

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
50-783**

Microbiology Review(s)

NDA#: 50-783
Periostat®
CollaGenex Pharmaceuticals, Inc.

Division of Anti-Infective Drug Products
Clinical Microbiology Review #1
Dental Consult for HFD 540

NDA#: 50-783
Date Completed: 12/20/00

Applicant:

Collagenex Pharmaceuticals, Inc.
41 University Drive
Newton, PA 18940

Contact Person:

Christopher Powala, Senior Director
Drug Development & Regulatory Affairs
215-579-7388

Therapeutic Type: Collengase Inhibitor

Providing for: Treatment of adult periodontitis

Product Name:

Proprietary: Periostat®
Established Name: Doxycycline hyclate tablets
Code Name/#'s: None
Chemical Name: 4-(demethylamino-1,4,4a,5,5a,6,11,12a-ocatahydro-3.5.10.12.12a-pentahydroxy-6methyl-1,11-diox-2-naphthacenecarboxamide monohydrochloride
Chemical formula (empirical): (C₂₂H₂₄N₂O₈•HCL)•C₂H O•H₂O
Molecular weight: 1025.89

Dosage form: Tablet

Strength: 20 mg of doxycycline

Route of administration: Oral

Dosage/Duration: 20 mg twice daily as an adjunct following scaling and root planing for up to 9 months

Dispensed:]

Initial Submission Dates:

Applicant submission date: 3/21/00

Received by CDER: 5/3/00

Received by reviewer: 5/20/00

Related Documents: NDA 50-744 (4/1/98), IND

NDA#: 50-783
Periostat®
CollaGenex Pharmaceuticals, Inc.

Remarks: This application is for a change in the dosage form of the drug from a capsule (20 mg) to a tablet (20 mg). The reader is referred to the microbiology review for NDA 50-744 that was for the original capsule dosage form for the microbiology review of this drug product.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

NDA#: 50-783
Periostat®
CollaGenex Pharmaceuticals, Inc.

INTRODUCTION:

The product Periostat® is used as an inhibitor of the collagenase activity of host cell response to periodontal infection. It is not used as an antibiotic to inhibit growth of bacteria associated with periodontal infection..

This application is for a change in the dosage form of the drug product Periostat® from a capsule containing 20 mg doxycycline to a tablet containing 20 mg doxycycline. The applicant has made no new microbiology claims for the product and thus has not changed the original label approved for the 20 mg doxycycline capsule.

Microbiology

This review will not be a comprehensive review of the product since it is only a request for a new dosage form. The reader is referred to NDA 50-744 (4/1/98) for this information. Since that review this Reviewer has not found any suggestions in the literature that the use of this product has been associated with permanent increases in tetracycline-resistance of the pathogens associated with periodontal disease or other bacteria in patients who have been treated with the product. The applicant has also not provided any information that this may be occurring. Therefore, this Reviewer concludes that there has not been any microbiology events that are detrimental to patients who have been treated with this product.

Pharmacokinetics/Bioavailability

These parameters are the most important in relation to the efficacy of this product. The applicant has provided information from a randomized, single-dose, 3- treatment, 3- period, 6-sequence crossover study to assess the effects of food on the pharmacokinetics of Periostat® (doxycycline hyclate tablets), 20 mg (NDA 50-744) (NDA 50-783, Vol. 1.1, pg. 1.1-088). This study was also done to assess the bioequivalence of the tablets compared with the approved Periostat® (doxycycline hyclate capsules), 20 mg (NDA 50-744) (NDA 50-783, Vol. 1.1, pg. 1.1-088).

The study included 20 healthy subjects, 11 females and 9 males, age 22 to 40 (mean 32.5) years. The pharmacokinetic parameters following a single 20 mg tablet were as follows:

C_{max} : 362 ± 101 ng/mL

T_{max} : 1.4 hr. (1.0 – 2.5 hr)

Cl/F 3.85 ± 1.3 L/hr.

$t_{1/2}$: 18.1 ± 4.85 hr

NDA#: 50-783
Periostat®
CollaGenex Pharmaceuticals, Inc.

It was observed that C_{max} was approximately 1.4 fold higher in women than in men, which is less than the 1.7 fold difference observed with the capsule (previously approved Periostat® labeling).

