CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-744

MEDICAL REVIEW(S)

JUL 27 1998

DENTAL OFFICER'S REVIEW AND SUMMARY OF NDA 50-744 (STUDY NUMBER 5732.11 H)

Drug: Periostat (Doxycycline hyclate 20 mg. capsules)

Sponsor: CollaGenex Pharmaceuticals Inc.
301 South State Street
Newtown, PA 18940

Submission Date: 3/31/98
Received Date: 4/1/98
Review Date: 6/18/98
Project Manager: Roy Blay, Ph.D

Reviewer: Clarence Gilkes, DDS

Pharmacologic Category: Anti-periodontitis (not antimicrobial at this dosage)

Proposed Indication:

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

Administrative Review:

The IND for this drug was IND It was originally submitted July 24, 1989 by Johnson and Johnson Consumer Products, Inc. In February 1992, Johnson and Johnson transferred the IND to CollaGenex, Inc. The prior submission of this NDA 50744 received a not approvable letter August 27, 1997. A meeting with the sponsor was held on November 17, 1997 during which the not approvable decision was discussed. After further consideration of the NDA and of the material presented at the meeting, it was decided that the application remain not approvable. A letter to that effect was issued December 31, 1997. Another meeting with the sponsor was held March 12, 1998 at which time it was agreed that the Agency would review the results of Study "H" as evidence for efficacy.

Doxycycline is approved as an antimicrobial at 100 mg. BID.

Formulation:

The formulation to be marketed is the same formulation that was utilized in all of the pivotal studies.

Mechanism of Action:

The mechanism of action defined by the sponsor is that the doxycycline reduces the elevated collagenase activity in the gingival crevicular fluid of patients with adult periodontitis.

Preclinical Pharmacology: See Pharmacologist's Review dated January 4, 1997.

Clinical Study:

Study Number: 5732.11 H

Title of Study: " A 9 Month, Multicenter, Double-Blind, Placebo-Controlled Trial Evaluating The Effect of Periostat (20 mg. doxycycline hyclate capsules) BID in Conjunction with Scaling and Root Planing Versus Placebo BID in Conjunction with Scaling and Root Planing on Attachment Level and Pocket Depth in Patient's With Adult Periodontitis."

Study Design:

This was a multicenter, placebo-controlled, double-blind, parallel study with a 9 month scheduled duration of treatment. Five university dental centers enrolled patients.

Investigators and Sites:

Dr. Jack Caton, Eastman Dental Center
Dr. Sebastian Ciancio, SUNY at Buffalo, New York
Dr. Richard Crout, West Virginia University
Dr. Arthur Hefti, University of Florida
Dr. Alan Polson, University of Pennysylvania

Inclusion Criteria:

1. Age Range: 30-75 years
2. Sex: Male and Female
   Female patients had to be postmenopausal (for at least two years) surgically sterilized or utilizing one of the following methods of birth control throughout the trial; IUD diaphragm, Depo Provera, Norplant or oral contraceptive with condom.
3. Patients selected for inclusion in this study had to be clinically diagnosed as having periodontitis in two tooth sites in each of two quadrants in the mouth.
4. Specific Requirements for the two tooth sites:
   - only 1 site per tooth is permitted;
   - each of the two sites had to have a pocket depth of ≥ 5 to ≤ 9 mm;
   - each of the two sites had to have an attachment level ≥ 5 to ≤ 9 mm;
   - it is preferable to select only 1 interproximal site per adjacent pair of teeth;
   - the two sites had to be inflamed at the baseline examination. The sites had

to be categorized as inflamed if they exhibit bleeding upon probing.

Exclusion Criteria:

1. Pregnant women or women of child-bearing potential who were not using an adequate form of birth control as described previously
2. Nursing women
3. Patients with a known hypersensitivity to tetracyclines
4. Patients on clinically significant concomitant drug therapy
5. Patients with diabetes mellitus
6. Patients with systemic infection
7. Patients who required prophylactic antibiotic coverage for routine dental therapy
8. Patients receiving antibiotics (excluding tetracyclines) within 6 weeks of baseline
9. Patients requiring chronic (>14 days) antibiotic therapy
10. Patients who had used tetracyclines within 90 days of baseline
11. Patients with serious medical illness, such as kidney or liver disease
12. Patients who had received a dental prophylaxis or periodontal treatment within 90 days of the baseline visit
13. Patients who had participated in a periodontal clinical trial within the past six months

Reviewer Comments:

The criteria listed above were from the sponsor's submission to IND dated May 16, 1996. It appears from the NDA 50744 submission dated March 31, 1998, that the sponsor did indeed adhere to each listed criteria.

Number of Subjects:

Study 5732.11H enrolled 190 patients. There were 94 in the scaling and root planing plus 20 mg. of doxycycline BID group and 96 in the scaling and root planing plus placebo BID group. 171 patients completed the study. 19 patients discontinued the study for reasons, such as, non-compliance, withdrawal of consent and one patient withdrew on the third day due to dizziness thought to be related to Periostat.

Primary Efficacy Variables:

1. Average change in attachment level(cALv) in mm. from baseline
2. Average change in pocket depth (PD) in mm. from baseline

Measurements were taken at the baseline 3,6 and 9 month visits. The University of North Carolina, number 15 (UNC 15) manual probe was used to measure attachment level and pocket depth.

Study Plan:

Patients were recruited to the study by the investigators. Once recruited, patients had to undergo a screening examination to determine whether they qualified for entry to the study. At the screening visit, patients had to complete a health history questionaire to insure that they medically qualify for participation in the study. The clinician reviewed the information and Medication History Forms with the patient. Patients were advised of their role in this study and asked to sign an informed consent. No patient was admitted to the study until the Informed Consent form was signed. After giving consent, patients had to undergo an oral pathology examination. After completion of the oral pathology examination, patients were given a full mouth manual probing to determine their periodontal status. To qualify for this study patients had to have two tooth sites with pocket depths $\geq$5mm to $\leq$9mm and attachment levels $\geq$5mm to $\leq$9mm in each of two quadrants. For this purpose, a periodontal pocket is defined as an abnormal extension of the gingival crevice caused by migration of the junctional epithelium along the root as the periodontal ligament is detached by a disease process.

After establishing that patients qualified for the study, the patients were randomly placed in one of two treatment groups. All patients had to undergo SRP in two qualifying quadrants. Each treatment group took either Periostat 20 mg. or placebo twice daily for nine months. Placebo capsules were the same size and color as the Periostat capsules but did not contain any doxycycline. The placebo treatment group took one placebo capsule in the morning and one in the evening for nine months. Those patients receiving Periostat took one capsule in the morning and one in the evening for nine months. All patients were evaluated for attachment level, pocket depth, bleeding on probing, gingival index and safety every three months during the nine months of double-blind treatment. Patients experiencing an attachment loss of $\geq$2mm (compared with baseline) had to have that site treated locally with mechanical therapy. Various laboratory periodontal disease indicators and blood parameters were recorded at baseline and during the entire study.

After three months, the patient returned for an examination. They had to return any unused medication and were given a new supply of medication for the next three months. Patients returned for examination every three months (6 and 9), each time returning unused medication and being dispensed a new supply of study drug. Throughout the study, telephone calls were made every 4 weeks to each patient to monitor for adverse events and to ensure compliance with the protocol. The 3, 6 and 9 month visits were based on a 30.5 day month. All subsequent

examinations took place within 10 days of the 3, 6 and 9 month anniversary. Full mouth manual probing measurements were obtained at months 3, 6 and 9 as was the modified Gingival Index and Bleeding on Probing. An oral pathology examination was also performed at the 3, 6 and 9 month visits. At the two preselected investigational centers, subgingival plaque samples were obtained for analysis of oral flora and antibiotic susceptibility at the 9 month visit. Blood samples were drawn from each patient for CBC and Chem 20 analysis at the 3, 6 and 9 month visits. Pregnancy tests were performed on women of childbearing potential at the 3, 6 and 9 month visits. All patients had to undergo a routine dental prophylaxis at the 9 month visit. Patients completed the study after finishing the 9 month examination.

Efficacy analyses at each post-baseline visit were based on mean changes from baseline values in Alv, PD, BOP, GI and the proportion of sites/patient with Als (or PD increase) $\geq$2 mm and $\geq$3 mm. In addition, the proportion of patients with at least 1 site with Als (or PD increase) $\geq$2 mm and $\geq$3 mm were compared between groups. Because of the large number of tooth sites per patient and the clinical relevance of those relatively few sites per patient which showed large degrees of deterioration, a worst site (WS) analysis was performed in which the four sites for each patient which showed the greatest deterioration or least improvement from baseline were analyzed separately. First, the change from baseline was calculated for each of the four sites, then the average change from baseline was calculated for each patient which was analyzed using the models described above at each post-baseline visit. In addition, the proportion of patients terminating prematurely due to lack of efficacy were compared statistically.

