsules, 20 mg as an adjunct to subgingival scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NSA 50-744

APPROVAL LETTER



NDA 50-744

SEP 30 1998

CollaGenex Pharmaceuticals, Inc.
Attention: Christopher Powala
Director, Drug Development and Regulatory Affairs
301 South State Street
Newtown, PA 18940

Dear Mr. Powala:

Please refer to your new drug application (NDA) dated August 30, 1996, received August 30, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Periostat™ (doxycycline hyclate USP) Capsules, 20 mg. We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated August 28, October 1, November 13, December 8, 1997; January 6, 14, and 19, February 10, March 2, 18, and 31, April 23 and 28, July 9 and 29, and September 3, 14, 16, 22, 24 (2), and 25, 1998. Your submission of March 31, 1998 constituted a full response to our August 27, 1997, action letter. The user fee goal date for this application is October 1, 1998.

This new drug application provides for the use of Periostat™ (doxycycline hyclate USP) Capsules, 20 mg as an adjunct to subgingival scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. We acknowledge your commitment made in the teleconference with this Division on September 16, 1998, to revise the carton and container labeling so that the prominence of the established name and tradename is commensurate and in accordance with 21 CFR 201.10(g)(2).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 50-744". Approval of this submission by FDA is not required before the labeling is used.

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We remind you of your Phase 4 commitments agreed to in your submissions dated August 3, 1998, and September 14, 1998. These commitments, respectively, are listed below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each clinical study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

NDA 50-744

Page 3

If you have any questions, contact Roy Blay, Ph.D., Project Manager, at (301) 827-2020.

Sincerely,

/s/

Jonathan K. Wilkin, M.D.

Director

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

Enclosure

SEP 30 1998

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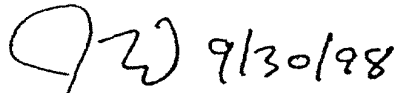
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NDA 50-744
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Jonathan K. Wilkin, M.D.

Director

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

Enclosure

APPROVED

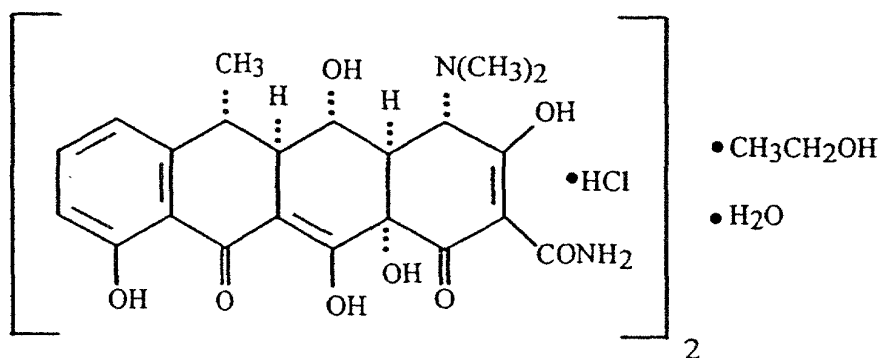
PERIOSTAT™
(doxycycline hyclate capsules)

SEP 30 1998

DESCRIPTION

Periostat™ is available as a 20 mg capsule formulation of doxycycline hyclate for oral administration.

Doxycycline is synthetically derived from oxytetracycline. The structural formula of doxycycline hyclate is:



with an empirical formula of $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$ and a molecular weight of 1025.89. The chemical designation for doxycycline is 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate.

Doxycycline hyclate is a light-yellow crystalline powder which is soluble in water.

Inert ingredients in the formulation are: hard gelatin capsules; magnesium stearate; and microcrystalline cellulose. Each capsule contains doxycycline hyclate equivalent to 20 mg of doxycycline.

CLINICAL PHARMACOLOGY

After oral administration, doxycycline hyclate is rapidly and nearly completely absorbed from the gastrointestinal tract. Doxycycline is eliminated with a half-life of approximately 18 hours by renal and fecal excretion of unchanged drug.