The results showed that the capsule and tablet formulations of doxycycline are bioequivalent; the 90% confidence interval for the ratio of means for both AUC and C_{max} fell within 80 % to 125%. A food effect was demonstrated. The 90% lower confidence limit for the ratio of means (fed to fasted) for AUC fell below 80%. The 90% lower confidence limit for the ratio of means (fed to fasted) for C_{max} fell below 70%. Food decreases the rate and extent of absorption and delays the time at which maximal plasma concentrations are reached.

Based on the fact that bioequivalence between the capsule and tablet was demonstrated the microbiology portion of the label requires no changes. The microbiology portion of the label for this dosage form (tablet) is the same as the label for the previously approved dosage form (capsule).

The microbiology portion of the package label as provided by the applicant in NDA 50-783 (Vol. 1.1, pg. 1.1-038, dated 3/31/00) is approved.

JS
12-21-00

Frederic J. Marsik, Ph.D.
Review Microbiologist

Cc: Original NDA 50-783
HFD-520 Divisional File
HFD-540 Divisional File
HFD-520/Micro/F. Marsik
HFD-540/DO/J. Kelsey
HFD-540/CSO/F. Cross

Concurrence Only

JS
12-22-01

HFD-520/TLMicro/AT Sheldon, Jr., Ph.D.
RD & Final Initiated 12/21/00 ATS

JS
HFD-520/Dep/Dir/L Garvilovich, MD

12-27-00

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
DENTAL CONSULT

AUG 3 1998

SUBMISSION TYPE: DOCUMENT DATE: CDER DATE: ASSIGNED DATE:
NDA 50-744 3/31/98 4/1/98 7/22/98
LABELING

Related documents: Microbiology Review - 2/19/97
Microbiology Review - 4/8/98

The following is suggested wording for the microbiology portion of the Periostat label.

MICROBIOLOGY:

DRAFT

PRECAUTIONS:

DRAFT

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.

DRUG INTERACTIONS: 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.

 /S/ 7/28/98
FREDERIC J. MARIK, Ph.D.
Microbiology Reviewer

cc: Original 50-744

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
DENTAL CONSULT

SUBMISSION TYPE: DOCUMENT DATE: CDER DATE: ASSIGNED DATE:
NDA 50-744 3/31/98 4/1/98 7/22/98
LABELING

/S/

HFD-520 Division Files
HFD-540/DO/J. Kelsey
HFD-540/DO/C. Gilkes
HFD-540/Chem/J. Vidra
HFD-540/Pharm/Tox/N. See
HFD-540/Stat/C. Dixon
HFD-540/Biopharm/D. Wang
HFD-540/CSO/R. Blay
HFD-520/Micro/ F. Marsik

Concurrence Only

HFD-520/Dep/Dir/L. Gavrilovich

HFD-520/TLMicro/A. T. Sheldon

8/3/98
8/3/98

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
DENTAL CONSULT

5/2/98

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
ND 50-744 3/31/98 4/1/98 4/8/98

NAME AND ADDRESS OF APPLICANT:

CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newton, PA 18940

CONTACT PERSON:

Christopher V. Powala
Director, Drug Development & Regulatory
Affairs
CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newton, PA 18940
Telephone #: 251-579-7619

DRUG PRODUCT NAME:

Proprietary:	Periostat™
Nonproprietary:	Doxycycline Hyclate Capsules USP
Code Name/#'s:	None
Chemical Name:	4-(dimethylamino-1,4,4a,5,5a,6,11,12a- -ocatahydro-3.5.10.12.12a-pentahydroxy- 6-methyl-1,11-dioxo-2- naphthacene-carboxamide monohydrochloride

INDICATIONS:

Treatment of Adult Periodontitis

DOSAGE FORM:

Capsule

STRENGTH:

20mg

ROUTE OF ADMINISTRATION:

Oral

RELATED DOCUMENTS:

IND [REDACTED]
IND [REDACTED]
AADA 62-374
AADA 62-839

REMARKS/COMMENTS: - This review is of the answers by the applicant to the microbiology questions asked of the company in the initial review dated 2/19/97 (see

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
DENTAL CONSULT

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ND 50-744	3/31/98	4/1/98	4/8/98

attached pages 1-10 of original review). The initial review should be consulted for the "Spectrum of Activity and Mechanism of Activity", "Mechanisms of Resistance", "Epidemiology", "Clinical Microbiology", "Microbiology Pharmacokinetics", "Developments of Resistant Bacteria", "Alterations in the Microbial Flora", and "References".