Any adverse event, including both observed or volunteered problems, complaints or symptoms, were to be recorded on the Adverse Event CRF. The need to capture this information was not dependent upon whether the adverse event was associated with the use of the study medication. Adverse events resulting from concurrent illnesses or reactions to concurrent medications were also recorded. Each adverse event was evaluated for duration, intensity and relationship with the study medication or other causes. The intensity of the adverse event was characterized as mild, moderate or severe.

Reviewer's Comments:

The sponsor accepted the Agency's suggestions regarding their study design. Scaling and root planing were performed in both the Periostat and placebo groups. This procedure replaced supra gingival scaling.

The sponsor's earlier studies, E, F and G included dosages of 10 mg of doxycycline Q. D., 20 mg of doxycycline Q.D. as well as the test product of 20 mg of doxycycline B.

I. D. This enabled the sponsor to arrive at the most effective dose and schedule.

Schedule of Visits

	Screen	Base-line	Month 3	Month 6	Month 9
Inclusion/Exclusion criteria	X				
Medical history	X				
Demographics collected	X				
Medications within 30 days recorded	X				
Prior/concommitant medications	X	X	X	X	X
Last visit to dentist?	X				
Oral hygiene practice recorded	X				
Tobacco use recorded	X				
Two quadrants SRP'd		X			
Randomization to treatment		X			
Serum pregnancy testing	X		X	X	X
Dispense study drug		X	X	X	
Dental Prophylaxis					X
PD, cALv, BOP - full-mouth	X	X	X	X	X
Ginigval Index - full-mouth	X	X	X	X	X
Adverse events	X	X	X	X	X
Laboratory tests	X	X	X	X	X
Oral patahology	X	X	X	X	X
Vital signs	X	X	X	X	X
Plaque samples		X	X	X	X
Note: PD=Pocket Depth; cALv=Clinical Attachment Level; BOP=Bleeding-on-probing; SRP= Scaling and root planing.					

The baseline visit occurred within two weeks after the Screen visit. The Months 3, 6 and 9 visits occurred approximately 3, 6 and 9 months following the Baseline visit.

Demographics:

One hundred and ninety patients were enrolled in Study H. The analysis of demographic characteristics was on the Intent-To-Treat-Population of 90 patients in the Periostat group and 93 patients in the placebo group. The only demographics that the sponsor addressed in analyzing Study H were age, sex and race.

The mean age for the Periostat group was 44.5 years. The range was years of age. The mean age of the placebo group was 47 years. The range was years of age. There were 44 males in the Periostat group and 50 in the placebo group. or females there were 46 in the Periostat group and 43 in the placebo group. The Periostat group was 80% Caucasian and the placebo group was 68% Caucasian. Most of the remaining patients were African American. There were 17% in thePeriostat group and 26% in the placebo group. Asians were 3% of the Periostat group and 2% of the placebo group. There were no Hispanics in the Periostat group and 4 in the placebo group.

Reviewer's Comments:

The groups were balanced, therefore the differences in racial distribution between treatment groups had no bearing on efficacy or safety results. The sponsor did not stratify patients according to their smoking habits.

Results: The efficacy analyses on the cALv, PD, and BOP data were performed on tooth sites stratified by disease severity as measured by Baseline PD (0-3 mm, 4-6 mm ≥7mm).Tooth sites with Baseline PD of 0-3 mm were considered normal or non-diseased, tooth sites with Baseline PD of 4-6 mm were considered mildly to moderately diseased and tooth sites with PD ≥7 mm were considered severely diseased. For sites within each stratum, the average change in cAlv, the average change in PD and the percentage of sites experiencing BOP were calculated for each patient at each visit.

Summary of Efficacy Results; Attachment Level, Pocket Depth and Bleeding-on Probing

Manual Probe Measurements			
Parameter	Baseline Pocket Depth		
	0-3 mm	4-6 mm	≥ 7 mm
Number of Patients	90	90	79
Mean change ALv at 9 months[1] Periostat™ 20 mg BID Placebo	 -0.25 mm -0.20 mm	 -1.03 mm* -0.86 mm	 -1.55 mm* -1.17 mm
Mean Change in PD at 9 months [1] Periostat™ 20 mg BID Placebo	 -0.16 mm** -0.05 mm	 -0.95 mm** -0.69 mm	 -1.68 mm** -1.20 mm
% of Sites with ALs ≥ 2 mm over 9 months Periostat™ 20 mg BID Placebo	 1.9 % 2.2 %	 1.3 % 2.4 %	 0.3 %* 3.6 %
% of Sites with ALs ≥ 3 mm over 9 months Periostat™ 20 mg BID Placebo	 0.49 % 0.64 %	 0.46 % 0.72 %	 0.17 % 0.63 %
% of Sites with BOP at 9 months Periostat™ 20 mg BID Placebo	 39 %** 46 %	 64 %* 70 %	 75 % 80 %

[1]A negative change indicates an improvement from Baseline. A positive change indicates a worsening from Baseline.
* $p < 0.050$ vs. the placebo control group, ** $p < 0.010$ vs. the placebo control group. Placebo values are in parentheses.

Reviewer's Comments:

There were statistically significant improvements from baseline in attachment gain and pocket depth at 9 months. For tooth sites with baseline pocket depth of 4-6 mm, the average attachment level improvement for the test group compared to scaling and root planing plus placebo was 0,17 mm and 0.38 mm for tooth sites with baseline pocket depth greater than 7 mm. For tooth sites with baseline pocket depth of 4-6 mm, the average improvement in pocket depth for the test group compared to scaling and root planing plus placebo was 0.26 mm. It was 0.48 mm for tooth sites with baseline pocket depth greater than 7 mm.

Treatment-Emergent Adverse Events
Occurring in ≥5% of Patients in Any Treatment Group

Incidence (%) of Adverse Reactions in Periostat™ Clinical Trial Combining SRP and Drug Treatment		
Adverse Reaction	**SRP + Periostat ™ 20 mg BID (n=94)**	**SRP + Placebo (n=96)**
Common Cold	27 (29%)	28 (29%)
Headache	26 (28%)	26 (27%)
Flu	10 (11%)	17 (18%)
Toothache	9 (10%)	13 (14%)
Sinus Congestion	8 (9%)	5 (5%)
Abscess Periodontal	3 (3%)	8 (8%)
Menstrual Cramp	6 (6%)	5 (5%)
Sinusitis	3 (3%)	7 (7%)
Tooth Disorder	5 (5%)	5 (5%)
Dyspepsia	7 (7%)	2 (2%)
Sinus Headache	5 (5%)	4 (4%)
Sore Throat	4 (4%)	5 (5%)

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

The most frequent TEAEs were the common cold, headache, flu, toothache and sinus congestion. In general, there were no apparent differences between treatment groups regarding the specific TEAEs.

The incidence of TEAEs considered to be "possibly" or "probably" related to study drug was small (6% in the SRP + Placebo treatment group and 13% in the SRP + Periostat treatment group). The difference between treatment groups (6% versus 13% was not significant ($p = 0.125$). The most frequent "possibly related" or "probably related" TEAE was dyspepsia which was experienced by 4% of patients in the SRP + Periostat treatment group compared to 0% in the SRP + Placebo treatment group.

<u>Other Clinical Trials:</u>

The clinical trials reported in the original NDA submission were numbered 5732.11E, 5732.11F and 5732.11G. hereinafter referred to as "E, F and G". (See Dental Officer's First Review dated March 27, 1997.) At a meeting with the sponsor March 12, 1998, the Agency agreed that though the protocols were different from 5732.11H, that "E, F and G" collectively could be considered supportive of an NDA if safety and efficacy results in "H" were acceptable. The supportive values for "E, F and G" are as follows:

The values reported below are all for the difference between the 20 mg. B.I.D. group and placebo from baseline to 12 months. A negative value reflects an improvement in all of these para- meters. Those values that are marked with an asterisk (*) achieved statistical signi- ficance at the p = .05 level.