Mechanism of Action: Doxycycline has been shown to inhibit collagenase activity in vitro.¹ Additional studies have shown that doxycycline reduces the elevated collagenase activity in the gingival crevicular fluid of patients with adult periodontitis.^{2,3} The clinical significance of these findings is not known.

Microbiology: Doxycycline is a member of the tetracycline class of antibiotics. The dosage of doxycycline achieved with this product during administration is well below the concentration required to inhibit microorganisms commonly associated with adult periodontitis. Clinical studies with this product demonstrated no effect on total anaerobic and facultative bacteria in plaque samples from patients administered this dose regimen for 9 to 18 months. This product should not be used for reducing the numbers of or eliminating those microorganisms associated with periodontitis.

Pharmacokinetics

The pharmacokinetics of doxycycline following oral administration of Periostat™ were investigated in 3 volunteer studies involving 87 adults. Additionally, doxycycline pharmacokinetics have been characterized in numerous scientific publications.⁴ Pharmacokinetic parameters for Periostat™ following single oral doses and at steady-state in healthy subjects are presented as follows:

Pharmacokinetic Parameters for Periostat™					
	n	C _{max} (ng/mL)	T _{max} (hr)	Cl/F (L/hr)	t _{1/2} (hr)
Single dose 20 mg	42	400 ± 142	1.5 (0.5 - 4.0)	3.80 ± 0.85	18.4 ± 5.38
Steady-State 20 mg BID	30	790 ± 285	2 (0.98 - 12.0)	3.76 ± 1.06	Not Determined

Absorption: Doxycycline is virtually completely absorbed after oral administration. Following 20 mg doxycycline, twice a day, in healthy volunteers, the mean peak concentration in plasma was 790 ng/mL and the average steady-state concentration was 482 ng/mL. The effect of food on the absorption of doxycycline from Periostat™ has not been studied.

Distribution: Doxycycline is greater than 90% bound to plasma proteins. Its apparent volume of distribution is variously reported as between 52.6 and 134 L.^{4,6}

Metabolism: Major metabolites of doxycycline have not been identified. However, enzyme inducers such as barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

Excretion: Doxycycline is excreted in the urine and feces as unchanged drug. It is variously reported that between 29% and 55.4% of an administered dose can be accounted for in the urine by 72 hours.^{5,6} Half-life averaged 18 hours in subjects receiving a single 20 mg doxycycline dose.

Special Populations

Geriatric: Doxycycline pharmacokinetics have not been evaluated in geriatric patients.

Pediatric: Doxycycline pharmacokinetics have not been evaluated in pediatric patients (See WARNINGS).

Gender: A study was conducted in 42 subjects where doxycycline pharmacokinetics were compared in men and women. It was observed that C_{max} was approximately 1.7-fold higher in women than in men. There were no apparent differences in other pharmacokinetic parameters.

Race: Differences in doxycycline pharmacokinetics among racial groups have not been evaluated.

Renal Insufficiency: Studies have shown no significant difference in serum half-life of doxycycline in patients with normal and severely impaired renal function. Hemodialysis does not alter the half-life of doxycycline.

Hepatic Insufficiency: Doxycycline pharmacokinetics have not been evaluated in patients with hepatic insufficiency.

Drug Interactions: See "Precautions"

Clinical Study

In a randomized, multi-centered, double-blind, 9-month Phase 3 study involving 190 adult patients with periodontal disease [at least two probing sites per quadrant of between 5 and 9 mm pocket depth (PD) and attachment level (ALv)], the effects of oral administration of 20 mg twice a day of doxycycline hyclate plus scaling and root planing (SRP) were compared to placebo control plus SRP. Both treatment groups were administered a course of scaling and root planing in 2 quadrants at Baseline. Measurements of ALv, PD and bleeding on probing (BOP) were obtained at Baseline, 3, 6, and 9 months from each site about each tooth in the two quadrants that received SRP using the UNC-15 manual probe. Each tooth site was categorized into one of three strata based on Baseline PD: 0-3 mm (no disease), 4-6 mm (mild/moderate disease), ≥ 7 mm (severe disease). For each stratum and treatment group, the following were calculated at month 3, 6, and 9: mean change in ALv from baseline, mean change in PD from baseline, mean percentage of tooth sites per patient exhibiting attachment loss of ≥ 2 mm from baseline, and percentage of tooth sites with bleeding on probing. The results are summarized in the following table.