QUESTION 1: "The potential for the development of tetracycline-resistant bacteria appearing in the gastrointestinal tract and/or the genitourinary tract in individuals taking Periostat needs to be addressed."

This question was asked because the applicant had not done fecal stool cultures on patients being treated with Periostat or placebo controls to look for the development of resistant bacteria.

The applicant has responded to this question by noting that they had submitted data in the original submission from studies looking for the development of resistant bacteria in the oral microflora of Periostat and placebo treated patients. These studies had been reviewed by this reviewer and the results were found to be consistent with the published literature and were acceptable. The applicant now states that because the organisms in the microbial flora of the oral cavity and the gastrointestinal tract are similar and their initial studies only detected a transient development of resistant bacteria in the oral cavity permanent colonization of the intestinal tract with resistant bacteria is very unlikely to occur. This reviewer after review of the published and in house data submitted (Study 5732.11H a multi-center, double-blinded controlled study of 78 patients receiving 20mg doxycycline hyclate bid to assess development of resistant bacteria) by the applicant concurs with the applicant that the potential for the gastrointestinal tract to become permanently colonized with resistant bacteria is highly unlikely. Even transient colonization by such bacteria is highly unlikely and if it were to occur has a extremely minimal chance of creating a medical problem. As for the potential that resistant bacteria may colonize the genitourinary tract of individuals treated with Periostat this reviewer believes that such a probability also is extremely low. One reason being that the dosage of Periostat is one-fifth to one-tenth that of the dosage normally given therapeutically treat bacterial infection. With such a low dose the potential for resistant bacteria to occur in the genitourinary tract has a very low possibility. A second reason being that in the female bacteria are often transferred from the intestinal tract to the genitourinary tract where colonization may occur. Since it is felt that the potential for the intestinal tract to be colonized for any extended period of time with resistant bacteria in patients treated with Periostat is minimal then the potential for transfer to the genitourinary tract is

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
DENTAL CONSULT

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ND 50-744	3/31/98	4/1/98	4/8/98

extremely low. Since the female because of her anatomy is more likely to be colonized colonization of the male is even less likely to occur.

QUESTION 2: "The potential for alterations in the microflora (e.g., overgrowth of yeast) or reduction in the colonization resistance of the gastrointestinal tract and/or genitourinary tract needs to be addressed."

The applicant in addressing this question states that their studies did not show any overgrowth in the oral cavity with any bacteria or yeasts in patients treated with Periostat. Thus they feel that such overgrowth is unlikely to occur in the intestinal tract or the genitourinary tract. They further state that their statistical analysis (Chi-Square test) showed no significant differences with regard to frequency of adverse events in any category within the digestive or genito-urinary system between any of the Periostat groups and placebo controls. While not direct evidence that colonization is or is not occurring such an analysis suggests that probably no medical problem is occurring due to colonization or overgrowth of bacteria or fungi.

The initial review of the data submitted by the applicant did not uncover any documentation of any overgrowth of the oral cavity by any particular bacteria or yeasts in patients treated with Periostat. The applicant in addressing this questions reiterates this again and notes that Periostat which is given at a dose of 20mg bid showed no clinically meaningful effect against *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, or *Porphyromonas gingivalis*; or on total anaerobic, *Fusobacteria*, or *Actinomyces* counts. Furthermore there was no detectable shift from Gram-positive to Gram-negative flora, nor was there any replacement or major shift of any of the 40 obligate anaerobes compromising the predominant flora. This evidence is consistent as noted in the original review that Periostat is not acting like an antibiotic to eliminate periopathogenic organisms but probably as an inhibitor of collagenase released by the cells of the diseased host. Because of the fact that Periostat is administered at one-tenth to one-fifth of the dose of doxycycline used to treat bacterial infections the potential for a major change in the gastrointestinal or genitourinary tract flora is in the opinion of this reviewer unlikely to occur and if it does occur it would most likely be transient and its potential to cause medical problems is unlikely to occur.

The above remarks as they relate to development of resistant bacteria, reduction in the colonization resistance of the gastrointestinal and genitourinary tract, and overgrowth of bacteria or yeasts address only the immunocompetent population of patients. Not enough data was presented by the applicant in any study in relation to these areas in the

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
DENTAL CONSULT

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
ND 50-744 3/31/98 4/1/98 4/8/98

immunocompromised patient. Thus this reviewer suggests that the following statements be incorporated under PRECAUTIONS in the labeling:

Draft

"The safety and effectiveness of Periostat has not been established for the treatment of periodontitis in patients with coexistent oral candidiasis."