Manual Probe Measurements			
Parameter	Baseline Pocket Depth		
	0-3 mm	4-6 mm	≥7 mm
Number of Patients	102	102	78
Number of Tooth Sites	10463	4561	624
Mean change cALv at 12 months[1]			
Periostat™ 20 mg BID	0.02 mm	-0.64 mm**	-1.37mm
Placebo	0.10 mm	-0.46 mm	-1.14mm
Mean Change in PD over 12 months [1]			
Periostat™ 20 mg BID	0.10 mm**	-0.68 mm**	-1.4mm
Placebo	0.12 mm	-0.47 mm	-1.11mm
% of Sites with ALs ≥ 2 mm over 12 months			
Periostat™ 20 mg BID	4.1 %**	2.8 %**	3.4%*
Placebo	6.3 %	5.2 %	6.5%
% of Sites with PD increase ≥ 2 mm over 12 months			
Periostat™ 20 mg BID	2.0 %**	1.4 %**	0.7%**
Placebo	4.1 %	3.6 %	5.3%
% of Sites with BOP over 12 months [1]			
Periostat™ 20 mg BID	26.3 %**	52.3 %**	69.1%**
Placebo	31.4 %	60.9%	79.5%

[1]A negative change indicates an improvement from Baseline. A positive change indicates a worsening from Baseline.
* $p < 0.050$ vs. the placebo control group, ** $p < 0.010$ vs. the placebo control group.

The following adverse events were reported in the submission as "most frequently reported" for the 20 mg. B.I.D. group and for the placebo group:

Adverse Event	20 mg. Doxycycline	Placebo
Headache	24%	25%
Common Cold	17%	15%
Nausea	10%	7%
Diarrhea	8%	6 %
Flu Syndrome	8 %	17%

Conclusion:

The sponsor has adhered to and met the Agency's decision rules as regards Study 5732.11 H. The 9 month study testing 20 mg. of doxycycline B.I.D. in conjunction with scaling and root planing versus placebo B.I.D. in conjuntion with scaling and root planing demonstrated improvement in attachment level and improvement in pocket depth.

Recommendation:

This product may be approved for marketing with modifications in labeling (See labeling review).

/S/

Clarence C. Gilkes, D.D.S., D.D.S.
(HFD-540)

cc:

Original to NDA 50744
HFD-540 Division File
HFD-540 DO/Gilkes/Hyman
HFD-540 DTL/Kelsey 7/23/98
HFD-540 PM/Blay
HFD-540 DO/Hyman 7/27/98
HFD-540 Pharm./See
HFD-540 Chem./Vidra
HFD-520 Micro./Marsik
HFD-725 Stat./Dixon
HFD-725 Stat./Srinivasan

SEP 16 1998

DENTAL OFFICER'S REVIEW OF LABELING OF NDA 50744
(Addressing Clinical Studies Only)

Reviewer:		Clarence C. Gilkes, D.D.S.
Project Manager:		Roy Blay, Ph.D.
Date Completed:		July 7, 1998
Name of Sponsor:		CollaGenex Pharmaceuticals, Inc. 301 South State Street Newton, PA 18940
Name of Drug:	Trade: Generic:	Periostat Doxycycline-hyclate
Pharmacologic Category of Drug:		Anti-periodontitis
Dosage Form:		Capsule (20 mg.)
Route of Administration:		Oral
Date of Submission:		March 31, 1998

Proposed Indication:

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

The attached annotated labeling for NDA 50744 was proposed by the sponsor, CollaGenex Pharmaceuticals, Inc., in their March 31, 1998 submission.

Dental Reviewer's Comments:

General Comments:

1. *The results of "Study H" which are on Page 9 of the sponsor's annotated labeling should be moved forward so* that *they precede the results of Studies E, F & G, since H was the study upon which NDA approval was primarily based. Adverse events for Study H should also be reported first.*

2. *When referring to Phases of study, Arabic numerals should be used (e.g. Phase 3).*

3. *In the tables proposed by the sponsor, the placebo values are put in parentheses below the value for the treatment, a fact that is then mentioned in an endnote. For clarity, the placebo values should be clearly labeled as such.*

4. *References to the efficacy parameters of percent of tooth sites with a change in attachment level or pocket depth greater than mm. should be deleted. Study H did not achieve statistical significance in this parameter, so it cannot be reported.*

Clinical Studies

1. *This section begins with a report of a study of collagenase levels in GCF in patients with periodontitis. While the information may be useful to clinicians, the number of subjects on study drug is small. These results should not be construed as establishing a mechanism of action for Periostat, so the words, "The clinical significance of these findings is unknown," should be added.*

2. *On page 5 in the first section that describes the three multi-center trials, the last sentence should be amended to say that the results summarized in the tables that follow are for all three studies combined.*

3. *In the sections that describe the pivotal trials, mention should be made of the fact that subjects with diabetes were excluded from the study since diabetes is a risk factor for periodontal disease.*

4. *On page 8, the entire section on Subtraction Radiography should be deleted. The number of subjects studied was very small, and the results were not statistically significant, so effect of Periostat on alveolar bone height has not been established.*

5. *On page 8, the section on Response to Tooth Sites subjected to Scaling and Root planing should be deleted. This parameter was not included in the data analysis plan, and the numbers of subjects is small. Also, the two treatment groups were not balanced at baseline in terms of disease severity. This section could be misleading.*

6. *On page 9 in the section on Manual Probe Measurements of the SRP'd*

*Quadrants, the last sentence should be amended to say that the "...mean percentage of tooth sites **per patient** exhibiting attachment loss ..."*

Indications and Usage

Dosage and Administration

Recommendation:

These changes should be incorporated into the labeling prior to NDA approval.

/S/

Clarence C. Gilkes, D.D.S.
(HFD-540)

cc:

Original to NDA 50744
HFD-540 Division File
HFD-540 Reviewer/Gilkes/Hyman
HFD-540 DTL/Kelsey
HFD-540 PM/Blay
HFD-725 Stat./Dixon
HFD-540 Pharm./See
HFD-540 Chem./Vidra

7/23/98

JUL 27 1998

Dental Team Leader Review - NDA 50-744

Date: July 21, 1998
Drug: Periostat™ (doxycycline hyclate capsules, USP)
Proposed Indication: "Periostat™ is indicated for use as an adjunct to supra- and sub-gingival scaling and root planing to promote and maintain attachment level gain and to reduce pocket depth in patients with adult periodontitis"
Sponsor: Collagenex Pharmaceuticals, Inc.
Primary Reviewer: Clarence Gilkes, DDS
Secondary Reviewer: John V. Kelsey, DDS, MBA

BACKGROUND:

This NDA was originally submitted on 8/30/96. The original submission included data from three Phase 3 studies (E, F & G) in support of the efficacy of this product as an "adjunct to a supra gingival scaling and prophylaxis." The initial clinical and statistical reviews stated that the sponsor had not achieved statistically significant results using the proposed statistical analysis plan. The biostatistics reviewer noted that the sponsor had made a number of post hoc changes to the statistical analysis plan. The clinical review went on to say that the difference in the primary efficacy variables (attachment level change and pocket depth change at 12 months) between active and placebo was too small to be considered clinically significant. A Not Approvable (NA) letter was issued on 8/27/97.

On receiving the NA letter the sponsor requested a meeting with the Division, which took place on 11/17/97. At that time the sponsor presented their rationale for the post hoc changes in the statistical analysis plan, including the use of the General Estimating Equation (GEE) method of data analysis in the NDA. There was also discussion about the indication. FDA expressed concern that the treatment might be promoted for use in lieu of scaling and root planing (SRP), which is standard first line therapy for moderate to severe periodontitis, characterized by 5-9 mm pockets as was studied in these trials. The sponsor countered that their proposed indication was as an adjunct to a supra gingival scaling and prophylaxis and not a "stand alone" treatment intended to replace other modalities.

FDA felt that the actual clinical results were modest. Attachment level differences of .32 mm. and .42 mm. at one year were not considered to be clinically significant, especially in view of the sponsor's a priori estimate of a .6 mm. difference. In an attempt to assess clinical significance, the results were compared to historical values for SRP (there was no concurrent SRP arm), and adjusted for the fact that a prophy was performed by assessing the change from baseline for the active arm. Other sponsors of stand alone periodontitis products have been told that their results have to be 75% as good as SRP and this level was not reached in these studies.

At the conclusion of the meeting, FDA agreed to accept the results of Studies E, F & G as statistically significant. However, the Agency continued to feel that the results were too modest to be considered clinically significant for a stand-alone indication. The sponsor said that they had completed an additional study (Study H) which looked at their product as an adjunct to SRP and presented preliminary results. FDA asked to see the complete study report of this study.

