CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
50-783

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: January 31, 2001 Number of Pages (including cover sheet) – 20

TO: Christopher Powala, Senior Director, Drug Development and Regulatory Affairs
COMPANY: Collagenex Pharmaceuticals, Inc.
FAX #: 215-579-8577

MESSAGE: For your review/concurrence please find attached to this facsimile transmission, draft labeling for your NDA 50-783, PERIOSTAT® (doxycycline hyclate tablets) 20 mg.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

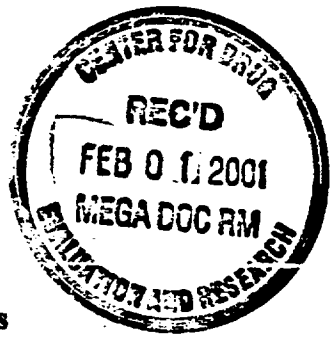
16 pages redacted from this section of the approval package consisted of draft labeling

pharmaceuticals

January 31, 2001

Jonathan K. Wilkin, M.D., Director
Division of Dermatological & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

NDA [illegible] AMENDMENT
BL



RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Draft Labeling

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg Tablets.

Additional reference is made to the Division's facsimile of January 31, 2001 which contained the final draft of the package insert for Periostat®. As requested, we have reviewed the labeling and it has come to our attention that reference No. 3 on page 8 is incorrect. It should read as follows:

"Golub L.M., Lee H.M., Greenwald R.A., Ryan M.E., Salo T., Giannobile W.V.: A Matrix Metalloproteinase Inhibitor Reduces Bone-Type Collagen Degradation Fragments and Specific Collagenases in Gingival Crevicular Fluid During Adult Periodontitis. Inflammation Research 1997; 46: 310-319."

Provided that we can make the above-mentioned correction, we find the package insert acceptable.

We trust that this adequately responds to your request. If you have any questions, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

ORIGINAL

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

ORIG AMENDMENT

BL

January 30, 2001

Jonathan K. Wilkin, M.D., Director
Division of Dermatological & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Labeling

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablet.

Additional reference is made to the January 26, 2001 telephone conversation between Cdr. Cross, Sr. Project Manager, HFD-540, Dr. Decamp, Supervisory Chemist, HFD-540 and the undersigned. During this conversation, it was agreed that CollaGenex would make revisions to the bottle, shipper and sample carton labels for Periostat® to include the word tablets within the established name as follows: (doxycycline hyclate tablets).

Submitted herewith, in Attachment 1, are revised labels which reflect the agreed upon change. We are also providing these labels on diskette which can be found in Attachment 2.

If you have any questions regarding this submission, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

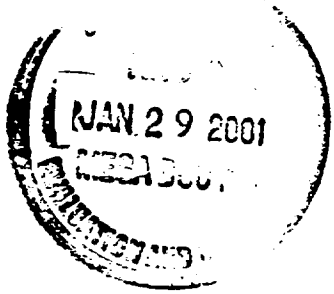
Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

DUPLICATE

8 pages redacted from this section of the approval package consisted of draft labeling

pharmaceuticals NDA AMENDMENT
BL

January 26, 2001



Jonathan K. Wilkin, M.D., Director
Division of Dermatological and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Response to FDA Request for Information

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets.

Additional reference is made to the sponsor's submission dated January 22, 2001 which requested changes to the table of pharmacokinetic parameters and the table of clinical results in the package insert. As a result of this submission, a teleconference was held between representatives of HFD-540 and the undersigned on January 23, 2001.

During this conference, it was agreed that the steady-state pharmacokinetic data would remain in the table, however, reference to capsules in the foot note would be removed and the single-dose data would be designated, in parentheses, as tablet. It was further agreed that the standard deviations of the efficacy variables would be included in the table of clinical results and the acronym for BOP would be described in the foot notes. These changes have been made to the package insert and are provided in Attachment #1 (also provided on diskette - MSWord 7.0).

Further reference is made to several communications between Cdr. Frank Cross, HFD-540 and Mr. Robert Ashley, CollaGenex on this date. During these communications, Cdr. Cross requested that CollaGenex provide the formula used to calculate the standard deviations of the efficacy variables and the data tables from NDA 50-744 (Study H) which provides the standard errors and "n" used to calculate the standard deviations.

The formula used in calculating the standard deviations is as follows:

ORIGINAL

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

The data tables from NDA 50-744 (Study H) which provide the standard errors and "n" for each efficacy variable (Mean gain in Alv, Mean decrease in PD, % of sites with loss of Alv $\geq$ 2 mm, and % of sites with BOP) can be found in Attachment #2.

Lastly, please note that the number of patients for the Periostat group and the placebo group in the clinical results table for which the standard deviations were based differ. We corrected the table by including the number of patients for each group.