CONCLUSION:

The answers given by the applicant to the original microbiology concerns have been satisfactorily addressed. As noted in this review a statement in the labeling under "PRECAUTIONS" is required since the issues raised have not been adequately addressed by the applicant in immunocompromised patients.


FREDERIC J. MARSIK, Ph.D.
Microbiology Reviewer

4/17/98

cc: Original 50-744
HFD-520 Division Files
HFD-540/DO/J. Kelsey
HFD-540/Chem/J. Vidra
HFD-540/Pharm/Tox/N. See
HFD-540/Stat/C. Dixon

Concurrence Only

HFD-520/Dep/Dir/L. Gavrilovich
HFD-520/TLMicro/A. T. Sheldon

RD 5/4/98 AS
Final 5/7/98

16 5/2/98

RF 5-15-97

MAY 15 1997

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

PAGE 1 OF 10

NDA#:50-744(20-642) MICROBIOLOGY REVIEW:#1 REVIEW DATE: 2/19/97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA	8/30/96	8/30/96	1/15/97

NAME & ADDRESS OF APPLICANT: COLLAGENEX PHARMACEUTICALS
301 SOUTH STATE STREET
NEWTON, PA 18940

CONTACT PERSON: Christopher Powala
Director, Drug Development
And Regulatory Affairs
Phone Number: 215-579-7388
Fax Number: 215-579-8577

DRUG PRODUCT NAME:

Proprietary:	PERIOSTAT
Nonproprietary:	Doxycycline Hyclate Caps (20mg)
Code names/#'s:	NA
Chemical Type:	Tetracycline
Therapeutic Class:	S3

ANDA Suitability Petition/DES/Patent Status:

US Patent 4,704,383 (expires 11/3/2004) The Research Foundation of State University of New York

US Patent 4,666,987 (expires 5/19/2004) The Research Foundation of State University of New York

US Patent 34,656(reissue) The Research Foundation of State University of New York

PHARMACOLOGICAL CATEGORY/INDICATION(S):
Tetracycline/Adult Periodontal Disease
Mechanism of Action: Inhibitor of Collagenase Activity

DOSAGE FORM: Capsules
STRENGTH: 20mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA 50-744(20-642)
COLLAGENEX PHARMACEUTICALS
PERIOSTAT CAPSULES

PAGE 2 of 10

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See Submission Vol.2, Section 2.1. The description in this section of the NDA is of a typical doxycycline hyclate moiety as described by the USP(1).

SUPPORTING DOCUMENTS: NA

RELATED DOCUMENTS: IND[]IND[]

CONSULTS: NA

REMARKS/COMMENTS:

This submission is for the use of doxycycline as an inhibitor of collagenase activity of host cell response to infection **not** as an antibiotic to treat bacterial infection.

CONCLUSIONS & RECOMMENDATIONS:

The data submitted by the applicant for the use of low-dose doxycycline not as an antibiotic but rather as an inhibitor of collagenase is in agreement with the published literature (11,12). The use of low-dose tetracycline while having a potential to bring about populations of bacteria resistant to tetracyclines as well as other antimicrobials and to cause alterations in the microflora of the gastrointestinal tract presents no more of a potential health threat than the use of tetracyclines at higher doses for the treatment of bacterial infections.

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA 50-744(20-642)
COLLAGENEX PHARMACEUTICALS
PERIOSTAT CAPSULES

PAGE 3 OF 10

INTRODUCTION: This review is of the product Periostat, which is doxycycline, and its use *not* as an antibiotic for the treatment of adult periodontitis but as an inhibitor of the collagenase produced by host cells in response to periodontal infection.

PRE-CLINICAL EFFICACY

SPECTRUM OF ACTIVITY AND MECHANISM(S) OF ACTION:

Periostat is a modified tetracycline known as doxycycline. The tetracycline class of antibiotics have a broad spectrum of activity against microorganisms including facultative, aerobic and anaerobic bacteria(2). This class of antibiotics is bacteriostatic with their main mechanism of action being to inhibit protein synthesis(2).

