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DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

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NDA#: 50-744 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
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NEWTON, PA 18940CONTACT PERSON: Christopher Powala
Director, Drug Development
And Regulatory Affairs
Phone Number: 215-579-7388
Fax Number: 215-579-8577DRUG PRODUCT NAME:
Proprietary: PERIOSTAT
Nonproprietary: Doxycycline Hyclate Caps (20mg)
Code names/#'s: NA
Chemical Type: Tetracycline
Therapeutic Class: S3ANDA Suitability Petition/DNS/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 YorkPHARMACOLOGICAL CATEGORY/INDICATION(S):
Tetracycline/Adult Periodontal Disease
Mechanism of Action: Inhibitor of Collagenase ActivityDOSAGE FORM: Capsules
STRENGTH: 20mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx

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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.

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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 minocyclins(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

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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**

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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 † within hr.
Stool † over 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).**

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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.

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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

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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.

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