I trust that this adequately responds to the Division's request. If there are any questions regarding this matter, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

13 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: January 17, 2001 Number of Pages (including cover sheet) – 20

TO: Christopher Powala, Senior Director, Drug Development and Regulatory Affairs
COMPANY: Collagenex Pharmaceuticals, Inc.
FAX #: 215-579-8577

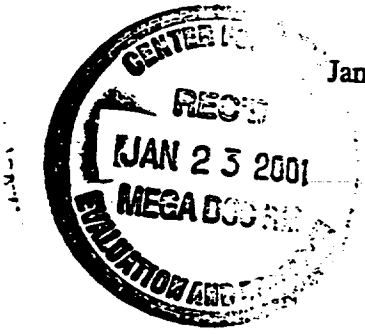
MESSAGE: For your review/concurrence please find attached to this facsimile transmission, draft labeling for your NDA 50-783, PERIOSTAT® (doxycycline hyclate tablets) 20 mg.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

19 pages redacted from this section of the approval package consisted of draft labeling

COLLAGENEX
pharmaceuticals



January 22, 2001

Jonathan K. Wilkin, M.D., Director
Division of Dermatological & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

NDA ORIG AMENDME

BL

RE: NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg Tablets
Response to FDA Comments: Labeling

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets.

Additional reference is made to the Divisions facsimile dated January 17, 2001 which contained a first draft of the product labeling for Periostat® tablets. Upon review of the labeling, we have the following revisions for your consideration.

Pharmacokinetics:

We propose including the "Steady-State 20 mg BID" data in the above-referenced table. Though these data was obtained following administration of the capsule formulation, we feel it is important information and as the Division has correctly pointed out in other sections of the labeling, the tablet formulation is bioequivalent. However, we do feel that the table should convey that the steady-state data are obtained from the administration of the bioequivalent capsule formulation. Therefore, we propose the table be revised as follows (All changes are highlighted):

ORIGINAL

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

Redacted 1

pages of trade secret and/or confidential commercial information

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pharmaceuticals

January 17, 2001

Dr. John V. Kelsey, Dental Team Leader
Division of Dermatological and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

NEW CORRESP
NC

RE: NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Submission of Periostat® Capsules (NDA 50-744) Quarterly Adverse Drug Experiences Report

Dear Dr. Kelsey:

Please refer to the pre-NDA meeting of October 26,1999 at which time you requested that CollaGenex provide, to your attention, a copy of the Quarterly Post-Marketing Report of Adverse Drug Experiences during the course of NDA review.

Submitted herewith, is a copy of the quarterly report that was submitted to the Division of Epidemiology and Pharmacovigilence on this date. During the reporting period of September 16, 2000 to December 15, 2000, there was no significant change in the overall incidence of adverse events, or in the incidence of specific adverse drug reactions as reported through post-marketing surveillance and in the literature. No significant safety issues were raised during the reporting period that are not addressed in the product labeling. Thus the safety data received to date remains consistent with the current product labeling for Periostat®.

If you have any questions regarding this submission, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

ORIGIN

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pharmaceuticals

January 10, 2000

Mr. Frank Cross, CDR
Sr. Regulatory Management Officer
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20850

RE: IND No. [redacted] - Periostat (doxycycline hyclate) 20 mg Tablets
Serial No. 002
Response to FDA Correspondence

Dear Mr. Cross:

Please refer to IND No. [redacted] for Periostat (doxycycline hyclate) 20 mg tablets which is proposed for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to the facsimile dated January 5, 2000 (see Attachment 1). It is my understanding that each of the issues raised has already been addressed, as outlined below. For ease in review, I have reiterated each comment which are followed by discussion:

1. **"The composition of the film coat excipient is not known."**

Discussion:

On the morning of November 23, 1999 a teleconference took place between Christopher Phillips, Director of Manufacturing, the undersigned, yourself and Dr. Vidra regarding this issue. Subsequently CollaGenex submitted a document dated November 23, 1999, Serial No. 001 in which the qualitative formula for the film coating and a certificate of analysis which included product specifications was provided. It was further noted during the teleconference that the coating is a proprietary formulation manufactured by [redacted] and all of its components meet USP, JP and EP specifications. CollaGenex agreed to provide, in the upcoming NDA submission for the tablets, a letter from [redacted] authorizing CollaGenex to reference their DMF for the film coating. Dr. Vidra agreed this would suffice.

2. **— month stability data for this drug product was faxed to the FDA on 11/23/99, however, the data lacked time zero data for proper comparison. Although the previously approved capsule formulation and new tablet formulation have similar excipients, additional stability data will still be required. Additional stability data should be reported throughout the EOP2 period until sufficient data is generated before Phase 3 clinical trials begin. If not, this limited data will provide only a limited expiration date.**

Discussion:

Immediately following the teleconference CollaGenex sent the referenced fax. Dr. Vidra then called to clarify where the initial data were. I pointed out the location on the second page of the fax. Furthermore, these data were also provided in the 11/23/99 submission (Serial No. 001).