After further discussion with the sponsor the FDA agreed to review the results of Study H and asked the sponsor to submit those results formally. The FDA agreed that if the results of Study H supported approval of Periostat as an adjunct to SRP, the collective results of studies E, F & G would be considered supportive and a second trial of the product as an adjunct to SRP would not be required for approval. In order to "win" on Study H, Periostat + SRP would have to be statistically significantly better than Placebo + SRP with respect to the primary efficacy variables; change in attachment level and pocket depth at 9 months.

CLINICAL EFFECTIVENESS STUDIES:
(Refer to Dental Officer's Review and Statistical Review for specific details)

Studies E, F & G:

Studies E, F & G were very similar and the results of all three have been combined. Each was a multicenter, double blind, placebo controlled trial of 12 months duration. Subjects were screened to determine if they met the inclusion criteria, which included a diagnosis of periodontal disease. A total of 437 subjects were enrolled and were randomized to one of four treatment groups:

1) Periostat 10mg. QD (Only Studies E & F)
2) Periostat 10mg. BID
3) Periostat 20mg. BID
4) Placebo BID.

Primary efficacy parameters were measured by both manual probing and a mechanical probe, the "Florida Probe." Data were collected with the Florida probe a four selected tooth sites, and with the manual probe at six sites around each tooth in the mouth. Subjects received a supra gingival prophylaxis (prophy) at baseline, 6 months and at study completion. Florida probe data were collected at baseline, 3, 6, 9 and 12 months. Manual probe data were collected at baseline and months 6 and 12.

The primary efficacy endpoints which had to be met to support product approval were change in attachment level and change in pocket depths at 12 months. Subjects were stratified into three groups by baseline PD:

0-3mm	No Disease
4-6mm	Mild to Moderate Disease
>7 mm	Severe Disease

As was discussed above, the results of Studies E, F & G , with respect to the primary efficacy variables, though eventually accepted by the FDA as statistically significant, were not deemed to be of sufficient magnitude to be clinically significant, so this product is not approved as an adjunct to supra gingival scaling and prophylaxis. The results of E, F & G were combined and are reported below. They are accepted as supportive of Study H for use of the product as an adjunct to SRP.

STUDIES E, F, & G COMBINED
Summary of Efficacy Results; Attachment Level, Pocket Depth and Bleeding-on Probing

Manual Probe Measurements			
Parameter	Baseline Pocket Depth		
	0-3 mm	4-6 mm	≥7 mm
Number of Patients	102	102	78
Number of Tooth Sites	10463	4561	624
Mean change cALv at 12 months[1]			
Periostat™ 20 mg BID	0.02 mm	-0.64 mm**	-1.37mm
Placebo	0.10 mm	-0.46 mm	-1.14mm
Mean Change in PD over 12 months [1]			
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% of Sites with ALs ≥ 2 mm over 12 months			
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% of Sites with PD increase ≥ 2 mm over 12 months			
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% of Sites with BOP over 12 months [1]			
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Placebo	31.4 %	60.9%	79.5%

[1]A negative change indicates an improvement from Baseline. A positive change indicates a worsening from Baseline.
* $p < 0.050$ vs. the placebo control group, ** $p < 0.010$ vs the placebo control group.

Study H:

Study H was a multicenter, double blind, placebo controlled trial of 9 months duration in which 190 subjects at five study sites were randomized to one of two treatment groups:

1) SRP+Periostat 20mg. BID
2) SRP+Placebo BID.

Subjects were screened to determine if they met the inclusion criteria, which included moderate to severe periodontal disease as evidenced by two tooth sites in each of two quadrants of the mouth with pocket depths and attachment levels ≥5mm and ≤9mm as measured by a manual probe. In addition, the selected sites had to bleed on gentle probing at baseline.

The two quadrants which were selected for treatment were scaled and root planed at baseline and study medication (or placebo) was dispensed. Subjects returned at Months 3, 6 and 9, at which time clinical attachment level, pocket depth and bleeding on probing were measured. Non-qualifying tooth sites were also assessed to assure that they were not experiencing significant deterioration during the study, but these data were not included in the analysis.

From these efficacy measurements the sponsor created a number of per patient efficacy parameters. Of these, the primary efficacy endpoints which had to be met to support product approval were change in attachment level and change in pocket depths at 9 months. Subjects were stratified into three groups by baseline PD:

0-3mm	No Disease
4-6mm	Mild to Moderate Disease
>7	Severe Disease

In order to "win" on the primary efficacy parameters, the treatment group had to be statistically significantly better than the placebo group.

All comparisons were performed on the Intent-to-treat (ITT) population at months 3, 6 and 9. The results are presented in the following table.

STUDY H

Summary of Efficacy Results; Attachment Level, Pocket Depth and Bleeding-on Probing

Manual Probe Measurements			
Parameter	Baseline Pocket Depth		
	0-3 mm	4-6 mm	≥ 7 mm
Number of Patients	90	90	79
Mean change ALv at 9 months[1]			
Periostat™ 20 mg BID	-0.25 mm	-1.03 mm*	-1.55 mm*
Placebo	-0.20 mm	-0.86 mm	-1.17 mm
Mean Change in PD at 9 months [1]			
Periostat™ 20 mg BID	-0.16 mm**	-0.95 mm**	-1.68 mm**
Placebo	-0.05 mm	-0.69 mm	-1.20 mm
% of Sites with ALs ≥ 2 mm over 9 months			
Periostat™ 20 mg BID	1.9 %	1.3 %	0.3 %*
Placebo	2.2 %	2.4 %	3.6 %
% of Sites with ALs ≥ 3 mm over 9 months			
Periostat™ 20 mg BID	0.49 %	0.46 %	0.17 %
Placebo	0.64 %	0.72 %	0.63 %
% of Sites with BOP at 9 months			
Periostat™ 20 mg BID	39 %**	64 %*	75 %
Placebo	46 %	70 %	80 %

[1]A negative change indicates an improvement from Baseline. A positive change indicates a worsening from Baseline.
* $p < 0.050$ vs. the placebo control group, ** $p < 0.010$ vs. the placebo control group. Placebo values are in parentheses.

With respect to change in attachment level, active was statistically significantly ($p<.05$) better than placebo at nine months in both the mild to moderate and the severe disease groups. The actual mean differences were .17mm and .38mm respectively. Similarly, with respect to pocket depth, active was statistically significantly ($p<.01$) better than placebo at nine months in both the mild to moderate and the severe disease groups. The actual mean differences were .26mm and .48mm respectively. A statistically significant difference of .11mm was also observed in the no disease group.

The sponsor has therefore met the decision rules for claiming gain in attachment level and reduction in pocket depths in patients with periodontitis when Periostat™ is used as an adjunct to SRP.

SAFETY:

Adverse event data were collected in essentially the same fashion in all of the trials. Adverse event information was collected from patient diaries, monthly phone contacts between visits and interviews at study visits. Blood samples were collected at baseline and at the Month 3, 6 and 9 visits and various histology and blood chemistry studies were performed. Oral pathology examinations were performed at all visits and vital signs were taken.

The adverse event profile is presented in Dr. Gilkes' review.

CONCLUSIONS:

I concur with Dr. Gilkes' recommendation for approval of Periostat™ as an adjunct to SRP with the modfications to the label enumerated in his labeling review, as is the specific wording of the indication.

/S/

John V. Kelsey, DDS, MBA

cc:
HFD-540/Division File
HFD-540/Gilkes/Hyman
HFD-540/DeCamp
HFD-540/Vidra
HFD-540/Jacobs
HFD-540/See
HFD-520/Sheldon
HFD-520/Marsik
HFD-725/Srinivasan
HFD-725/Dixon
HFD-880/Bashaw
HFD-880/Wang

As above. I concur that, although Studies E, F, & G were not significant statistically for attachment levels of 0.6 mm difference, that there still was a demonstration of the effect of this product when used as an adjunct to a supra gingival scaling and prophylaxis that was statistically, but not clinically significant in that setting. However, this evidence of an effect coupled with the results of Study H support the recommendations of Drs. Gilkes & Kelsey for approval of Periostat as an adjunct to SRP.

/S/

7/27/99

Dental Team Leader Memo - NDA 50-744
Response to Meeting of 11/17/97

Date: December 15, 1997

Drug: Periostat™ (doxycycline hyclate capsules, USP)

Sponsor: Collagenex Pharmaceuticals, Inc.