Clinical Results at Nine Months as an Adjunct to SRP			
Parameter	Baseline Pocket Depth		
	0-3 mm	4-6 mm	≥ 7 mm
Number of Patients	90	90	79
Mean Gain in ALv			
Periostat™ 20 mg BID	0.25 mm	1.03 mm*	1.55mm*
Placebo	0.20 mm	0.86 mm	1.17mm
Mean Decrease in PD			
Periostat™ 20 mg BID	0.16 mm**	0.95mm**	1.68mm**
Placebo	0.05 mm	0.69 mm	1.20mm
% of Sites with loss of ALv ≥ 2 mm			
Periostat™ 20 mg BID	1.9. %	1.3 %	0.3%*
Placebo	2.2 %	2.4 %	3.6%
% of Sites with BOP			
Periostat™ 20 mg BID	39%**	64%*	75%
Placebo	46%	70%	80%

* $p < 0.050$ vs. the placebo control group, ** $p < 0.010$ vs. the placebo control group.

INDICATIONS AND USAGE

Periostat™ is indicated for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP AND IN PREGNANT OR NURSING MOTHERS UNLESS THE POTENTIAL BENEFITS MAY BE ACCEPTABLE DESPITE THE POTENTIAL RISKS.

All tetracyclines form a stable calcium complex in any bone forming tissue. A decrease in fibula growth rate has been observed in premature infants given oral tetracyclines in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Doxycycline can cause fetal harm when administered to a pregnant woman. 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.

The catabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

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.

PRECAUTIONS

While no overgrowth by opportunistic microorganisms such as yeast were noted during clinical studies, as with other antimicrobials, Periostat™ therapy may result in overgrowth of nonsusceptible microorganisms including fungi.

The use of tetracyclines may increase the incidence of vaginal candidiasis.

Periostat™ should be used with caution in patients with a history or predisposition to oral candidiasis. The safety and effectiveness of Periostat™ has not been established for the treatment of periodontitis in patients with coexistent oral candidiasis.

If superinfection is suspected, appropriate measures should be taken.

Laboratory Tests: In long term therapy, periodic laboratory evaluations of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

Drug Interactions: Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic antibiotics, such as the tetracycline class of antibiotics, may interfere with the bactericidal action of members of the β -lactam (e.g. penicillin) class of antibiotics, it is not advisable to administer these antibiotics concomitantly.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium and by iron-containing preparations. Absorption is also impaired by bismuth subsalicylate.

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

The concurrent use of tetracycline and Penthrane (methoxy-fluorane) has been reported to result in fatal renal toxicity.

Concurrent use of tetracycline may render oral contraceptives less effective.

Drug/Laboratory Test Interactions: False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Doxycycline hyclate has not been evaluated for carcinogenic potential in long-term animal studies. Evidence of oncogenic activity was obtained in studies with related compounds, i.e., oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors).

Doxycycline hyclate demonstrated no potential to cause genetic toxicity in an *in vitro* point mutation study with mammalian cells (CHO/HGPRT forward mutation assay) or in an *in vivo* micronucleus assay conducted in CD-1 mice. However, data from an *in vitro* assay with CHO cells for potential to cause chromosomal aberrations suggest that doxycycline hyclate is a weak clastogen.