The statement that "additional stability data should be reported throughout the EOP2 period until sufficient data is generated before Phase 3 clinical trials begin" is contrary to the agreement we reached during the October 26, 1999 Pre-IND/EOP2/Pre-NDA meeting, which was further confirmed during the 11/23/99 teleconference. It was agreed that no Phase 3 clinical studies need to be conducted as the Periostat 20 mg capsule is already approved. Since CollaGenex was not seeking a change in the indication, only a bioequivalence study bridging the capsules and tablets was necessary. Given the understanding that CollaGenex will be filing the Periostat Tablet NDA on March 31, 2000, it was agreed during the 11/23/99 telephone conversation that CollaGenex will submit —month stability data from 2 batches and— months stability data from 4 batches in the NDA. It was further agreed that CollaGenex would be able to submit a "Minor Amendment" during the review period to provide additional stability data (2 batches with — months and 6 batches with —nonths) along with statistical projection to support expiration dating.

Please acknowledge that this is your understanding of the agreement.

3. **"Impurity specifications are required."**

Discussion:

Per our previous discussions with the Division, CollaGenex intends to manufacture the 20 mg doxycycline hyclate tablets in accord with USP monograph which, like the capsules, does not require impurity testing/specification. However, we routinely report total impurities [redacted] The specifications for the drug product (i.e., current USP) were identified in Volume 2 of 2, page 112 of the original IND application. Please confirm the Division's acceptance of the USP specifications.

1.1-073

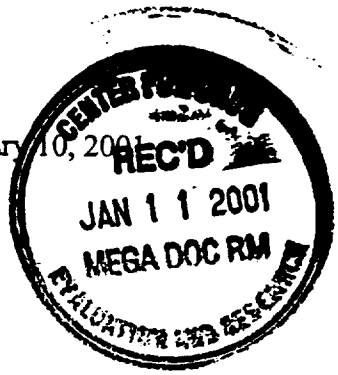
I feel it would be prudent to schedule a teleconference to clear up any misconception either of us have regarding the Tablet IND and upcoming NDA. I will contact you in a day or so to schedule the teleconference. In the meantime, if you have any questions regarding this submission, please contact me at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

1.1-074

COLLAGENEX
pharmaceuticals



January 10, 2001

Dr. James Vidra, Reviewing Chemist
Division of Dermatological & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

NDA ORIG AMENDMENT

BC

RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Chemistry, Manufacturing and Controls
Response to Request for Information

Dear Dr. Vidra:

In response to your phone communications of January 8th and 9th, 2001, I am providing herewith, additional chemistry, manufacturing and controls information. For ease in review, each of your requests are reiterated and are followed by our response.

1. Please provide the 12 month stability data from the 3 Periostat tablet validation lots.

Provided herewith, are 12 month room temperature (25°C/60%RH) stability data from the 3 validation lots. The table below identifies the location of the data for each lot per package configuration.

Attachment No.	Lot Number - Package Configuration
1	Lot # 990204 - 120cc Bottles
2	Lot # 990204 - 325cc Bottles
3	Lot # 990204 Blister Packs
4	Lot # 990205 - 120cc Bottles
5	Lot # 990205 - 325cc Bottles
6	Lot # 990205 Blister Packs
7	Lot # 990206 - 120cc Bottles
8	Lot # 990206 - 325cc Bottles
9	Lot # 990206 Blister Packs

ORIGINAL

Please provide information regarding the revision to the USP moisture specification for doxycycline hyclate 20 mg.

Attachment # 2 contains a letter from USP regarding the revision to the moisture specification from [redacted] to [redacted]%.

Furthermore, the sponsor is providing, as a separate desk copy, Supplement 001 for Periostat Capsules (NDA 50-744) that provides data to support this change in moisture specification.

I trust that this adequately responds to your requests. If you have any questions regarding this matter, please contact me at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

cc: Vidva
DeCamp
Wilkin
Diffie
Cross

FACSIMILE TRANSMISSION

DATE: January 5, 2000 Number of Pages (including cover sheet) - 1

TO: Christopher Powala, Director, Drug Development, Regulatory Affairs
COMPANY: Collagenex Pharmaceuticals, Inc.
FAX #: 215-579-1062

MESSAGE: Comments from our Chemistry Review of your original IND [redacted] follow:

1. The composition of the Film Coat excipient is not known.

2. — month stability data for this drug product was faxed to the FDA on 11/23/99, however, the data lacked time zero data for proper comparison. Although the previously approved capsule formulation and the new tablet formula have similar excipients, additional stability data will still be required. Additional stability data should be reported throughout the EOP2 period until sufficient data is generated before Phase 3 clinical trials begin. If not, this limited stability data will provide only a limited expiration date.