Re: Clinical Significance of NDA Results

This memo is to comment on the issue of the clinical significance of the results of the studies submitted to support approval of Periostat™, NDA 50-744. This is in follow-up to a meeting with the sponsor on November 17, 1997, during which both the statistical significance and the clinical significance of the sponsor's study results were discussed. The Clinical Review of this NDA and the Team Leader's Memo of August 8, 1997 had opined that the results were not clinically significant. After further review, I continue to hold that opinion.

Use of this product as an "adjunct to a supra gingival scaling and prophylaxis (prophy)" which is the way the sponsor seeks to use this product, is an odd choice for this patient population, though the Agency did not object to this indication. Though it may improve the outcome slightly, prophylaxis is not standard therapy for moderate to severe periodontitis, characterized by 5-9 mm pockets. A prophy would be a weak positive control in a study of moderate to severe periodontitis.

Statistical issues aside, the mean difference in attachment levels of .32 mm. (p=.071) and .42 mm. (p=.012) in the two studies looking at the Florida probe data after 12 months of therapy seem very modest. In evaluating the clinical significance of these results the sponsor's own opinion about what they would view as clinically significant was considered first. In response to a question from FDA at a meeting on 9/28/92, the sponsor stated, "...our target is a treatment effect of at least .6 mm after 12 months of therapy."

Next the literature was consulted for guidance about what constitutes a clinically significant effect. Because supra gingival scaling and prophylaxis is not standard therapy for moderate to severe periodontitis, there are no studies that looked at this therapy in this group. This use is more like a "stand-alone" periodontitis indication (treatment in lieu of SRP) and the Division has said in the past that in studies for the "stand-alone" periodontitis indication, efficacy endpoints at least 75% as good as SRP would be required. This position is consistent with comments in the ***Proposed guidelines for American Dental Association acceptance of products for professional, non-surgical treatment of adult periodontitis,*** as developed by the Taskforce on Design and Analysis in Dental and Oral Research:

"To accept products, however, based solely on statistical superiority to a negative control was widely viewed as too permissive for evaluating an antiperiodontitis agent to be used in any setting. By acceptance of products with statistically significant but small effects compared to a negative control, the ADA would risk endorsing products which informed members of the periodontal community might disdain to recommend because of insufficient benefit."

In assessing the clinical significance of the results presented were compared to the historical results of SRP, which is the standard therapy for moderate to severe periodontal disease. From a summary of the literature presented in the proceedings of the ***1996 World Workshop in Periodontics***, SRP results in an average .55 mm. improvement in attachment levels in moderate sites (4-6 mm) and 1.29 mm. in severe sites (>7 mm) for an average of .92 mm. The patients in the group from which the sponsor has taken its pivotal results had initial pocket depths of 5-9 mm., so were somewhat more severe at baseline than the patients reported in the literature summary. Also, the sponsor's own Study H, in 140 patients, includes an SRP only arm. FDA has not reviewed the results of that study, but the sponsor presented preliminary results of a 1.2 mm. improvement in attachment level in patients with ≥7 mm. pockets, with SRP alone. This is consistent with results in the literature.

There is some beneficial effect to performing a prophy in this patient group as evidenced by the improvements in AL seen in the placebo groups in these studies (all patients got a prophy). In contrast, the AL improvements reported for SRP in the literature are simply pre- and post-values, so the differences reported are from baseline. To more accurately compare the groups, the absolute improvement in attachment levels from baseline were assessed. The differences from baseline in attachment levels were .56 mm. in both studies. These values are still short of 75% of the historical values for SRP (.69 mm.).

The sponsor reported an analysis of subjects who had sites that deteriorated more than 2 mm. or more than 3 mm. A reduction in this parameter would be clinically relevant, though this reviewer could not find a study that evaluated this parameter in conjunction with SRP. In assessing the supportive value of these results in approving the NDA, it was noted that the sponsor achieved statistically significant results in the moderate and severe disease groups in only one study, even though a large number of sites were included - this was for the >2 mm. group. Interestingly, these results are from the one study (Study F) that did not support the efficacy findings for attachment levels around which the sponsor is trying to accumulate support for approval (Studies E & G). There were three identical studies done, but the results of the second (Study F) were quite different than the other two (Studies E & G). The fact that there was so much variability among the three identical studies does not lend comfort in accepting the limited support for efficacy that E & G provide.

The data on change in probing pocket depths were also reviewed. In the **World Workshop** proceedings, the literature review showed mean reductions in pocket depth of 1.29 mm. in the moderate group and 2.16 mm. in the severe group. Again, there was considerable variability. If the absolute improvement in the parameters from baseline is considered, the improvement was .71 mm. in the moderate group for all studies combined and 1.39 mm in the severe group for all

studies combined. These results were again short of the 75% of SRP threshold (.97 mm. & 1.62 mm.).

In conclusion, the data are hardly robust. If results from the study that were significant at p=.071 are accepted, the sponsor was able to show a modest difference in attachment levels in one stratum in two of three studies. Attachment level differences of .32 mm. and .42 mm. at one year are not considered to be clinically significant, especially in view of the sponsor's a priori estimate of a .6 mm. difference.

In an attempt to assess clinical significance, the results were compared to historical values for SRP (there was no concurrent SRP arm), and adjusted for the fact that a prophy was performed by assessing the change from baseline for the active arm. Sponsors of stand alone periodontics products have been told that their results have to be 75% as good as SRP and this level was not reached. Their data regarding deterioration of attachment levels beyond threshold limits was also reviewed, but the results were not statistically significant. Data on changes in pocket depth were considered and again, the changes did not reach the level of 75% of SRP. I continue to feel that the result are not clinically significant.

There are several options that can be offered to the sponsor:

1. Conduct two new studies for the "adjunct to prophylaxis" indication with the hope of achieving a .6 mm. attachment level difference.

2. Submit the results of their Study "H," which looks at their product as an adjunct to SRP, along with a confirmatory study. If both are positive, the sponsor could get a claim for their product as an adjunct to SRP. We would carefully consider what, if anything, could be put in the labeling based on the studies being reviewed now. This option would be easier than option 1. because it would require only 2 arms.

3. If the results of their Study "H" are not positive, the sponsor would have to do two new studies to get an "adjunct to SRP" claim.

The sponsor should be informed of the Division's decision that clinically significant results have not been achieved in two well-controlled studies and that the Not Approvable decision stands. The sponsor should also know that the Division will be happy to discuss the options available at this point.

/S/

John V. Kelsey, D.D.S., M.B.A.

cc:

Original NDA 50-744
HFD-540/Div. Files
HFD-105/Office Director

HFD-540/DD/Wilkin 12/30/97
HFD-540/Kozma-Fornaro
HFD-540/Blay
HFD-540/Gilkes
HFD-540/DeCamp
HFD-540/Vidra
HFD-540/Jacobs
HFD-540/See
HFD-520/Sheldon
HFD-520/Marsik
HFD-725/Srinivasan
HFD-725/Dixon
HFD-880/Bashaw
HFD-880/Wang

AUG 17 1997

Dental Officer's Review of NDA 50744
(Related IND

Drug: Periostat (Trade Name)
Doxycycline hyclate
20 mg. (Generic Name)

Sponsor: Colla Genex Pharmaceuticals, Inc.
301 South State Street
Newtown, PA 18940

Submission Date: 8/30/96
Received Date: 9/9/96
Review Date: 3/27/97
PM: Harold Blatt
DO: Clarence Gilkes, DDS

Proposed Indication: To treat adult periodontal disease

Pharmacologic Category: Anti-periodontitis, not antimicrobial at this dosage.

Background: Doxycycline is approved as an antimicrobial at 100 mg. The related IND was originally submitted by . The sponsor states that at 20 mg, B.I.D., doxycycline reduces the elevated collagenase activity in the gingival crevicular fluid of patients with adult periodontitis, dontitis.

Resume: There are three Phase 3 studies submitted to support claims of safety and efficacy for this New Drug Application. The studies were all multicentered and of 12 months duration.

Chemistry: See chemist's review dated March 24, 1997.

Pharmacology: See pharmacologist's review dated January 14, 1997.

Statistics: See statistician's review dated January 29, 1997.

Study Numbers: The three pivotal studies are designated as 5732.11E, 5732.11F and 5732.11G.

Labeled Indication:

"Periostat is indicated for use as part of a professional oral health program to promote attachment gain and reduce bone loss, pocket depth, and bleeding on probing in patients with adult periodontal disease."

Principal Investigators:

The investigators who participated in the multicentered study designated 5732.11E were Dr. J. Caton, Dr. S. Ciancio, Dr. R. Crout, Dr. R. Nagy and Dr. R. O'Neil. There were six centers in this study.

Principal Investigators:

The investigators who participated in the multicentered study designated 5732.11F were Dr. S. Ciancio, Dr. R. Crout, Dr. R. Nagy and Dr. R. O'Neil. There were four centers in this study.

The investigators who participated in the multicentered study designated 5732.11G were Dr. D. Adams, Dr. C. Quinones, Dr. E. Taggart and Dr. M. Wolff. There were four centers in this study.

Duration of the Studies:

All three studies were conducted for one year.

Number of Subjects:

There were a total of 437 subjects in the three studies.

Study 5732.11E involved 160 subjects, 40 in each of the following 4 groups. (There were 6 centers.)

1. 10 mg of doxycycline Q.D.
2. 20 mg of doxycycline Q.D.
3. 20 mg of doxycycline B.I.D.
4. Placebo B.I.D.

Study 5732.11F involved 160 subjects, 40 each, randomized into the same groups as listed above. (There were 4 centers.)

Study 5732.11G involved 117 subjects randomly assigned into 3 groups of 39 each. (There were 4 centers)

1. 20 mg of doxycycline Q.D.
2. 20 mg of doxycycline B.I.D.
3. Placebo B.I.D.

Inclusion Criteria:

1. Age Range: 18-75 years

2. Sex: Male and Female

3. Patients selected for inclusion in this study must be clinically diagnosed as having periodontitis.

4. At a pre-screening examination, patients must have periodontal pockets greater that 3 mm and attachment loss in at least four interproximal sites and must have at least two

maxillary interproximal sites with collagenase values over 30 collagenase units.

5. Patients must have at least two maxillary interproximal sites with collagenase values over 30 collagenase units at the screening examination in order to qualify for the baseline examination.

6. Patients will be required to have collagenase levels in at least two maxillary interproximal sites of greater than 30 C.U. at the baseline examination in order to continue to qualify for the study.

7. Patients must demonstrate bleeding upon stimulation as assessed by the Eastman Interdental Bleeding Index at the prophylaxis examination in at least one interdental site.

8. Patients must have at least fourteen teeth.

9. Each patient should be reasonably expected to complete the full course of study.

10. Each patient must complete an Informed Consent Form.

Exclusion Criteria:

1. Pregnant women

2. Nursing women

4. Patients with known hypersensitivity to tetracycline

5. Patients on significant concomitant drug therapy

6. Patients with diabetes mellitus

7. Patients with systemic infection

8. Patients receiving antibiotics within the last 3 months

9. Patients with serious medical illness such as kidney or liver disease as stated in the medical history

Study Design:

All studies were randomized, double blind, parallel in design.

Study Plan:

The primary parameter was attachment level. The secondary param-

meters were pocket depth, bleeding on probing and alveolar bone loss. Pocket depth (PD) provides a hybrid assessment of both the inflammation of the gingiva and the degeneration of the bone. All treatment groups, including the placebo control group, received a supra-gingival scaling and dental prophylaxis at baseline and at 6 and 12 months.

Study Results:

There were 3 pivotal studies submitted to support the NDA. To qualify for the studies, subjects had to have at least two pockets of 5-9 mm. probing depth. Subjects were stratified by baseline pocket depth into into three groups as follows:

0 - 3 mm.	No disease	10,463 sites
4 - 6 mm.	Mild to moderate	4,561 sites
Greater than 7 mm.	Severe	624 sites

The primary efficacy parameter was change in attachment level from baseline to 12 months. Attachment levels were measured using both the Florida automated probe and a manual probe. Data obtained using the Florida probe looked at only "selected sites" since it is impractical to obtain readings on each tooth using the Florida probe. Treatment comparisons are on a per patient basis as stated in the original protocol. For purposes of this review, attachment level data using the manual probe were analyzed because only the manual probe was used to assess all of the proposed efficacy parameters (attachment level, pocket depth and bleeding on probing). The values reported below are all for the difference between the 20 mg. B.I.D. group snd placebo from baseline to 12 months. The change in attachment levels and pocket depths are reported in mm. Bleeding on probing is reported as percent of sites that bleed on probing. A negative value reflects an improvement in all of these parameters. Those values that are marked with an asterisk (*) achieved statistical significance at the p=.05 level.

	Change in A.L. (mm)			Change in P.D. (mm)			B.O.P. (% Sites)		
	0-3	4-6	>7	0-3	4-6	>7	0-3	4-6	>7
E	.01	-.24	-.22	-.06	-.17*	-.44	-10.5	-12.4*	-12.9
F	-.13	-.23*	-.18	.13*	-.23*	-.15	1.6	-4.4	-9.9
G	-.13*	-.22	-.49	-.09	-.25*	-.61*	-6.2	-9.1	-9.4

Aveolar bone loss is a parameter that was not adequately studied. There were only 23 patients evaluated using digital subtraction radiography (DSR) and the results of this very small group were not

statistically significant. The following adverse events were reported in the submission as "most frequently reported", for the 20 20 mg. B.I.D. group:

Adverse Event	20 mg. Doxycycline	Placebo
Headache	24%	25%
Common Cold	17%	15%
Nausea	10%	7%
Diarrhea	8%	6%
Flu Syndrome	8%	17%

Discussion:

The claim "reduce bone loss" was not adequately studied in the pivotal trials submitted by the sponsor. Protocol number 5732.11E entered 7 subjects on the placebo and 7 subjects on 20 mg. B.I.D. of doxycycline hyclate. Twelve months later at the conclusion of the study there were only 5 subjects in each group that were to be evaluated. Protocol F enrolled 6 on placebo and 8 on the test product. At the end of 12 months there were 6 and 7 subjects in the respective groups to be evaluated. Protocol G did not measure any of the subjects for bone loss. Alveolar bone loss was measured in "pixels". This unit of measurement was utilized in digital subtraction radiography.

The results of the pivotal studies are detailed in the chart above. As discussed in depth in the statistical review of this application the sponsor was unable to show a statistically significant differrence between active and placebo for any of the efficacy parameters in any stratum in any two of the studies submitted, when using the data analysis plan proposed prior to breaking the blind. Change in attachment level at 12 months was the primary efficacy variable. In the two instances where a statistically significant difference in attachment level was achieved, the actual differences were .13 and .23 mm. respectively. These changes are not clinically significant in the opinion of this reviewer. A millimeter rule is provided to better visualize the sponsor's results.

Changes in the secondary parameters pocket depths and bleeding on probing were unimpressive. For decrease in pocket depth, statistical significance was achieved in the mild to moderate groups in all 3 studies, but the actual change was .25mm. or less. Again, this reviewer does not consider those levels clinically significant. Change in bleeding on probing score was statistically significant in only one cell, the 4-6 mm. group in study E.

It should be further noted that all three of the pivotal studies utilized various dosages. Protocols E and F had cells taking doxycycline 10 mg. Q.D., 20 mg. Q.D. and 20 mg. B.I.D. Protocol G had cells taking doxycycline 20 mg. Q.D. and 20 mg. B.I.D. These are cells that we would expect to be employed in dose response studies.

There were 3 investigators who participated in 2 of the 3 studies. They were Doctors Nagy, Crout and Ciancio.

Currently, the common standard of treatment for periodontal disease is deep scaling and root planing. Plans for future trials should address the need for an active control arm (i.e., deep scaling and root planing). None of the pivotal studies utilized such a group. All of the subjects only had a supragingival prophylaxes at baseline, six and twelve months.

Summary and Conclusions:

This application is not approvable under section 505 (b)(1) clinical (safety and efficacy) and 505 (b)(6) labeling.

The sponsor should be notified of the deficiences cited by all the disciplines involved.

Recommendations:

1. The sponsor should conduct two new clinical trials to support claims of safety and efficacy.

2. Since the recommended dosage of doxycycline is 20 mg. B.I.D., no other dosages should be utilized.

3. For a "stand alone" indication the trial should have 4 arms as follows:

   active
   placebo
   positive control (SRP)
   negative control (Oral Hygiene Instruction)

4. Submit protocol to the Agency for comment prior to initiating trials.

/S/

Clarence C. Gilkes, D.D.S.
(HFD-540)

cc:
Orig. to NDA 50744
HFD 540 Div. File
HFD 540 DO/Gilkes
HFD 540 DD/Wilkin
HFD 540 DTL/Kelsey
HFD 540 PM/Blatt
HFD 540 Pharm./See
HFD 540 Chem./Vidra
HFD 725 Stat./Dixon
HFD 725 Srinivasan

8/8/97

8/12/97

August 8, 1997

AUG 17 1997

Dental Team Leader comments on Clinical Review of NDA 50-744, Periostat® (doxycycline hyclate, USP) 20 mg Capsules

I concur with the Dr. Gilkes' clinical review, with the minor changes noted.