Oral administration of doxycycline hyclate to male and female Sprague-Dawley rats adversely affected fertility and reproductive performance, as evidenced by increased time for mating to occur, reduced sperm motility, velocity, and concentration, abnormal sperm morphology, and increased pre- and post-implantation losses. Doxycycline hyclate induced reproductive toxicity at all dosages that were examined in this study, as even the lowest dosage tested (50 mg/kg/day) induced a statistically significant reduction in sperm velocity. Note that 50 mg/kg/day is approximately 10 times the amount of doxycycline hyclate contained in the recommended daily dose of Periostat™ for a 60 kg human when compared on the basis of body surface area estimates (mg/m²). Although doxycycline impairs the fertility of rats when administered at sufficient dosage, the effect of Periostat™ on human fertility is unknown.

Pregnancy: Teratogenic Effects: Pregnancy Category D. (See WARNINGS.) Results from animal studies indicate that doxycycline crosses the placenta and is found in fetal tissues.

Nonteratogenic effects: (See WARNINGS).

Labor and Delivery: The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers: Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from doxycycline, the use of Periostat™ in nursing mothers is contraindicated. (See WARNINGS)

Pediatric Use: The use of Periostat™ in infancy and childhood is contraindicated. (See WARNINGS)

ADVERSE REACTIONS

Adverse Reactions in Clinical Trials of Periostat™: In clinical trials of adult patients with periodontal disease 213 patients received Periostat™ 20 mg BID over a 9 - 12 month period. The most frequent adverse reactions occurring in studies involving treatment with Periostat™ or placebo are listed below:

Incidence (%) of Adverse Reactions in Periostat™ Clinical Trials		
Adverse Reaction	Periostat 20 mg BID (n=213)	Placebo (n=215)
Headache	55 (26%)	56 (26%)
Common Cold	47 (22%)	46 (21%)
Flu Symptoms	24 (11%)	40 (19%)
Tooth Ache	14 (7%)	28 (13%)
Periodontal Abscess	8 (4%)	21 (10%)
Tooth Disorder	13 (6%)	19 (9%)
Nausea	17 (8%)	12 (6%)
Sinusitis	7 (3%)	18 (8%)
Injury	11 (5%)	18 (8%)
Dyspepsia	13 (6%)	5 (2%)
Sore Throat	11 (5%)	13 (6%)
Joint Pain	12 (6%)	8 (4%)
Diarrhea	12 (6%)	8 (4%)
Sinus Congestion	11 (5%)	11 (5%)
Coughing	9 (4%)	11 (5%)
Sinus Headache	8 (4%)	8 (4%)
Rash	8 (4%)	6 (3%)
Back Pain	7 (3%)	8 (4%)
Back Ache	4 (2%)	9 (4%)
Menstrual Cramp	9 (4%)	5 (2%)
Acid Indigestion	8 (4%)	7 (3%)
Pain	8 (4%)	5 (2%)
Infection	4 (2%)	6 (3%)
Gum Pain	1 (1%)	6 (3%)
Bronchitis	7 (3%)	5 (2%)
Muscle Pain	2 (1%)	6 (3%)

Note: Percentages are based on total number of study participants in each treatment group.

Adverse Reactions for Tetracyclines: The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with vaginal candidiasis) in the anogenital region. Hepatotoxicity has been reported rarely. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving the capsule forms of the drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (SEE DOSAGE AND ADMINISTRATION.)

Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See WARNINGS.)

Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See WARNINGS.)

Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdose.

DOSAGE AND ADMINISTRATION

THE DOSAGE OF PERIOSTAT™ DIFFERS FROM THAT OF DOXYCYCLINE USED TO TREAT INFECTIONS. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS INCLUDING THE DEVELOPMENT OF RESISTANT MICROORGANISMS.

Periostat™ 20 mg twice daily as an adjunct following scaling and root planing may be administered for up to 9 months. Safety beyond 12 months and efficacy beyond 9 months have not been established.

Periostat™ should be administered at least one hour prior to morning and evening meals.