3. Impurity specifications are required.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

COLLAGENEX
pharmaceuticals

ORIG AMENDMENT
BC

January 5, 2001

Dr. James Vidra, Reviewing Chemist
Division of Dermatological & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Response to Chemistry Comments

Dear Dr. Vidra:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets.

Additional reference is made to the teleconference between the Dr. Vidra and Cdr. Frank Cross, HFD-540 and representatives from CollaGenex. During this teleconference, Dr. Vidra asked that the company provide a response to the following questions. Each of Dr. Vidra's questions are italicized and are followed by the Company's response.

1. ***Please describe the sampling plan for Periostat tablets?***

The sampling procedure is provided in Attachment # 1. Exact requirements for sampling Periostat Film-Coated Tablets for _____ are described in the current manufacturing process. Specifically, this can be found in Volume 1.3, page 115, item C. 10. A copy of this page is provided in Attachment # 2.

_____

_____ 50 tablets
100 tablets

2. ***Please provide a rationale for changing the hardness specification from _____ to report.***

At the suggestion of FDA (October 26, 1999 pre-IND/pre-NDA meeting) a hardness specification of _____ was added to the product specification for Periostat film-coated tablets. This specification was taken from the in-process tablet compression specifications listed in the manufacturing instructions for the core tablet.

ORIGINAL

Upon review of subsequent stability testing results, it was determined that the tablets (as is common for most tablet formulations) appear to soften over time, especially under accelerated conditions. However, all other test results remained well within specification - most notably, friability (NMT —%).

Given this data, the sponsor determined that the in-process specification of ——— was not appropriate for stability evaluation as long as the tablets remained intact (i.e., friability & appearance) and functioning properly (i.e., dissolution). Therefore, the specification was changed to report.

I trust that this adequately responds to each of your questions. If you have any questions regrading this matter, please contact me at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

Faxed Copy: Cdr. Frank Cross, Sr. Project Manager, HFD-540

COLLAGENEX
pharmaceuticals

March 31, 2000

ORIGINAL NDA SUBMISSION

Food and Drug Administration
Center for Drug Evaluation and Research
Documents and Records Section
12420 Parklawn Drive
Rockville, MD 20852

Attention: Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products (HFD-540)

RE: Original NDA Submission # 50-783
Periostat® (doxycycline hyclate tablets), 20 mg

Dear Dr. Wilkin:

Pursuant to Section 505 of the Federal Food Drug and Cosmetic Act and in reference to 21 CFR 314, we submit in duplicate, this original New Drug Application # 50-783 for Periostat® (doxycycline hyclate) 20 mg Tablets which was approved on September 28, 1998, in capsule form, for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

This application was the topic for discussion of an End-of-Phase 2/Pre-NDA Meeting held between CollaGenex and the Division of Dermatologic and Dental Drug Products on October 26, 1999. A subsequent teleconference was held on November 23, 1999 to discuss the Chemistry, Manufacturing and Controls section of this application. All agreements made at these meetings and subsequent communications have been included in this NDA.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(J).

If there are any questions regarding this application, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

COLLAGENEX
pharmaceuticals

March 30, 2000

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and
Dental Drug Products (HFD-540)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Wilkin:

The United States Federal Food, Drug and Cosmetic Act contains a requirement that sponsors of new drugs report to the U.S. Food and Drug Administration (FDA) whether they utilized the services of any person or firm in connection with the development or submission of a new drug application, abbreviated new drug application or antibiotic application that has itself been debarred by FDA or whose employees involved with the application have been debarred by FDA or convicted of certain acts. CollaGenex, Inc. is providing the following information:

1. CollaGenex is not currently, nor has it ever been, debarred by FDA.

2. CollaGenex is not currently, nor has it ever been, involved in a debarment proceeding with FDA.

3. CollaGenex has not within the past five years, nor has it ever, been convicted of a felony under U.S. federal law for conduct relating to the development or approval, including the process for development or approval, of any new drug applications (NDA), abbreviated new drug applications (ANDA) or abbreviated antibiotic drug applications (AADA) or convicted of a conspiracy or accessory to do the same.

4. CollaGenex has not within the past five years, nor has it ever, been convicted of a misdemeanor under U.S. federal law or a felony under state law for conduct relating to development of approval, of any NDA, ANDA or AADA or convicted of a conspiracy or accessory to do same.

5. No employee of CollaGenex who worked on the Periostat Tablet NDA or data to support any premarket approval application is not currently, or has ever been, debarred by FDA.

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

1.1-020

6. No employee of CollaGenex who worked on an application or data to support the Periostat Tablet NDA is currently, or ever has been, involved in a debarment proceeding with FDA.