MECHANISMS OF RESISTANCE:

Tetracycline resistance is widespread among bacteria(3). This resistance may be do to: 1) limiting access of tetracycline to the ribosomes, 2) altering the ribosome to prevent effective binding of tetracycline, or 3) producing tetracycline-inactivating enzymes(4). Combinations of these mechanisms of resistance have been described (4).

Fourteen determinants coding for tetracycline resistance in bacteria are currently known. Of these tet(A-E), tet(G), tet(K), tet(L), and tet(P) encode proteins that mediate an efflux mechanism for tetracycline and the tet(M), tet(O), and tet(Q) genes encode proteins that prevent tetracycline from attaching to the ribosomes. A third class of genes, including tet(X), encode proteins mediating the breakdown of tetracycline. The mechanism of the tet(F) determinant has not been conclusively determined(5). All but classes C, D, K, and L confer resistance to minocycline(5). Tet(M) confers resistance to both tetracycline and minocycline as well as all second generation tetracycline analogs(6). Many of the tetracycline genes from gram-negative

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA 50-744(20-642)
COLLAGENEX PHARMACEUTICALS
PERIOSTAT CAPSULES

PAGE 4 OF 10

bacilli are located on plasmids and are readily transmissible within and between species(5). Other transmissible tetracycline-resistance genes particularly those found in gram-positive organisms are located on transposable chromosomal elements that can be transferred between organisms by conjugation(7).

EPIDEMIOLOGY

Development of resistance to tetracycline among organisms isolated from the periodontal pockets is frequently seen in patients with periodontal disease treated with tetracycline(8). The presence of tetracycline-resistant organisms in the oral microflora of individuals with no periodontitis and not receiving tetracycline has also been described. These tetracycline-resistant bacteria have been shown to constitute between 2 - 6% of the viable count in subgingival samples(9).

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
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DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA 50-744(20-642)
COLLAGENEX PHARMACEUTICALS
PERIOSTAT CAPSULES

PAGE 5 OF 10

MICROBIOLOGY REVIEW

MICROBIOLOGY DATA SUBMITTED: (volumes 2.1, 2.2, 2.12, 2.13, 2.18,
2.19)

DOSAGE: 20mg b.i.d.

PHARMOKINETICS/BIOAVAILABILITY:

Plasma - Mean peak concentration

790 +/- 285ng/mL.

Average steady state concentration 482 +/-
142ng/mL.

Note: Doxycycline has been shown to concentrate in the gingival crevicular fluid two to three times the concentration found in plasma over the same time interval(10). This is believed in part to be due to doxycycline's affinity for calcium containing substances(10).

Elimination - Urine 60% within 92hr.

Stool 30% over 5 days

CLINICAL EFFICACY

CLINICAL MICROBIOLOGY:

The uniqueness of this NDA submission is that the applicant is not claiming Periostat, which is doxycycline, as an antibiotic to eliminate periopathogenic organisms but rather as an inhibitor of collagenase released by the cells of the diseased host. Collagenase has been shown to cause tissue as well as bone damage(11). Tetracyclines have been shown to inhibit the activity of collagenase(10,12). This activity does not appear to be related to the antibiotic's antibacterial properties since modified tetracyclines with no antibacterial activity have been shown to exhibit anticollagenase activity(13).

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA 50-744(20-642)
COLLAGENEX PHARMACEUTICALS
PERIOSTAT CAPSULES

PAGE 6 OF 10

The non-claim of Periostat as an antibiotic is based on the daily dose of 20mg twice a day. This dose is well below the usual dosage of doxycycline(i.e. 200mg first day followed by 100mg for the next 7 to 10 days) given to eradicate bacteria at the site of infection(14).

OBJECTIVES OF REVIEW:

The intent of this review is not to assess the activity of doxycycline against periopathogenic bacteria. Therefore this review will not address "Isolates/relevance to approved indications", "Disk content studies", "MIC broth/agar dilution comparisons", "MIC/Disk diffusion Correlation Studies", "Quality Control Studies(MIC and Disk diffusion)", "Anaerobe studies", "Haemophilus and Neisseria Studies", "Bacteriological Efficacy", "Isolates Approved" and "Establishment of Interpretive Criteria".