Administration of adequate amounts of fluid along with the capsules is recommended to wash down the drug and reduce the risk of esophageal irritation and ulceration. (SEE ADVERSE REACTIONS.)

HOW SUPPLIED

Periostat™ (white capsule imprinted with "Periostat™ ") containing doxycycline hyclate equivalent to 20 mg doxycycline. Bottle of 100 (NDC XXXX-XXXX-XX).

Storage: All products are to be stored at controlled room temperatures of 59°F - 86 °F (15 °C - 30 °C) and dispensed in tight, light-resistant containers (USP).

Rx Only

PERIOSTAT™ is a trademark of CollaGenex Pharmaceuticals, Inc., Newtown, PA, 18940

Manufactured by
Applied Analytical Inc.
Wilmington, NC, 28403

Marketed by
CollaGenex Pharmaceuticals, Inc.
Newtown, PA, 18940

REFERENCES

1. Golub L.M., Sorsa T., Lee H-M., Cincio S., Sorbi D., Ramamurthy N.S., Gruber B., Salo T., Kontinen Y.T.: Doxycycline Inhibits Neutrophil (PMN)-type Matrix Metalloproteinases in Human Adult Periodontitis Gingiva. *J. Clin. Periodontol* 1995; 22: 100-109.
2. Golub L.M., Cincio S., Ramamurthy N.S., Leung M., McNamara T.F.: Low-dose Doxycycline Therapy: Effect on Gingival and Crevicular Fluid Collagenase Activity in Humans. *J. Periodont Res* 1990; 25: 321-330
3. Golub L.M., Lee H.M., Greenwald R.A., Ryan M.E., Salo T., Giannobile W.V.: A Matrix Metalloproteinase Inhibitor Reduces Bone-type Collagen Degradation Fragments and Specific Collagenases in Gingival Crevicular Fluid During Adult Periodontitis. *Inflammation Research* 1997; 46: 310-319.
4. Saivain S., Houin G.: Clinical Pharmacokinetics of Doxycycline and Minocycline. *Clin. Pharmacokinetics* 1988; 15: 355-366.
5. Schach von Wittenau M., Twomey T.: The Disposition of Doxycycline by Man and Dog. *Chemotherapy* 1971; 16: 217-228.
6. Campistron G., Coulais Y., Caillard C., Mosser J., Pontagnier H., Houin G.: Pharmacokinetics and Bioavailability of Doxycycline in Humans. *Arzneimittel Forschung* 1986; 36: 1705-1707.

6.75"

CollaGenex, Inc.

INERT INGREDIENTS:
Microcrystalline Cellulose, NF
Magnesium Stearate, NF

See package insert for dosage
information.

Store at controlled room temperature
15°-30°C (59°-86°F).

NDC XXXXX-XXX-XX

Periostat™
Doxycycline Hyclate
Capsules USP

20 mg

100 Bottles X 100s

Manufactured for:
CollaGenex, Inc.
Newtown, PA 18940

Manufactured by:
AAI, Inc.
Wilmington, NC 28403

Exp:

Lot:

(Control No.)

CAUTION: Federal (U.S.A.) law prohibits
dispensing without a prescription.

4"

(ACTUAL SIZE)

4-0022

5.5"

CollaGenex, Inc.

NDC XXXXXX-XXX-XX

PeriostatTM
Doxycycline Hyclate
Capsules USP

20 mg

100 Capsules

INERT INGREDIENTS:

Microcrystalline Cellulose, NF

Magnesium Stearate, NF

See package insert for dosage
information.

Store at controlled room temperature
15°-30°C (59°-86°F)

Manufactured for:

CollaGenex, Inc.

Newtown, PA 18940

Manufactured by:

AAI, Inc.

Wilmington, NC 28403

Exp:

Lot:

CAUTION: Federal (U.S.A.) law prohibits
dispensing without a prescription.

(Control No.)

(TWICE SIZE)

For Readability Only

4-0020