7. No employee of CollaGenex who worked on an application or data to support the Periostat Tablet NDA has in the past five years, or ever, been convicted of any of the following acts:

   (I) a felony relating to the development or approval, including the process for development or approval, of any drug product or to any act relating to the regulation of any drug product under the U.S. Federal Food, Drug and Cosmetic Act, or a conspiracy to commit or an accessory in such a felony;

   (II) a misdemeanor under U.S. federal law or a felony under U.S. state law relating to the development or approval, of any drug product or to any act relating to the regulation of drug products under the Food, Drug and Cosmetic Act, or a conspiracy or accessory to commit the forgoing or a felony under U.S. federal law relating to the same;

   (III) a felony under either federal or state law (U.S.) which involved: bribery, payment of illegal gratuities, fraud, perjury, false statement, racketeering, blackmail, extortion, falsification or destruction of records, or interference with, obstruction of an investigation into, or prosecution of, any criminal offense or a conspiracy or accessory to do the same.

Certified and attested to this 30th Day of March, 2000, by:

Christopher Powala

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

CollaGenex Pharmaceuticals, Inc. hereby certifies that at no time did it utilize the services of any person or firm that has been debarred under subsections (a) or (b) [section 306 (a) or (b)] of the Federal Food, Drug and Cosmetic Act, in connection with this new drug application.

The following contract research organizations were employed by CollaGenex during the development of Periostat ® Tablets and are accompanied by a letter of certification reporting their position of good standing:

1. [redacted]

2. **Pharmaceutical Manufacturing Research Services, Inc. (PMRS), 423 Sargon Way, Horsham, PA 19044**

3. [redacted]

1.1-022

COLLAGENEX
pharmaceuticals

March 30, 2000

Cdr. Frank Cross, Project Manager
Division of Dermatologic and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Pre-Submission Desk Copy of Proposed Periostat Labeling

Dear Cdr. Cross:

Please refer to NDA No. 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets which will be submitted to the Division on March 31, 2000.

Additional reference is made to our March 29, 2000 telephone conversation. During this conversation you requested that I provide you with an advanced copy of the proposed Periostat labeling.

Submitted herewith is an advance hard copy of the Periostat labeling and on diskette (WordPerfect 6.1). Please note that the only changes made to the label are those references to capsules, Dosage and Administration section, How Supplied section and the Pharmacokinetics section. As requested by Dr. Jake Kelsey during the October 26, 1999 pre-IND/pre-NDA meeting, no changes were made to the Clinical Study section, Indications and Usage section or the Adverse Reactions section. I am also enclosing a copy of the previously approved labeling for Periostat capsules for use as a reference.

Further to our conversation, please be advised that the User Fee payment was made on March 30, 2000. Provided herewith is a copy of the payment documentation.

If you have any questions regarding this submission, please contact me at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

45 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

cc: Ghosh
Bushaw
Kelsey
Cross
Div. File
Archival File

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 28, 2000 Number of Pages (including cover sheet) - 1

TO: Christopher Powala, Director, Drug Development, Regulatory Affairs
COMPANY: Collagenex Pharmaceuticals, Inc.
FAX #: ~~215-579-1062~~ 215-579-8577

MESSAGE: Comments from our Biopharamceutics review of your original IND [redacted] follow:

1. The subjects should be healthy human volunteers between the age of 18 and 40 years (population).

2. As blood samples will be withdrawn up to 72 hours, each subject will be participating for about 82 hours for each of three study periods. Therefore, Duration of Subject Participation (3.5.1) needs to be changed accordingly (Study Duration).

3. A table for six possible order sequence permutation of treatments needs to be clarified (Dosage and Administration).

4. The term [redacted]' should be replaced with "indeterminant" in sections 5.5 and 5.6.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

COLLAGENEX
pharmaceuticals

April 24, 2000

Jonathan K. Wilkin. M.D., Director
Division of Dermatological & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

NDA [illegible] AMENDMENT

BC

RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Environmental Assessment Information

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets which is proposed for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to the April 13, 2000 telephone conference between the undersigned, Cdr Frank Cross, Project Manager, HFD-540 and Dr. James Vidra, Chemistry Reviewer, HFD-540. During this conversation, Dr. Vidra requested that in addition to CollaGenex claiming categorical exclusion pursuant to 21 CFR § 25.31(a), the Division would like to see the MEEC value recalculated to account for the potential of concurrent [redacted] distribution of Periostat capsules and tablets.

In response to Dr. Vidra's request, CollaGenex is providing herewith, a recalculation of the MEEC.

we trust that this adequately responds to Dr. Vidra's request. If there are any questions regarding this submission, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

ORIGINAL

COLLAGENEX
pharmaceuticals

April 24, 2000

Ralph Lillie, Pharm.D., Director
Division of Pharmacovigilence &
Epidemiology (HFD-730)
Room: B15-33
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Approved NDA 50-744 for Periostat® (doxycycline hyclate) 20 mg Capsules
Post-Marketing Reporting of Adverse Drug Experiences - Quarterly Report

Dear dr. Lillie:

Please refer to NDA 50-744 for Periostat® (doxycycline hyclate) 20 mg capsules which was approved on September 30, 1998 as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Submitted herewith, is CollaGenex's quarterly report of adverse drug experiences covering the period of December 16, 1999 to March 15, 2000.