This review will attempt to: 1) verify the summary presentation of the study data; 2) assess from the study data and from the published literature if the use of this product could potentially cause the occurrence of abnormally high concentrations of antibiotic-resistant bacteria in patients being treated with the product, and 3) whether there could be an alterations in the microbial ecology of various anatomical sites of the patient in such a way as to bring about adverse side effects.

STUDIES SUBMITTED:

Three(3) studies were conducted to address the issues of: 1) antimicrobial activity, and 2) assessment of bacterial resistance.

Data for different dosage regimens was submitted. The applicant is applying for a regimen of 20mg b.i.d. All microbiology comments in this review are based on the 20mg b.i.d. regimen.

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA 50-744(20-642)
COLLAGENEX PHARMACEUTICALS
PERIOSTAT CAPSULES

PAGE 7 OF 10

MICROBIOLOGY PHARMOKINETICS:

The mean Cmax levels for doxycycline normally required to eradicate infecting organisms is $>1\text{mcg/mL}$ (15). While approximately 23% of the subjects given Periostat had Cmax levels exceeding the threshold effect of 1mcg/mL , the mean Cmax levels did not exceed 1mcg/mL .

The antimicrobial activity of Periostat was studied by characterizing the microbial flora of the gingival crevices of study patients at baseline and after 18 months of treatment with Periostat. These studies were done using either DNA probes or culture techniques to detect and quantitate organisms known to be associated with periodontal disease as well as those which are considered to be part of the "normal" microbial flora(16). None of the studies demonstrated any obvious changes in the distribution of Gram-positive or Gram-negative morphotypes isolated at baseline and after treatment. There were, however, some reductions in the numbers of certain bacteria in those individuals receiving Periostat. No overgrowth by opportunistic microorganisms such as the yeast was noted in any of the studies. Based on the "MICROBIOLOGY PHARMOKINETICS" and the characterization of the microbial flora studies Periostat given according to the applied for dosage regimen does not seem to act as an antibiotic.

DEVELOPMENT OF RESISTANT BACTERIA:

Studies submitted addressing the development of resistant bacteria at the site of infection showed a transient increase of tetracycline resistance in the marker organisms *Actinomyces viscosus* and *Fusobacterium nucleatum*. The increases occurred at 12 months for *A. viscosus* and 18 months for *F. nucleatum*. In both cases baseline values returned by 12 months for *A. viscosus* and 6 months for *F. nucleatum* post therapy. No cross resistance to ampicillin, benzylpenicillin, cefoxitin, erythromycin, or metronidazole were noted in the marker organisms *A. viscosus* or *F. nucleatum* during the studies. The data submitted with this

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA 50-744(20-642)
COLLAGENEX PHARMACEUTICALS
PERIOSTAT CAPSULES

PAGE 8 OF 10

application is consistent with the published literature which indicates that resistant populations of bacteria do not permanently develop as a result of treating adult periodontitis with tetracycline(17,18).

ALTERATIONS IN THE MICROBIAL FLORA:

No data were submitted addressing the issues of development of tetracycline-resistant bacteria in the gastrointestinal tract, genito-urinary tract or other body sites of individuals receiving Periostat.

No data were submitted in relation to the gastrointestinal tract specifically addressing alterations in the microflora of the gastrointestinal tract such as: 1) overgrowth of already present microorganisms such as yeast and *Clostridium difficile*; or 2) reduction in colonization resistance.

REFERENCES

1. USP Dictionary. 1996. Doxycycline hyclate USP. USP dictionary of USAN and International Drug Names. US Pharmacopieal Convention, Inc., Rockville, MD.
2. Standiford, H.C. 1995. Tetracyclines and chloramphenicol, p. 306-310. In G. L. Mandell, J. E. Bennett, R. Dolin(ed.), Principles and Practice of Infectious Diseases, 4th ed., Churchill Livingstone, NY.
3. Levy, S.B. 1988. Tetracycline resistance determinants are widespread. ASM News 54:418-421.
4. Speer, B., N.B. Shoemaker, and A.A. Salyers. 1992. Bacterial resistance to tetracycline; mechanisms, transfer, and clinical significance. Clin. Microbiol. Rev. 5:387-399.
5. Olsvik, B., I. Olsen, F. Tenover. 1994. The tet(Q) gene in

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA 50-744(20-642)

PAGE 9 OF 10

COLLAGENEX PHARMACEUTICALS

PERIOSTAT CAPSULES

bacteria isolated from patients with refractory periodontal disease. Oral Microbiol. and Immunol. 9:251-255.