The data presented in this application do not support a showing of efficacy because the sponsor failed to show statistical significance for any of the outcome measures in any two of the clinical trials using the data analysis planned prior to breaking the blind. The specifics are outlined in Dr. Dixon's statistical review of this application.

One aspect of the study design that was unusual for a pivotal trial was that it included a dose ranging component. The arms were:

10mg. QD (only study 5732.11E)
20mg. QD
20mg. BID
Placebo

One result of this design was that the active treatment arm included only 119 of the 437 patients in the collective studies.

In considering what additional information might be required to permit approval of this product, some attention should be given to past interaction with and advice given to the sponsor. During the period while this application was under review, the Division policy on requirements for clinical trials to support periodontitis claims was evolving. In reviewing the record of the interactions between the Division and the sponsor regarding study design requirements, it appears that the sponsor was given advice regarding study design that has since been superseded. Specifically, it is now Division policy that trials for "stand-alone" products to treat periodontitis (to be used in lieu of scaling and root planing), must have four arms as follows:

1) Active
2) Placebo
3) Scaling and Root Planing (Positive Control)
4) Oral Hygiene (Negative Control)

The sponsor would have to show that their product is at least 75% as good as SRP (we have used the 75% standard with other sponsors) and better than placebo. The data analysis plan must be detailed before the blind is broken.

With regard to the question of clinical significance, the sponsor originally stated that they expected to see a difference in attachment level between active and placebo of .6mm. When we look at the results of their data analysis, they come close to having significance in change in attachment level in two studies at the p=.05 level, but the actual amount of difference in attachment level is .13 to .23mm. This is only about ~~one~~ third of what they expected to get at the beginning of the study, and in my opinion is not clinically significant.

In mid June, the sponsor was asked for a chronology of their interactions with the Agency as background for secondary review of this application. The sponsor provided a comprehensive chronology. At the same time, they expressed dismay that we were asking for this information late in the NDA review process and asked for a meeting to discuss any concerns that we might have. They were told by phone that there were no issues to be discussed at this point and that we expected to complete the review within the PDUFA review timeline. The sponsor followed up with a request for a pre-NDA meeting to discuss submission of what they have been viewing as a Phase 4 protocol. The purpose of the Phase 4 study

The Division has agreed to schedule a meeting, though a date has not yet been set. As a practical matter, it is unlikely that anything can be arranged prior to the time that the sponsor is informed of the NA decision. Since the company will presumably request a meeting in response to the NA letter, the issue of the study design for the adjunctive indication can be taken up at that time.

/S/ 8/8/97

John V. Kelsey, D.D.S., M.B.A.

cc: Original IND
HFD-540/Div. File
HFD-540/DD/Wilkin
HFD-540/DTL/Kelsey
HFD-540/PM/(Blatt)

8/17/92

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-744

CHEMISTRY REVIEW(S)

SEP 16 1998

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-744 **CHEM.REVIEW #**: 3 **REVIEW DATE**: 10-Sep-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	30-Aug-96	03-Sep-96	Chm. Review #1
BC	02-Apr-97	03-Apr-97	Chm. Review #2
AZ	31-Mar-98	01-Apr-98	Chm. Review #2

NAME & ADDRESS OF APPLICANT:

CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newtown, Pennsylvania 18940
ATTN: Christopher Powala
Director, Drug Development & Regulatory Affairs
Telephone No. 215-579-7388, X-16
Fax No. 215-579-8577

DRUG PRODUCT NAME

Proprietary:	Periostat™
Nonproprietary/USAN:	Doxycycline Hyclate USP (USP 23 & USP 23 Alternate)
Code Names/#'s:	GS-3065, Jenacyclin; Supracyclin;
Chemical Type/	Vibramycin
Therapeutic Class:	3-S

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE

PHARMACOLOGICAL CATEGORY/INDICATION: Adult Periodontal Disease

DOSAGE FORM:	Capsule
STRENGTHS:	20 mgs.
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, 4MOL.WT:
2-Naphthacenecarboxamide,4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-,monohydrochloride, compound with ethanol (2:1), monohydrate, [4S-(4α,-4aα,5α,5aα,-6α,12aα)] (USP 23)

Molecular Formula:
Empirical Formula: $(C_{22}H_{24}N_2O_8 \cdot HCl)_2C_2H_6O \cdot H_2O$
Molecular Weight: 1025.89 as doxycycline hyclate
888.88 as doxycycline base
CAS No.: 24390-14-5
SUPPORTING DOCUMENTS: NOT APPLICABLE

CONSULTS: NOT APPLICABLE

REMARKS/COMMENTS:
The PERIOSTAT™ final proofs for both carton and container were reviewed in NDA 50-744/000, Vol. 2.4, Section 4.0, pp.4-0018 to 4-0021 for their labeling and label according to 21 CFR 201.10(g)(2). No major discrepancies were noted, however, one minor labeling discrepancy was

observed. In 21 CFR 201.10(g)(2), it is stated the proprietary name (PERIOSTAT) and established name (Doxycycline Hyclate) should have commensurate prominence. This was not indicated in the PERIOSTAT™ Final Proof Labeling where the proprietary name was in bold print while the established name was in standard print. Both names should be commensurate. It is therefore requested that at the next labeling printing, that CollaGenex Pharmaceuticals correct for this minor discrepancy.

The FUR Inspection status during this review period remained ACCEPTABLE.

Additionally, the Environmental Assessment (EA) deficiencies noted in the original NDA 50-744/000 review were resubmitted, reviewed in Chemistry Review #2 and found ACCEPTABLE in that review. Although these results were not emphasized in the Conclusion Section of Chemistry Review #2, it should now be noted that all EA deficiencies have been corrected.

CONCLUSIONS & RECOMMENDATIONS:
The PERIOSTAT™ final proofs for both carton and container label and labeling were reviewed and RECOMMENDED FOR APPROVAL. However, it is requested that at the next labeling printing, the prominence of both proprietary and established names in the carton and container label and labeling be commensurate.
In addition, all EA deficiencies have been corrected and the inspection status for this NDA remains acceptable.

/S/ , 9/16/98
James D. Vidra, Ph.D.
Review Chemist

cc: Orig. NDA 50-744
HFD-540/Division File
HFD-540/DivDir/Wilkin
HFD-540/PrjMgr/Blay
HFD-540/DO/Kelsey
HFD-540/PharmTox/See
HFD-540/BioPharm/Wang
HFD-540/Chm/Vidra
HFD-540/ChmTL/WHDeCamp WD 9/16/98

filename: N50744Lab

9/21/98

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-744 **CHEM.REVIEW #**: 2 **REVIEW DATE**: 08-Jun-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	30-Aug-96	03-Sep-96	APPROVABLE
BC	02-Apr-97	03-Apr-97	10-Apr-97
AZ	31-Mar-98	01-Apr-98	06-Apr-98

NAME & ADDRESS OF APPLICANT: CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newtown, Pennsylvania 18940
ATTN: Christopher Powala
Director, Drug Development & Regulatory Affairs
Telephone No. 215-579-7388, X-16
Fax No. 215-579-8577

DRUG PRODUCT NAME
Proprietary: Periostat™

Nonproprietary/USAN: Doxyclcline Hyclate USP
Code Names/#'s: GS-3065, Jenacyclin; Supracyclin;
Chemical Type/ Therapeutic Class: Vibramycin 3-S

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE

PHARMACOLOGICAL CATEGORY/INDICATION: Adult Periodontal Disease

DOSAGE FORM: Capsule
STRENGTHS: 20 mgs.
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, 4MOL.WT:
2-Naphthacenecarboxamide,4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-,monohydrochloride, compound with ethanol (2:1), monohydrate, [4S-(4α,-4aα,5α,5aα,-6α,12aα)] (USP 23)

Molecular Formula:
Empirical Formula: $(C_{22}H_{24}N_2O_8 \cdot HCl)_2C_2H_6O \cdot H_2O$
Molecular Weight: 1025.89 as doxycycline hyclate
888.88 as doxycycline base
CAS No.: 24390-14-5
SUPPORTING DOCUMENTS: NOT APPLICABLE

CONSULTS: NOT APPLICABLE

REMARKS/COMMENTS:
The following represents sponsor's replies to FDA's five CMC comments made from the Original NDA Review. The five original FDA Informational Requests, the sponsor's replies to these IRs and the second review are listed below:
CMC Comment #1: "Sponsor failed to include information on disposal sites

and on the method of disposal for the drug substance and drug product."
Sponsor's Reply to Comment #1: Response provided in Vol.1, Tab 1, page 001.

- DRUG SUBSTANCE MANUFACTURER:

- DRUG PRODUCT MANUFACTURER:
- Sites & disposal of both drug substance and drug product at are described in DMF
- Standard Operating Procedure SF 09723D, "Waste Disposal Policy".
- EPA ID NO.: NCR000006817
  EPA ID NO.: NC0000096990
  EPA ID NO.: NCD037149663
  EPA ID NO.: NCD982165995

Reviewer's Comments: ADEQUATE

CMC Comment #2: "The drug product manufacturer, was not subscribed any emission permits or license as per 11/95 FDA Guideline, p.13."
Sponsor's Reply: The response to comment #2 is provided in Vol.1, Tab 2, page 013. Air Permit #6580R3 for was issued by the State of North Carolina, Dept. Environment, Health & Natural Resources (DEHNR), Div. Air Quality and attached to sponsor's reply.
Reviewer's Comments: ADEQUATE

CMC Comment #3: "Sponsor is requested to conduct a light protection study during the manufacturing of both drug substance and drug product and during the development of your analytical methodologies."
Sponsor's Reply: Sponsor contends that no protection from light in the manufacturing area is needed since in vitro laboratory light studies indicate no drug substance deterioration. Data provided in Vol. 1.3, pp.3-0188 to 3-0201 and 3-0215 to 3-0222. Laboratory data indicates no light degradation in either drug substance or in drug product after 72 hours of exposure.
Reviewer's Comments: ADEQUATE

CMC Comment #4: "Explain why there are four positive stability slopes for all four primary stability batches (pp.3-0314 to 3-0316 and 3-0321)."
Sponsor's Reply: True that all four stability lots showed positive regression line slopes for expiration dating using the FDA's STAM computer program. However, following a review of this data using the statistical program "JMP", the statistical significance of these slopes are not significantly different from zero. Three of the four projected stabilty lots had 12 months or six individual data points used for their projection. The fourth lot only three data points.
Reviewer's Comments: An ADEQUATE explanation for a questionable computer statistical program. Although the sponsor's JMP Program found all slopes to be zero when projected for 48 months, an expiration date of 18 months continues to be recommended. This 18 month expiry date can be extended as additional acceptable stability data become available. The JMP Program should not be used for such lengthy time projections since one outlier time point can produce major projection errors.

CMC Comment #5: "In the labeling of the drug product, the chemical designation for doxycycline hyclate and the drug product storage conditions both require corrections."

Sponsor's Reply: The reviewer's comments are acknowledged and the final labeling were revised as suggested.
Reviewer's Comments: ADEQUATE

An amendment to one of the specifications was also submitted for the Periostat Blend assay. The sponsor requested the original specification for the current % doxycycline hyclate in the drug product be modified to read % doxycycline hyclate.

CONCLUSIONS & RECOMMENDATIONS:
This Major Amendment NDA 50-744/AZ is RECOMMENDED FOR APPROVAL for all five Informational Requests plus the Periostat Blend Assay amendment.

/S/

James D. Vidra, Ph.D.
Review Chemist

cc: Orig. NDA 50-744
HFD-540/Division File
HFD-540/DivDir/Wilkins
HFD-540/PrjMgr/Blay
HFD-540/DO/Kelsey
HFD-540/PharmTox/See
HFD-540/BioPharm/Wong
HFD-540/Chm/Vidra
HFD-540/ChmTL/WHDeCamp WD 9/1/98

filename: N50744.AZ

9/19/98

JUL - 1 1997

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-744 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 6/20/97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Pre-NDA Submission	5/31/96	6/3/96	
Original NDA	8/30/96	9/3/96	9/9/96
NDA 50-744/BC (minor amendment),	4/2/97	4/3/97	4/10/97

NAME & ADDRESS OF APPLICANT: CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newtown, Pennsylvania 18940
ATTN: Christopher Powala
Director, Drug Development &
Regulatory Affairs
Telephone No. 215-579-7619
Fax No. 215-579-8577

DRUG PRODUCT NAME

Proprietary:	Periostat™
Nonproprietary/USAN:	Doxyclcline Hyclate USP (USP 23 & USP 23 Alternate)
Code Names/#'s:	GS-3065, Jenacyclin; Supracyclin;
Chemical Type/	Vibramycin
Therapeutic Class:	3-S

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE

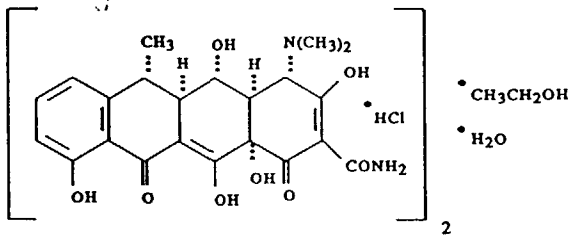
PHARMACOLOGICAL CATEGORY/INDICATION: Adult Periodontal Disease

DOSAGE FORM:	Capsule
STRENGTHS:	20 mgs.
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

2-Naphthacenecarboxamide,4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-,monohydrochloride, compound with ethanol (2:1), monohydrate, [4S-(4α,-4aα,5α,5aα,-6α,12aα)] (USP 23). See APPENDIX #1.

Molecular Formula:



Empirical Formula:	$(C_{22}H_{24}N_2O_8 \bullet HCl)_2C_2H_6O \bullet H_2O$
Molecular Weight:	1025.89 as doxycycline hyclate
	888.88 as doxycycline base
CAS No.:	24390-14-5

SUPPORTING DOCUMENTS (See APPENDIX #2):

AADA 62-374	**DMF**	**DMF**
AADA 62-839	**DMF**	**DMF**
DMF	**DMF**	**DMF**
DMF	**DMF**	**DMF**
DMF	**DMF**	

CONSULTS:

(1) Nomenclature & Labeling Committee - Trademark Reviewed on 3/4/97

(2) Environmental Assessment - Telephone discussion with W.H. DeCamp on 4/4/97.

REMARKS/COMMENTS:

NDA 50-744 has a 3-S classification for a new dosage form, doxycycline hyclate capsules, USP. Doxycycline hyclate, USP, is used in PERIOSTAT™ Capsules, 20 mgs., for the indication of adult periodontitis. The drug substance is manufactured by while the drug product is manufactured, packaged and labeled by for the NDA Sponsor, CollaGenex Pharmaceuticals.

Synthesis of the drug substance was well organized and controlled by as verified in the review of the previously updated doxycycline AADA 62-374 and AADA 62-839.

The Drug Product's Regulatory Specifications and Methods Section of the NDA had informational requests in the following areas:

- There was no mention of light protection for the light-sensitive doxycycline hyclate during product development of the drug product, commercial bulk upgrading, or during use of the Reference Standard in the development of analytical methods. A Phase IV committment is thereby requested to conduct a

- An explanation from this sponsor on why there are four positive stability slopes for all four primary stability batches (pages 3-0314, 3-0315, 3-0316 and 3-0321).
- The capsule fill modification for content uniformity as described on page 3-0246 will be referred to the Compendial Liaison.
- The chemical designation for doxycycline and the storage conditions of the labeling required corrections.

Although the NDA Sponsor requested a 24 month expiration date, an 18 month expiry was recommended on the basis of the available 12 months of acceptable stability data. A longer expiration date can be obtained as additional stability data becomes available.

Although this Environmental Assessment was found deficient all EA's are currently undergoing review thus the status on this deficiency might change.

CONCLUSIONS & RECOMMENDATIONS:
This original NDA 50-744 is APPROVABLE. A listing of the informational requests and deficiency associated with this NDA are described above in the Remarks/Comments Section.

/S/ 6/23/97

James D. Vidra, Ph.D.
Review Chemist

cc: Orig. NDA 50-744
HFD-540/Division File
HFD-540/ProjMan/Blatt
HFD-540/Pharm/See
HFD-540/Chm/Vidra
HFD-540/ChmSup/WHDeCamp WJ 6/26/97
HFD-540/DenOffr/Gilkes
HFD-540/Stat/Srinivasan
HFD-830/Chem/Chen 7/1/97
filename: N50744