If you have any question regarding this matter, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

Redacted 33

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COLLAGENEX
pharmaceuticals

April 19, 2000

Jonathan K. Wilkin, M.D., Director
Division of Dermatological and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drug
Rockville, MD 20857

NDA [illegible] AMENDMENT

RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Additional Safety Information

Dear Dr. Wilkin:

SU

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets which is proposed for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to the April 19, 2000 telephone conversation between the undersigned and Cdr. Frank Cross, Project Manager, HFD-540. During this conversation, Cdr. Cross requested that CollaGenex re-integrate the safety summary submitted in NDA 50-744 to include the data from the bioequivalence/food effect study. Because there were only a total of two subjects who experienced adverse events (sore throat, sinus congestion and headache) during the bioequivalence/food effect study (see Volume 1.8, page 066 of NDA 50-783) it was agreed that a re-integration of the safety summary would not be necessary. Cdr. Cross then asked that CollaGenex submit to NDA 50-783, the annual frequency and trend analysis from the spontaneous reporting of adverse events which was part of the Annual Report submitted to NDA 50-744 on November 30, 1999.

Submitted herewith, is the above-mentioned analysis of adverse events. It should be noted that the overall incidence of adverse drug reactions, and the incidence of specific, listed, adverse reactions, as reported through post-marketing surveillance and in the scientific literature, were consistent with the current product labeling for Periostat.

If there are any questions regarding this submission, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

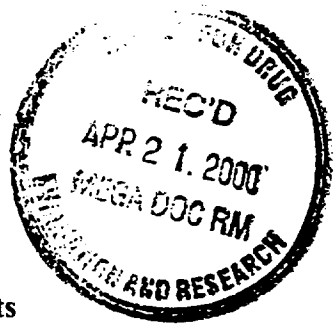
ORIGINAL

COLLAGENEX
pharmaceuticals

April 20, 2000

XR

Jonathan K. Wilkin, M.D., Director
Division of Dermatological & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857



RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Patent Information

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets which is proposed for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to the April 10, 2000 conversation between the undersigned and Cdr. Frank Cross, Project Manager, HFD-540. During this conversation, Cdr. Cross stated that although CollaGenex provided patent information/certification in NDA 50-783 by reference of NDA 50-744, it would be helpful if a full copy of the patent information/certification could be submitted to NDA 50-783.

In response to Cdr. Cross' recommendation, CollaGenex is submitting herewith, a complete copy of the patent information/certification to support NDA 50-783.

If you have any questions regarding this submission, please contact the undersigned at 215-579-7388 (telephone) and 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

ORIGIN.

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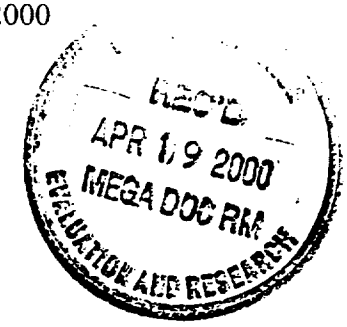
COLLAGENEX
pharmaceuticals

April 18, 2000

Jonathan K. Wilkin. M.D., Director
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

NEW CORRESP



RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Pediatric Waiver Request Supplementation

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets which is proposed for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to the Pediatric Wavier Request located in Volume 1, page 030 of the above-mentioned NDA. During an April 10, 2000 conversation between Mr. Christopher Powala, CollaGenex and Cdr. Frank Cross, Project Manager, HFD-540, Cdr. Cross stated that the Pediatric Waiver Request only addressed children less than or equal to eight years of age and requested that the company address those children between the age of 8 and 18 years. Provided below is a supplement to the existing Pediatric Waiver request:

Pediatric Waiver Request Supplementation:

In accord with the provisions of 21 CFR 314.55(2), CollaGenex hereby requests a full waiver of the requirement to submit data to support the safety and efficacy of Periostat in a pediatric population. Justification to support this request is provided below:

1. The warning section of the product labeling specifically states that tetracycline drugs are contraindicated in children from infancy to the age of 8 years. For ease in review, this warning is reiterated as follows. " The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used in this age group and in pregnant or nursing mothers unless the potential benefits may be acceptable despite the potential risk." A copy of the complete Periostat labeling can be found in Attachment 1 of this submission.

ORIGINAL

2. Periostat in indicated for the adjunctive treatment of ***Adult*** periodontitis. Adult periodontitis is a disease that rarely affects people under the age of 35 years with the majority of disease (90%) affecting those adults aged 55 to 64 years (see Attachment 2 which contains a position paper prepared by the American Academy of Periodontology). Therefore the indication proposed for Periostat has no impact on the pediatric population between the ages of infancy and 18 years.