6. LaCroix, J., and C.B. Walker. 1995. Detection and incidence of the tetracycline resistance determinant tet(M) in the microflora associated with adult periodontitis. J. Periodontol. 66:102-108.

7. Clewell, D.B., S.E. Flannagan, and D.D. Jaworski. 1995. Unconstrained bacterial promiscuity: the Tn 916 - Tn 1545 family of conjugative transposons. Trends in Microbiol. 3:229-236.

8. Magnusson, I., R.G. Marks, W.B. Clark, et al. 1991. Clinical, microbiologic and immunological characteristics of subjects with "refractory" periodontal disease. J. Clin. Periodontol. 61:686-691.

9. Fiehn, N.E., and J Westergard. 1990. Doxycycline-resistant bacteria in periodontally diseased individuals after systemic doxycycline therapy and in healthy individuals. Oral Microbiol. and Immunol. 5:219-222.

10. Sorsa, T., V.J. Uitto, V.J. Suomalainen, et al. 1988. Comparison of interstitial collagenases from human gingival sulcular fluid and polymorphonuclear leukocytes. J. Periodontol. Res. 23:386-393.

11. Golub, L.M., N.S. Ramamurthy, and T.F. McNamara. 1991. Tetracyclines inhibit connective tissue breakdown: New therapeutic implications for an old family of drugs. Critical Rev. in Oral Biol. and Med. 2:297-322.

12. Seymour, R.A., and P.A. Heasman. 1995. Tetracyclines in the management of periodontal disease. J. of Clin. Periodontol. 22:22-35.

13. Golub, L.M., T.F. McNamara, G.D. D'Angelo, et al. 1987. A

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NDA 50-744(20-642)

PAGE 10 OF 10

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non-bacterial chemically modified tetracycline inhibits mammalian collagenase activity. J. of Dental Res. 66:1310-1314.

14. Vibramycin(doxycycline). 1996. Physician's Desk Reference. Medical Economics Data Production Co., Montvale, NJ.

15. Goodson, J.M. 1994. Antimicrobial strategies for treatment of periodontal diseases. Periodontology 2000. 5:142-168.

16. Moore, W.E.C., and L.V.H. Moore. 1994. The bacteria of periodontal diseases. Periodontology 2000. 5:66-77.

17. Greenstein, G. 1995. Bacterial resistance to tetracyclines. J. of Periodontol. 66:925-932.

18. Crout, R.J., H.M. Lee, K. Schroeder, et al. 1996. The "cyclic" regimen of low-dose doxycycline for adult periodontitis: A preliminary study. J. of Periodontol. 67:506-514.

[*man / S / man*]
Frederic J. Marsik, Ph.D.
Microbiology Reviewer.

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HFD-520 Division File
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[*JS*] *5/15/97*
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70 5/15/97

16 5/21/97

Electronic Mail Message

Date: 1/12/01 1:57:05 PM
From: Albert Sheldon (SHELTON)
To: Frank Cross, Jr. (CROSSF)
To: Albert Sheldon (SHELTON)
Subject: Re: NDA 50-783: Pedioostat

Neither of these sections are addressed by Dr. Marsik in his review.
This leads me to conclude that we have no issues in these sections.

AL

>Hi Al,

>

> Thank you for letting me know. I was also wondering about the
>Precautions Section and the Drug Interactions Section as well.

>

> Please let me know when you get a chance.

>

>

>

>

Thanks,

>

Frank

>

>

>Frank,

-->>>I read Dr. Marsik's final review and he states "The microbiology
>portion
>>>>of the package label as provided by the applicant in NDA 50-783
(Vol.

>>>>1.1, pg. 1.1-038, dated 3/31/00) is approved."

>>>>

>>>>Thus, if the microbiology portion of the PI you sent to me by e-mail
>is

>>>>identical to the microbiology portion of the PI originally submitted
>to

>>>>Dr. Marsik, you may conclude that it is satisfactory. I did not see
>the

>>>>original PI so I can not make a comparison to the PI that was
>recently

>>>>provided.

>>>>

>>>>I did read the PI appended and conclude that the statements made are
>>>>truthful and accurate since the doxycycline is not being touted as
an

>>>>antimicrobial due to the concentration used. Thus, I find the label
>>>>satisfactory.

>>>>AL