3. Based on the above information, Periostat meets the requirement of 21 CFR § 314.55(c)(2)(iii) which states that there is evidence strongly suggesting that the drug product would be ineffective and/or unsafe in all pediatric age groups.

I trust that this Pediatric Waiver Request Supplementation adequately responds to the issue raised by Cdr. Cross. If you have any questions regarding this matter, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

HFD-540 / F.H.C. 055

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-783

APR 18 2000

Collagenex Pharmaceuticals, Inc.
Attention: Christopher Powala
Senior Director, Drug Development & Regulatory Affairs
41 University Drive
Newtown, PA 18940

Dear Mr. Powala:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Periostat (doxycycline hyclate) Tablets, 20mg

Therapeutic Classification: Standard (S)

Date of Application: March 31, 2000

Date of Receipt: April 3, 2000

Our Reference Number: NDA 50-783

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 2, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be Feburary 3, 2001 and the secondary user fee goal date will be April 3, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Frank H. Cross, Jr., Project Manager, at (301) 827-2020.

Sincerely,

[(S)] 4/18/00

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Archival NDA 50-783
HFD-540/Div. Files
HFD-540/F.H.Cross
A.Jacobs
W.DeCamp

DISTRICT OFFICE

Drafted by: smc/April 10, 2000

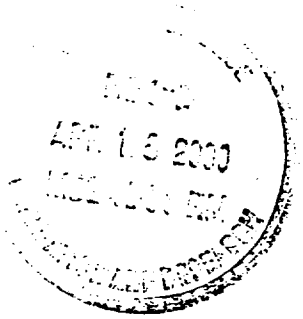
filename: N50783.AC

ACKNOWLEDGEMENT (AC)

COLLAGENEX
pharmaceuticals

April 17, 2000

Jonathan K. Wilkin. M.D., Director
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857



RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Notification of Inspection Readiness

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets which is proposed for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

This minor amendment provides notification that the following facilities who take part in the manufacture, packaging, release and stability testing of Periostat tablets are ready for inspection by the Agency. Each facility and their function is identified as follows:

Drug Substance Manufacturer:

The doxycycline hyclate raw material is synthesized, released and stability tested by the following:

Drug Product manufacturer:

The Periostat (doxycycline hyclate) 20 mg tablets are manufactured, by the following:

Pharmaceutical Manufacturing Research Services, Inc.
423 Sargon Way
Horsham, PA 19044
Phone: 215-957-9400
FAX: 215-957-6161

ORIGINAL

Drug Product Packaging:

The Periostat (doxycycline hyclate) 20 mg tablets are packaged and labeled by the following:

If you have any questions regarding this submission, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

Desk Copy: Cdr. Frank Cross, Project Manager, HFD-540

COLLAGENEX
pharmaceuticals

May 4, 2000

AMENDMENT

Bm

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Quarterly Post-Marketing Adverse Drug Experiences Report

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets which proposed for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

At the request of Cdr. Frank Cross, Project Manager, HFD-540, we are providing herewith, a copy of the April 24, 2000 Quarterly Report of Post Marketing Adverse Drug Experiences.

In addition, Cdr. Cross requested that we clarify the Commitment section located Volume 1.1, page 030 of NDA 50-783. Item 3. is hereby clarified to reflect that the Phase 4 requirement for NDA 50-744 for Periostat Capsules is referring to food versus fasting study that is presented in NDA 50-783.

I trust that this submission adequately responds to the Division's request. If there are any questions relating to this matter, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

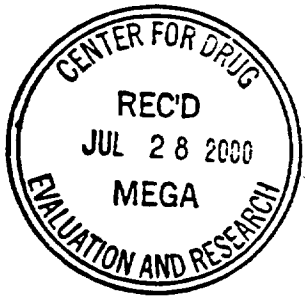
Desk Copy: Cdr. Frank Cross, Project Manager, HFD-540 (cover letter only)

DUPLICATE

COLLAGENEX
pharmaceuticals

July 27, 2000

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857



- AMENDMENT
BM

RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Quarterly Report of Adverse Drug Experiences

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets which was filed on March 31, 2000.

Per the request of Dr. John Kelsey, Dental Team Leader, HFD-540, we are providing herewith, a copy of the Post-Marketing Quarterly Report of Adverse Drug Experiences which was filed on this date with the Division of Pharmacovigilence and Epidemiology (HFD-730).

We trust that this adequately responds to Dr. Kelsey's request. If there are any questions regarding this submission, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

ORIGINAL

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

COLLAGENEX
pharmaceuticals

October 30, 2000

Ralph Lillie, Pharm.D., Director
Division of Pharmacovigilence &
Epidemiology (HFD-730)
Room: B15-33
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Approved NDA 50-744 for Periostat® (doxycycline hyclate) 20 mg Capsules
Post-Marketing Reporting of Adverse Drug Experiences - Quarterly Report

Dear Dr. Lillie:

Please refer to NDA 50-744 for Periostat® (doxycycline hyclate) 20 mg capsules which was approved on September 30, 1998.

Submitted herewith, is CollaGenex's quarterly report of adverse drug experiences covering the period of June 16, 2000 to September 15, 2000.

If you have any questions regarding this matter, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

cc: Dr. John Kelsey, HFD-540

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COLLAGENEX
pharmaceuticals

October 11, 2000

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

NDA ORIG AMENDMENT

BC

RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Updated Stability

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets.

Additional reference is made to the October 26, 1999 pre-NDA meeting and the November 23, 1999 teleconference between Dr. James Vidra, Reviewing Chemist and Mr. Christopher Powala, CollaGenex. During this meeting and subsequent teleconference, it was agreed that CollaGenex would submit additional stability data as a minor amendment to support the proposed expiration dating for the tablets.

Provided herewith are updated stability data on six individual batches of Periostat tablets. The table below describes the data currently available. Detailed findings from the stability testing can be found in Attachment 1.

Batch No.	Type of Batch	Batch Size	Months @ —	Months @ —
990061	Feasibility	—		
990062	Feasibility	—		
990175	Pilot	—		
990204	Validation	—		
990205	Validation	—		
990206	Validation	—		

It should be noted that all assay and related substances results remain well within specification after – months at . ——— and – months at ———

ORIGINAL

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

In addition, these data have been subjected to statistical analysis in order to project shelf life. [redacted] a SAS program for conducting stability analysis and expiration dating estimation was used to analyze the data. The results of these analyses can be found in Attachment 2. It should be noted that the projected shelf life extends long past the proposed expiration dating.

Should the Division have any questions regarding this submission, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

COLLAGENEX
pharmaceuticals

November 6, 2000

Dr. John V. Kelsey, Dental Team Leader
Division of Dermatological and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

NDA ORIG AMENDMENT

BM

RE: NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Submission of Periostat® Capsules (NDA 50-744) Quarterly Adverse Drug Experiences Report

Dear Dr. Kelsey:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets that was filed on March 30, 2000.

Further reference is made to the October 26, 1999 pre-NDA meeting. During this meeting, you requested that CollaGenex provide a copy of the Quarterly Post-Market Report of Adverse Drug Experiences, to your attention, during the course of NDA review. Submitted herewith, is a copy of the Quarterly report that was submitted to the Division of Epidemiology and Pharmacovigilence on October 30, 2000.

During the reporting period (June 16, 2000 - September 15, 2000), there was no significant change in the overall incidence of adverse events, or in the incidence of specific adverse drug reactions, as reported through post-marketing surveillance and in the scientific literature. No significant safety issues were raised during the reporting period that are not addressed in the product labeling. Thus, the safety data received to date remain consistent with current product labeling for Periostat.

In addition, I would like to bring your attention to the time this NDA has been under review. During the October 26, 1999 meeting, Dr. Wilkin indicated that the Division would review this NDA in a 6 month time period. It is our understanding from verbal comments of Mr. Frank Cross that the NDA is under review and the Dental Division is awaiting comments from the Biopharmaceutics Division. As the NDA was filed on March 31, 2000 the 6 months would have expired on October 1, 2000. The PDUFA deadline aside, given the straightforward nature of this submission, it would seem reasonable that a review could have been prepared in a more timely fashion.

Furthermore, I would like to point out that the _____ on April 30, 2000. The _____

DUPLICATE

It is disappointing that despite filing the NDA with FDA 30 days prior to [redacted] Is there anything CollaGenex can do to expedite the review process. At the least, can the Division provide CollaGenex with an indication of any outstanding issues from the Division's perspective?

If you have any questions regarding this matter, please contact me at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

COLLAGENEX
pharmaceuticals

BC

December 19, 2000

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food & Drug Administration
9201 Corporate Drive
Rockville, MD 20857

RE: NDA 50-783 - Periostat® (doxycycline hyclate) 20 mg Tablets
Minor Amendment: Environmental Assessment Information

Dear Dr. Wilkin:

Please refer to NDA 50-783 for Periostat® (doxycycline hyclate) 20 mg tablets which is proposed for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to the December 19, 2000 teleconference between the undersigned and Cdr. Frank Cross, Sr. Project Manager, HFD-540. During this teleconference, Cdr. Cross referred the Sponsor to the Environmental Assessment section of NDA 50-783 and requested that CollaGenex formally request a claim for categorical exclusion.

In response to this request, CollaGenex is hereby requesting a claim for categorical exclusion.

If there are any questions regarding this matter, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

Desk Copy: Cdr. Frank Cross, HFD-540

DUPLICATE

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax