



West-ward
PHARMACEUTICAL CORP.

465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

August 13, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

A. ACTION REQUESTED

On August 30, 2001, West-ward Pharmaceutical Corporation ("West-ward") submitted an abbreviated new drug application ("ANDA") for doxycycline hyclate capsules, 20 mg, claiming Periostat® capsules, 20 mg, as the reference listed drug. FDA accepted the application, ANDA 65-103, for filing as of August 31, 2001 by letter dated September 28, 2001. At that time, and to this date, Periostat® capsules have been listed as a reference listed drug in Approved Drug Products with Therapeutic Equivalence Evaluations, or the "Orange Book."

In a Citizen Petition dated July 10, 2002, CollaGenex Pharmaceuticals, Inc. ("CollaGenex") claims that it withdrew its NDA for Periostat® (doxycycline hyclate) 20 mg capsules in September 2001 in accordance with 21 C.F.R. § 314.150(c).¹ In its petition, CollaGenex requests the Commissioner to refuse to approve ANDAs for generic Periostat® capsules: (a) until FDA determines that the drug product was not withdrawn for reasons of safety and effectiveness; and (b) unless the application is accompanied by a petition seeking such a determination as provided under 21 C.F.R. § 314.122. CollaGenex further requests that FDA move Periostat® capsules to the "Discontinued Drug Product List" in the Orange Book and announce the withdrawal of approval of the NDA in the Federal Register as provided by 21 C.F.R. § 314.152, and make these actions retroactively effective to the date the NDA allegedly was withdrawn.

West-ward's ANDA 65-103 was received by FDA and accepted for filing before CollaGenex voluntarily withdrew its NDA. Thus, FDA need not determine that Periostat® was not withdrawn for reasons for safety and effectiveness pursuant to procedures under 21 C.F.R. § 314.122. CollaGenex's request for inclusion of Periostat® capsules on the "Discontinued Drug Product List" in the Orange Book, and its request for an announcement of the withdrawal of

¹ FDA's regulation provides that, "FDA will withdraw approval of an application or abbreviated application if the applicant requests its withdrawal because the drug subject to the application or abbreviated application is no longer being marketed, provided none of the conditions listed in paragraphs (a) and (b) of this section applies to the drug." 21 C.F.R. §314.150(c). (Paragraphs (a) and (b) involve conditions relating to safety and effectiveness.)

approval of the NDA in the Federal Register, likewise have no bearing on FDA's ability to approve ANDA 65-103 as submitted. The application not only preceded the filing of the CollaGenex petition, it was accepted for filing long before sales of Periostat® capsules by CollaGenex's customers stopped. The sales were made pursuant to prescriptions of dentists to whom CollaGenex promoted the drug.

Nevertheless, in the interest of preventing any delay in the approval of its ANDA, West-ward is submitting this petition under 21 C.F.R. §§ 10.25(a), 10.30, 314.122, and 314.161 to request the Commissioner of Food and Drugs to make a determination that Periostat® capsules were withdrawn for reasons other than safety or effectiveness. Alternatively, if FDA determines that Periostat® 20 mg capsules should continue to be listed as a reference listed drug and/or agrees that this petition is not required under the regulations as discussed above, West-ward requests that FDA promptly deny the CollaGenex petition, as well as dismiss this petition.

B. STATEMENT OF GROUNDS

1. Background

FDA approved NDA 50-744 for Periostat® (doxycycline hyclate USP) capsules, 20 mg, by letter dated September 30, 1998. A copy of the approval letter is attached as **Exhibit A**. CollaGenex began commercially distributing the capsules in November 1998. A copy of a CollaGenex press release announcing the product launch is attached as **Exhibit B**.

CollaGenex submitted NDA 50-783 for a 20 mg tablet formulation of Periostat® dated March 31, 2000. FDA approved NDA 50-783 on February 2, 2001. A copy of the approval letter is attached as **Exhibit C**. CollaGenex launched the tablet formulation of Periostat® in July 2001. A copy of a CollaGenex press release announcing the product launch is attached as **Exhibit D**. In the press release, CollaGenex stated that the tablets "will eventually replace the current capsule formulation."

On August 30, 2001, West-ward submitted an abbreviated new drug application ("ANDA") for doxycycline hyclate capsules, 20 mg, claiming Periostat® capsules, 20 mg, as the reference listed drug. FDA accepted the application for filing as of August 31, 2001 by letter dated September 28, 2001. A copy of FDA's letter is provided as **Exhibit E**. Periostat® capsules were then and continue to be listed as a reference listed drug in Approved Drug Products with Therapeutic Equivalence Evaluations, or the "Orange Book."

West-ward recently learned from a citizen petition submitted by CollaGenex that, by letter dated September 24, 2001, CollaGenex purported to withdraw NDA 50-744 for Periostat® capsules in accordance with 21 C.F.R. § 314.150(c). A copy of CollaGenex's citizen petition is attached as **Exhibit F**. In its withdrawal letter, CollaGenex refers to a prior agreement with the agency "to withdraw NDA 50-477 after the transition from capsules to tablets was complete."

2. Evidence Demonstrating Periostat® Capsules Were Withdrawn
for Reasons Other than Safety or Effectiveness

Publicly available documents identify several reasons unrelated to Periostat® safety or effectiveness for CollaGenex's decision to voluntarily withdraw Periostat® capsules from the market:

- NDA 50-744 was approved upon condition that CollaGenex conduct a Phase 4 study or studies. See Exhibit A at 2, which does not disclose the exact nature of all Phase 4 commitments because the pertinent text is redacted. However, it appears that at least one of the commitments, and the principal one at that, was an in vivo food effect study. As noted in the pre-IND/End of Phase II meeting minutes discussing the tablet dosage form and its relationship to the approved capsules, "[t]he protocol as designed will address the impact of food on the Periostat dosage form and thus fulfill the Agency Bipharmaceutic's Phase 4 request for NDA 50-744." Exhibit G at 3. The minutes then reflect that "the FDA would release the Sponsor [CollaGenex] from their previous phase IV commitment related to the capsule [provided] the capsule would no longer be in the marketplace." *Id.*
- The only clinical evaluation of the new tablet dosage form CollaGenex was required to perform was a bioequivalence study to show that the tablets were therapeutically equivalent to the approved capsules pursuant to the draft Food-Effect Bioavailability Bioequivalence Studies Guidance issued October 1997. *Id.* Indeed, the only apparent reason that the tablets were approved pursuant to an NDA submission was that CollaGenex declined to seek and file the alternative ANDA. It was told by FDA that it could "submit this application as a 505(b)(1) application or submit a suitability petition for this application to be granted ANDA status." *Id.* at 1. It should go without saying that an ANDA suitability petition may not be granted, and FDA would not suggest consideration of one to a new drug sponsor, if the predicate drug was regarded as unsafe or ineffective and the covering application should be withdrawn on safety or lack of effectiveness grounds.
- In a press release announcing the approval of Periostat® tablets, CollaGenex represented that the "tablets can be manufactured at a lower cost than capsules, and we expect to experience improvements in our gross margin after the tablets are launched later this year." A copy of the press release is provided as Exhibit H. A press release announcing the launch of Periostat® tablets further explained: "The newly-developed manufacturing method of tablets allows our contract manufacturer to produce substantially larger batch sizes than previously . . . which leads to considerable improvements in manufacturing efficiency. We expect to see the full financial impact of this in the fourth quarter of this year." A copy of the press release is provided as Exhibit D. Neither of these releases suggests that CollaGenex had reservations about, or had received notice from FDA concerning, a lack of safety of the capsules. Effectiveness could hardly be an issue in that the two dosage forms are bioequivalent.

- The press release announcing the launch of Periostat® tablets reflects that strategic marketing purposes also motivated the switch from capsules to tablets. In the release, CollaGenex stated: "Many patients find tablets easier to swallow than capsules, and tablets are a much preferred dosage formulation in Europe One additional benefit of the tablet formulation is that the CollaGenex salesforce will now be able to sample a convenient blister pack to dentists to facilitate trial of Periostat in their patients. Previously, sampling had been limited to the provision of a bottle of 100 capsules, from which the dentist had to dispense samples for patients." See Exhibit D.

These documents demonstrate that CollaGenex's decision to withdraw Periostat® capsules was due to economic and strategic marketing reasons.

3. Evidence Demonstrating Periostat® Capsules Were Not Withdrawn for Reasons of Safety or Effectiveness

West-ward has reviewed publicly available documents relating to the approval of NDA 50-744 and 50-583 for Periostat® 20 mg capsules and 20 mg tablets and found no evidence that CollaGenex withdrew its capsules NDA for reasons of safety or effectiveness. These documents show that the currently marketed tablet formulation is, other than in dosage form, essentially identical to the withdrawn capsule formulation, and that the NDA for the tablet formulation referenced the safety and efficacy studies that supported the capsule NDA. FDA's review and evaluation of pharmacology/toxicology data for the tablet formulation states that the "formulations and proposed usage of the two [capsule and tablet] products are identical, with the exception that the tablets contain [redacted] (a film coating agent) in lieu of a hard gelatin capsule." A copy of the review is provided as **Exhibit I**. The only additional studies conducted in support of the NDA for Periostat® tablets were the bioequivalence studies to demonstrate equivalence with the capsules. See FDA's Chemistry Reviews for NDA 50-783 provided as **Exhibit J**.

It stands to reason, therefore, that the capsules could not be withdrawn for reasons of safety or effectiveness without similar issues affecting the currently marketed tablets. There is no indication that the hard gelatin capsule presented any safety or effectiveness issues.

We also note that no recalls or other enforcement action, other than untitled letter issued by the Division of Drug Marketing, Advertising and Communication ("DDMAC") in October 2000 regarding certain advertisements for Periostat®, have been reported for Periostat® capsules.

C. ENVIRONMENTAL IMPACT

The action requested is categorically excluded under 21 C.F.R. §§ 25.30(a) and 25.31(d) and, therefore, no environmental assessment or environmental impact statement is required.

D. ECONOMIC IMPACT

Economic impact information will be provided if requested by the Commissioner.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



Elizabeth A. Marro
Senior Director
Regulatory Affairs and Quality Assurance
West-ward Pharmaceutical Corporation
465 Industrial Way West
Eatontown, NJ 07724
(732) 542-1678

Of Counsel:

Eugene M. Pfeifer
Elizabeth S. Crockett
King & Spalding
1730 Pennsylvania Avenue, N.W.
Washington, D.C. 20006
(202) 737-0500



NDA 50-744

SEP 30 1998

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

Dear Mr. Powala:

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

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

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

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

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

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

NDA 50-744

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

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

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

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

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

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

NDA 50-744

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

Sincerely,

/s/

Jonathan K. Wilkin, M.D.

Director

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

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August 7, 2002

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Investor Relations

Press Releases

CollaGenex Pharmaceuticals, Inc. (ticker: CGPI, exchange: NASDAQ) News Release - 11/18/1998

CollaGenex Launches Periostat First-Of-Its-Kind Medication in Capsule Form for Adult Periodontitis

NEWTOWN, Pa.--Nov. 18, 1998--CollaGenex Pharmaceuticals Inc. (Nasdaq CGPI) announced Wednesday that Periostat(R), a unique, first-of-its-kind oral medication for the adjunctive treatment of adult periodontitis, is now available by prescription.

Approved by the U.S. Food and Drug Administration (FDA) on September 1998, Periostat is to be used following scaling and root planing (SRP) to improve the effectiveness of this standard periodontal procedure.

The new medication was recently unveiled to the nearly 20,000 dental professionals attending the American Dental Association's (ADA) annual meeting in late October. Periostat has achieved widespread distribution in the largest drug wholesalers and many of the leading retail pharmacy chains.

Periostat is the first medication specifically indicated for the treatment of periodontitis to be made available to patients through their pharmacies. A capsule taken twice a day over a period of months, Periostat is prescribed by the periodontist or dentist following SRP.

Clinical studies have shown that Periostat administered after SRP improve clinical attachment level by up to 52% and reduced pocket depth by as much as 67% compared to SRP plus placebo. These benefits were observed as early as three months into the study and were maintained over the nine month period of the trial.

"Since FDA approval, dental professionals have expressed tremendous interest in Periostat and the clinical benefits it provides as part of regular periodontal care," said president and chief executive officer Brian M. Gallagher, PhD.

"We are pleased to now make this safe, effective and convenient treatment available to them and to their patients through their local pharmacist. We have worked hard to ensure that Periostat is readily available in the chain and independent pharmacies and we're very pleased with the pharmacy acceptance of the product."

Periostat is the only treatment for adult periodontitis that has been shown to suppress the tissue-destroying activity of collagenase, an enzyme

overproduced by the body in response to bacterial infection in the periodontal pocket.

Collagenase breaks down the supporting structures (gums, ligaments, bone) that hold the teeth in place. Recent research has demonstrated that periodontitis, the leading cause of adult tooth loss, is most effectively combated with a treatment approach that addresses the two key components of the disease - bacterial infection and the enzymes that destroy connective tissues.

In spite of heightened public awareness and greater emphasis on oral hygiene, the prevalence of periodontitis in the U.S. had declined little over the past generation. The disease now affects an estimated one out of every three adults in the U.S., leading to expenditures of approximately \$6 billion annually for disease treatment.

Recent research has suggested that people with periodontitis may be at increased risk for heart disease, stroke and having low birth-weight babies.

CollaGenex Pharmaceuticals is an emerging pharmaceutical company that is developing and commercializing innovative proprietary medical therapies for the treatment of periodontal disease and other pathologies characterized by the progressive degradation of the body's connective tissues.

The company's core technology involves modulating the body's pathologic response to certain acute and chronic illnesses.

In particular, CollaGenex has developed inhibitors of certain chronic degenerative processes that lead to the destruction of connective tissue during inflammation. These inhibitors have shown the potential to treat a variety of diseases including periodontal disease and inflammatory disease of the musculoskeletal, respiratory and gastrointestinal systems.

CollaGenex and its collaborators also are researching and developing other potential applications of its technology, particularly cancer metastasis and diabetic complications.

For more information about Periostat and for full prescribing information, contact CollaGenex Professional Relations at 888/339-5678. To receive additional information on CollaGenex, please visit the Company's web site at www.collagenex.com, which is not a part of this press release.

This news release contains certain forward-looking statements within the meaning of section 21E of the Securities and Exchange Act of 1934, as amended.

Investors are cautioned that forward-looking statements involve risks and uncertainties which may affect the Company's business and prospects, including without limitation the successful implementation of the company sales and marketing plans and uncertainties relating to clinical trials of products under development, all as discussed in the Company's periodic filings with the U.S. Securities and Exchange Commission.

CONTACT: CollaGenex
Nancy C. Broadbent, C.F.O.
or
Mark E. Greenlee, D.D.S., Director, Professional Relations





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-783

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

Dear Mr. Powala:

Please refer to your new drug application (NDA) dated March 31, 2000, received April 3, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Periostat[®] (doxycycline hyclate tablets) 20 mg.

We acknowledge receipt of your submissions dated April 17, 18, 19, 20 and 24, May 4, July 27, October 11, November 6, December 19, 2000 and January 5, 10, 17, 22, 26, 30 and 31, 2001.

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

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 50-783." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

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

If you have any questions, please call Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

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August 7, 2002

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Investor Relations

Press Releases

CollaGenex Pharmaceuticals, Inc. (ticker: CGPI, exchange: NASDAQ) News Release - 7/2/2001

CollaGenex Pharmaceuticals Introduces Periostat Tablet; Tablets Offer Significant Manufacturing Efficiencies and Patient Benefits Compared Current Capsule Formulation

NEWTOWN, Pa., Jul 2, 2001 (BUSINESS WIRE) -- CollaGenex Pharmaceuticals, Inc. (Nasdaq:CGPI) today announced the launch of a tab formulation of Periostat(R), the Company's lead drug for the adjunctive treatment of adult periodontitis.

The tablets will eventually replace the current capsule formulation of Periostat and offer significant manufacturing efficiencies and patient benef

"We are pleased to be introducing our tablet formulation of Periostat ahea of schedule," said Brian M. Gallagher, PhD, chairman, president and chief executive officer of CollaGenex. "Many patients find tablets easier to swallow than capsules, and tablets are a much preferred dosage formulation in Europe, where we hope to begin receiving the necessary regulatory approvals for marketing later this year."

"The newly-developed manufacturing method for tablets allows our contra manufacturer to produce substantially larger batch sizes than previously," continued Dr. Gallagher, "which leads to considerable improvements in manufacturing efficiency. We expect to see the full financial impact of this the fourth quarter of this year."

One additional benefit of the tablet formulation is that the CollaGenex salesforce will now be able to sample a convenient blister pack to dentists facilitate trial of Periostat in their patients. Previously, sampling had been limited to the provision of a bottle of 100 capsules, from which the dentist had to dispense samples for patients.

In line with its stated goal to outsource capital-intensive operations such a manufacturing and packaging, CollaGenex has contracted with PMRS Inc., Horsham, PA, to manufacture Periostat tablets for worldwide supply, and P Inc., Philadelphia, PA to pack product for the US market.

CollaGenex Pharmaceuticals, Inc. is a specialty pharmaceutical company focused on providing innovative medical therapies to the dental market.

The Company's lead product, Periostat, was approved by the FDA in September 1998 and is the first and only pharmaceutical to treat periodon

disease by inhibiting the enzymes that destroy periodontal support tissues

In February 2001, the FDA granted marketing approval for a new tablet formulation for Periostat. Periostat is marketed to the dental community by CollaGenex through a professional pharmaceutical sales force composed of approximately 120 sales representatives and managers.

Currently, the Company's dental sales force is also marketing Vioxx(R), a Merck & Co. drug that CollaGenex co-promotes for the treatment of acute dental pain, and Dentaplex(TM), a unique formulation of vitamins and mineral supplements developed by CollaGenex and MediNiche, Inc. to promote oral health.

Research has shown that the enzyme suppression technology underlying Periostat may also be applicable to other diseases involving destruction of the body's connective tissues, including cancer metastases (Metastat) and a broad range of inflammatory diseases.

CollaGenex is developing a series of novel, proprietary compounds known as IMPACS (Inhibitors of Multiple Proteases and Cytokines) to address these applications. The Company intends to pursue further research and development of these technologies primarily through partnerships with third parties.

To receive additional information on the Company, please visit our Web site at www.collagenex.com, which is not a part of this press release.

Periostat(R), Metastat(R), IMPACS(R) and Dentaplex(TM) are trademarks of CollaGenex Pharmaceuticals, Inc. CollaGenex(R) and Periostat(R) are trademarks of CollaGenex International Limited. VIOXX(R) is a trademark of Merck & Co., Inc.

CONTACT: CollaGenex Pharmaceuticals, Inc.
Nancy C. Broadbent, 215/579-7388
or
Investor Relations:
In-Site Communications, Inc.
Lisa Carlton-Wilson, 212/759-3929

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July 10, 2002

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Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

A. Action Requested

CollaGenex Pharmaceuticals, Inc. ("CollaGenex") submits this petition under Sections 505(j)(2)(A) and 505(j)(7)(C) of the Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. §§ 10.30, 314.122, 314.127(a)(11), and 314.161(a)(1) to request that, because Periostat (doxycycline hyclate) 20 mg capsules ("the capsules") were voluntarily withdrawn from sale in the United States in 2001, the Commissioner of Food and Drugs refuse to approve any ANDA for a generic version of the capsules until FDA determines that they were not withdrawn for reasons of safety or effectiveness. CollaGenex also asks that the Commissioner refuse to receive or approve any abbreviated new drug application ("ANDA") for a generic version of the capsules that is not accompanied by a petition seeking a determination about whether they were withdrawn for safety or effectiveness reasons, and rescind any previous receipt or approval of any ANDA which refers to the capsules as the listed drug.

CollaGenex further asks the Commissioner to immediately move the capsules to the "Discontinued Drug Product List" in Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the "Orange Book," and to publish a Federal Register notice announcing the withdrawal of the NDA for the capsules. Both actions should take effect retroactive to the date of the capsules' withdrawal from sale.

CollaGenex also is filing a Petition for Stay of Action asking the Commissioner to stay the receipt or approval of any ANDAs until final resolution of the issues raised in this Citizen Petition.

B. Statement of Grounds

FDA approved Periostat capsules in September 1998. The agency approved Periostat tablets in February 2001.

CollaGenex voluntarily stopped the distribution and marketing of Periostat capsules in August 2001. Since then, it has sold only Periostat tablets. In September 2001, it wrote to the agency to withdraw the new drug application (NDA) for Periostat capsules in accordance with 21 C.F.R. § 314.150(c). A copy of the letter is attached as Exhibit A. CollaGenex also filed

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under 21 C.F.R. § 314.81(b)(3)(iii) the required FDA Form 2657 regarding the capsules' withdrawal from sale. A copy is attached as Exhibit B. In short, the capsules were voluntarily withdrawn from sale, and CollaGenex submitted to FDA the required paperwork for voluntary withdrawals from sale.

FDA did not, however, publish a notice in the Federal Register announcing the withdrawal of the NDA for Periostat capsules, as it is required to do under 21 C.F.R. § 314.152. Nor did it move the capsules to the "Discontinued Drug Product List," which the Orange Book states is the appropriate list for "approved products that ... have been discontinued from marketing[.]" Orange Book, Section 2.1, p. 2-1. Thus, would-be ANDA applicants have been unable to learn from the usual public sources that the capsules were voluntarily withdrawn from sale.

FDA's regulations require an ANDA that "refers to...a listed drug that has been voluntarily withdrawn from sale in the United States" to be accompanied by a petition requesting a determination that it was not withdrawn for safety or effectiveness reasons (a "§ 314.122 petition"). 21 C.F.R. § 314.122(a). Because the capsules were voluntarily withdrawn from sale in 2001, FDA cannot receive or approve an ANDA that refers to them unless the ANDA is accompanied by a § 314.122 petition.

CollaGenex believes that at least one ANDA has been submitted for a generic version of the capsules. Specifically, it has learned that West-Ward Pharmaceutical Corporation has asked to add its version of the capsules to the New Jersey Drug Utilization Council's list of approved generic substitutions, List of Interchangeable Drug Products, August 2002 Proposed Amendments, available at www.state.nj.us/health/mgmt/rulepro0802a.htm, a step generic drug companies usually take only after submission of an ANDA. Although 21 C.F.R. §§ 10.25 and 10.30 require § 314.122 petitions to be publicly available, CollaGenex has found no such petition in FDA's dockets. It therefore believes that any ANDAs for the capsules were not accompanied by the required § 314.122 petitions.

If sponsors have submitted ANDAs not accompanied by § 314.122 petitions, it may well be due to their unawareness of the need for a § 314.122 petition, because of FDA's failure to withdraw the NDA for Periostat capsules and move the capsules to the Orange Book's discontinued list. FDA's mistakes cannot, however, justify allowing ANDAs referring to Periostat to be received or approved without an accompanying § 314.122 petition. Somerset Pharmaceuticals, Inc. v. Shalala, 973 F. Supp. 443 (D. Del. 1997).

FDA should now take all steps necessary to rectify the situation:

1. FDA should refuse to approve any ANDA for a generic version of the capsules until FDA determines that they were not withdrawn for reasons of safety or effectiveness.
2. FDA should refuse to receive or approve any ANDA that is not accompanied by a § 314.122 petition, and rescind any previous receipt or approval of any ANDA that refers to the capsules as the listed drug.
3. FDA should immediately move the capsules to the Discontinued Drug Product List in the Orange Book and publish a Federal Register notice withdrawing the NDA for the

capsules, both of which should be retroactive to the date of the capsules' voluntary withdrawal from sale.

C. Environmental Impact

The action requested qualifies for categorical exclusion from the requirement of issuance of an environmental assessment under 21 C.F.R. § 25.31(a). CollaGenex does not believe that any environmental impact will result from the granting of this petition.

D. Economic Impact

In accordance with 21 C.F.R. § 10.30(b), CollaGenex will provide data concerning the economic impact of the action sought if requested by the Commissioner.

E. Certification

CollaGenex certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to CollaGenex that are unfavorable to the petition.

Christopher V. Powala/aeb

Christopher V. Powala
Senior Director, Drug Development
and Regulatory Affairs
CollaGenex Pharmaceuticals, Inc.
41 University Drive
Newtown, PA 18940
(215) 579-7388

Of Counsel:

Nancy L. Buc
Abby E. Brandel
Buc & Beardsley
919 Eighteenth Street, N/W.
Suite 600
Washington, D.C. 20006
(202) 736-3600

Exhibit A



September 24, 2001

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

**RE: NDA No. 50-744 - Periostat® (doxycycline hyclate) 20 mg Capsules
Annual Report and Withdrawal of NDA**

Dear Dr. Wilkin,

During the pre-IND/NDA meeting held on October 26, 1999, CollaGenex agreed to withdraw NDA 50-744 after the transition from capsules to tablets was complete (see Attachment 1). In accord with that agreement CollaGenex Pharmaceuticals, Inc. is hereby withdrawing NDA 50-744 for Periostat® Capsules. The last batch of capsules was manufactured and released in May 2001. All capsules have been shipped from our warehouse. For your information we are also enclosing a copy of the completed Form 2657 delisting Periostat® Capsules (see Attachment 2), which was submitted to the Information Management Team on August 8, 2001.

In withdrawing the NDA, we are providing, herewith, the final Annual Report for NDA 50-744 for Periostat® (doxycycline hyclate) 20 mg Capsules.

If you have any questions, please contact the undersigned at 215-579-7388 (voice) or 215-579-8577 (facsimile).

Sincerely,

A handwritten signature in black ink, appearing to read "Christopher Powala", written over a horizontal line.

Christopher Powala, Senior Director
Drug Development and Regulatory Affairs

Exhibit B

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
DRUG PRODUCT LISTING
(In accordance with Public Law 92-387)

NAME AND ADDRESS OF FIRM
COLLAGENEX PHARMACEUTICALS, INC.
41 UNIVERSITY DRIVE, SUITE 200
NEWTOWN, PA 18940

Form Approved: OMB No. 0910-0045, Expiration Date: April 30, 2001. See OMB Statement on Reverse.

LABELING REVISION
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 OTHER (Specify)

FOR CONTROL NO. RECORD ID
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Meeting Date: October 26, 1999
Meeting ID# 4819

Time: 1000

Location: N225

IND [redacted] Periostat® (doxycycline hyclate USP) 20 mg, Capsules

Indication: Periodontitis

Sponsor: Collagenex Pharmaceuticals

Pre-IND/End of Phase 2 Meeting

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR, Project Manager

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Tapash Ghosh, Ph.D., Biopharmacist, DPEIII, HFD-880
John V. Kelsey, D.D.S., M.B.A., Dental Team Leader, DDDDP, HFD-540
Clarence Gilkes, D.D.S., Dental Reviewer, DDDDP, HFD-540
Fred Hyman, D.D.S., M.P.H., Dental Reviewer, DDDDP, HFD-540
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Shahla Farr, Ph.D., Biostatistician, DOBIV, HFD-725
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Christopher Powala, Director, Drug Development, Regulatory Affairs, CGPI
Christopher Phillips, Director of Manufacturing, CGPI

Patrick McNally, Director, Quality Management, Pharmaceutical Manufacturing Research Services, Inc.

Meeting Objectives:

Pre-IND/End of Phase 2 Meeting

With reference to the Meeting Request/Briefing Package, submitted August 26, 1999, the following discussion took place:

Divisional Comments:

1. The Sponsor is requested to submit the proposed Biopharmaceutic's study to a separate IND.
2. The Sponsor can submit this application as a 505(b)(1) application or submit a suitability petition for this application to be granted ANDA status. In addition, the Sponsor is advised that exclusivity may not be granted for the new Periostat formulation.

Sponsor: The Sponsor intends to submit this application as a 505(b)(1) application.

3. Does the Sponsor intend to co-market this new tablet formulation with the approved capsule formulation?

Sponsor: The Sponsor will withdraw NDA 50-744, Periostat (doxycycline hyclate USP) 20 mg, Capsules, upon approval of this new Periostat tablet formulation.

5. The Sponsor should request a Pediatric Waiver Request in accordance with 21CFR 314.55(c).

6. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

7. If the Sponsor has an Information for Patients leaflet/labeling, please submit it with the proposed NDA.

Chemistry, Manufacturing and Controls:

1. The Sponsor was advised that the proposed submission should be submitted as an original NDA.

2. Sponsor's Discussion Point #1 from the August 26, 1999, Meeting Briefing Package:

a. "Collagenex intends to market Periostat Tablets in the following container closure systems":

Agency:

The Sponsor should provide general container closure description, or if the same as the container closure system used in NDA 50-744, a reference to that NDA and a description of the [redacted]

b. Collagenex will be requesting — year expiration date based upon statistical projections. . .":

Agency:

A — year expiration date cannot be approved based upon three months stability data conducted at — and — on three commercial scale batches. If the three-month stability data were submitted, reviewed and found acceptable, the expiration date would only be — months.

Addendum:

The proposal to submit — months of data from one pilot batch of the Periostat Tablets and — months data from three commercial scale validation batches falls short of what was submitted with NDA 50-744. If this limited amount of data is deemed acceptable for filing, and if it is then updated with the — and — month results during review (i.e., at approximately — and — months post-submission), then the maximum expiry dating that could be accepted would be — months.

The filing and review standards will be the same for the proposed application as for the approved application.

c. "Does the reviewer agree with the proposed stability protocol?"

Agency:

Both long-term () and accelerated () proposed conditions appear to be acceptable, however, additional product quality tests for a tablet formulation should be added. The additional tests should include: hardness testing, color, odor and friability/brittleness.

2. Additional Comments:

The components and composition of the new drug product, the PERIOSTAT Tablet, should be provided.

Specifications for the new drug product should be provided.

3. Sponsor's Discussion Point #2 from the August 26, 1999, Meeting Briefing Package:

"Does the reviewer have any comments regarding the table of contents/format of the supplement?"

Yes, in general the table of contents deals exclusively with the drug product. The following are several suggestions for additional data:

- a. Section 3.1 ??, Add a drug substance section here which references the original approved NDA 50-744 and updated Letters of Authorization from your bulk drug supplier(s).
- b. Section 3.2.4.1, A copy of the active ingredient's Certificate of Analysis (COA) should be included here.
- c. Section 3.2.4.2, Identify those inactive ingredients, or excipients, as either compendial (USP, NF, etc.) or non-compendial. If non-compendial, then the COA or a detailed description of each non-compendial excipient specification should be submitted.
- d. Section 3.2.7, Add Sampling Procedures to this section.
- e. Section 3.3.5, To include those analytical methods that pertain to the Identity and Assay of the drug substance (DS), and its impurities, and for the assay procedure for the drug product and its impurities.

Pharmacology/Toxicology:

The proposed NDA submission should include a risk-benefit assessment of the proposed use of each excipient, including discussion, supported by data as appropriate, of the toxicology of each excipient. Published articles, compliance with official compendia, and marketing history may be adequate to qualify the excipients.

Biopharmaceutics:

The protocol as designed will address the impact of food on the Periostat dosage form and thus fulfill the Agency Biopharmaceutic's Phase 4 request for NDA 50-744. As for the new tablet dosage form, the protocol, as designed will address the degree of bioequivalency between the tablet and capsule dosage form. In regards to this new dosage form, the need for an in vivo food effect study will be dependent upon the results of this current study and the products in vitro performance (see pages 2-3 of the DRAFT Food-Effect Bioavailability and Bioequivalence Studies Guidance (Issued October 1997)).

Provided that the new Periostat tablet will replace the capsule on the marketplace and not be a co-marketing of products (except during a changeover period), then the Sponsor should re-design their study to investigate the food-fed performance of the tablet dosage form. In this situation the FDA would release the Sponsor from their previous phase IV commitment related to the capsule as the capsule would no longer be in the marketplace.

IND [redacted] Periostat® (doxycycline hyclate USP) 20 mg, Capsules
Pre-IND/End of Phase 2 Meeting Minutes
Page 4

Clinical:

The proposed labeling for the new tablet formulation should be identical to the approved labeling, except for the description of the dosage form.

Biostatistics:

No comments.

Decisions (agreements) reached:

Unresolved issues or issues requiring further discussion:

None.

Signature, minutes preparer: [Signature]

Concurrence Chair (or designated signatory): [Signature]

Handout: Briefing Package, dated August 26, 1999

cc:

IND [redacted] Division File
HFD-105/OFFICE DIR/DeLap
HFD-540 HFD-540/DIV DIR/Wilkin
HFD-540/CHEM TL/DeCamp/10.26.99
HFD-540/CHEM/Vidra
HFD-540/PHARM TOX TL/Jacobs/10.26.99
HFD-540/PHARM TOX/See/10.26.99
HFD-880/BIOPHARM TL/Bashaw/10.26.99
HFD-880/BIOPHARM/Ghosh/10.26.99
HFD-540/DENTAL TL/Kelsey/10.26.99
HFD-540/DO/Gilkes/10.26.99
HFD-540/DO/Hyman
HFD-725/BIOSTAT TL/Srinivasan/10.26.99
HFD-725/BIOSTAT/Farr/10.26.99
HFD-540/PM/Cross
Drafted by: fbc/October 26, 1999
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Initialed by:
final:

MEMORANDUM OF MEETING

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August 7, 2002

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Investor Relations

Press Releases

CollaGenex Pharmaceuticals, Inc. (ticker: CGPI, exchange: NASDAQ) News Release - 2/5/2001

CollaGenex Receives FDA Approval to Market Periostat Tablets

NEWTOWN, Pa.--(BUSINESS WIRE)--Feb. 5, 2001--CollaGenex Pharmaceuticals, Inc. (Nasdaq: CGPI) today announced that the U.S. Food and Drug Administration has granted marketing approval for a new tablet formulation of Periostat(R), which is indicated for the adjunctive treatment of adult periodontitis. Periostat is the first orally administered, systemically delivered drug targeted for use in conjunction with treatments for adult periodontitis, a major cause of tooth loss in adults. Periostat tablets will be manufactured by Pharmaceutical Manufacturing Research Services, Inc. of Horsham, PA.

"The approval of Periostat tablets by the FDA is an important milestone in the development of our regulatory and commercial strategies," said Brian Gallagher, PhD, chairman, president and chief executive officer of CollaGenex. "This is our second NDA approval and was achieved less than one year from filing, validating the company's ability to bring prescription products to the market. Periostat tablets offer patients a significant advantage over the current capsule formulation, as they are smaller and easier to swallow. Tablets can be manufactured at a lower cost than capsules, and we expect to experience improvements in our gross margin after the tablets are launched later this year."

Periostat tablets were approved for sale in the United Kingdom in December 2000. Periostat capsules have been available in the U.S. for two years. More than 850,000 prescriptions, written by more than 32,000 dentists, have been filled since the launch of Periostat. Periostat is the first and only prescription pharmaceutical product to treat adult periodontitis adjunctively by suppressing the enzymes that destroy the periodontal support tissues.

CollaGenex has initiated a direct-to-consumer advertising campaign in the Philadelphia, Washington, Houston, Chicago, Tampa and St. Louis markets. The company plans a further expansion of this campaign in up to eight additional markets during 2001. "The introduction of Periostat tablets will augment our consumer marketing strategy, providing additional opportunity for growth during 2001," said Dr. Gallagher.

Periostat is marketed to the dental community in the United States by CollaGenex through a professional pharmaceutical sales force. Currently, the company's sales force is also marketing VIOXX(R), a Merck & Co. drug that the company promotes for the treatment and relief of acute dental pain, and Denavir(R), a Novartis Pharmaceuticals Corporation product for the

treatment of cold sores. Periostat is marketed directly to the periodontal profession in the U.K. by CollaGenex International Limited.

Research has shown that the enzyme suppression technology underlying Periostat may also be applicable to other diseases involving destruction of the body's connective tissues, including cancer metastases (Metastat(R)) a broad range of inflammatory diseases. CollaGenex is developing a series novel, proprietary compounds known as IMPACS(R) (Inhibitors of Multiple Proteases and Cytokines) to address these applications. The company intends to pursue further research and development of these technologies primarily through partnerships with third parties.

For additional information on CollaGenex or on Periostat, please visit the company's websites at www.collagenex.com and www.periostat.com, neit of which are part of this press release.

This news release contains forward-looking statements within the meaning Section 231E of the Securities and Exchange Act of 1934, as amended. Investors are cautioned that forward-looking statements involve risks and uncertainties, which may affect the company's business and prospects. Th company's business of selling, marketing and developing pharmaceutical products is subject to a number of significant risks, including marketing plans; risks inherent in research and development activities; risks associa with conducting business in a highly regulated environment and uncertain relating to clinical trials of products under development, all as discussed in the company's periodic filings with the US Securities and Exchange Commission.

Periostat(R), Metastat(R) and IMPACS(R)are trademarks of CollaGenex Pharmaceuticals, Inc.

CollaGenex(R)and Periostat(R) are trademarks of CollaGenex Internationa Limited

VIOXX(R) is a trademark of Merck & Co., Inc.

Denavir(R) is a trademark of Novartis Pharmaceuticals Corporation

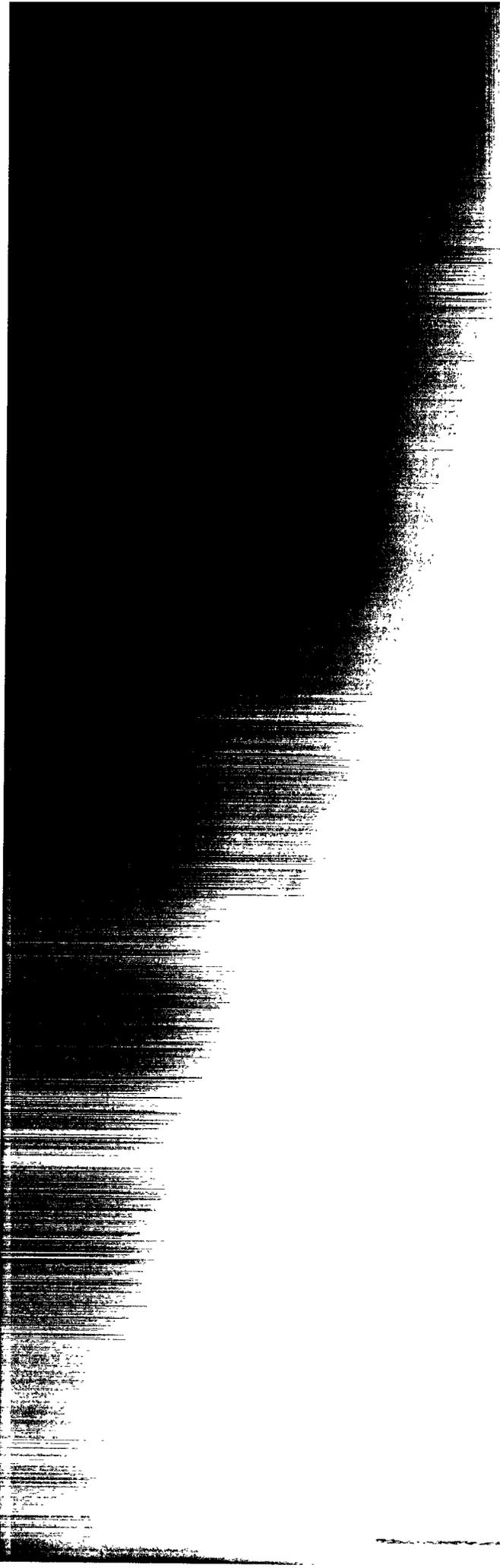
--30--twt/ix*

CONTACT: CollaGenex Pharmaceuticals, Inc.

Robert A. Ashley, 215/579-7388

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[Investor Relations](#) / [Core Technologies](#) / [Resources](#)



CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
50-783**

Pharmacology Review(s)

NDA 50-783

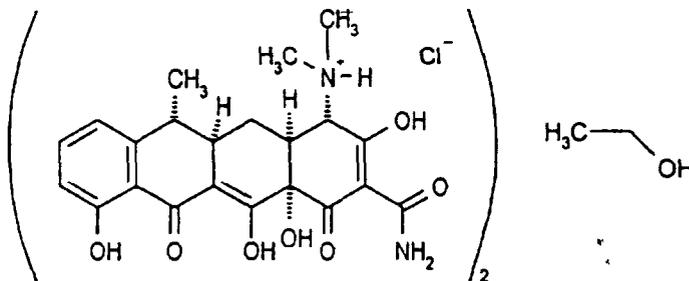
SEP 25 2000 ^{Per} (CFS)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Doxycycline; periodontitis
Reviewer Name: Norman A. See, Ph.D.
Division Name: DDDDP; HFD-540
Review completion Date: 18-SEP-2000
Review number: 001
IND/NDA number: NDA 50-783
Serial number of submission: 000
Letter date of submission: 31-MAR-2000
Center receipt date: 03-APR-2000
Information to sponsor: Yes () No (X)
Sponsor (or agent): Collagenex Pharmaceuticals, Inc.

Drug:

Code name: None
Generic name: Doxycycline Hyclate, USP
Trade name: Periostat tablets
Chemical name: 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride
CAS registry number: 17086-28-1
Molecular formula/Molecular weight: $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6 \cdot H_2O / 1025.89$
Structure:



Relevant INDs/NDAs/DMFs: IND [redacted] NDA 50-744

Drug class: Antibiotic. However, it is used as a collagenase inhibitor at a sub-antimicrobial level in connection with this application.

Indication: Treatment of periodontitis

Clinical formulation: Tablets that contain:

	<u>mg per Tablet</u>
Doxycycline hyclate, USP.....	23.00*
Microcrystalline cellulose, NF.....	
Magnesium stearate, NF.....	

*Equivalent to 20.0mg doxycycline

Route of administration: Oral

Proposed clinical protocol or use: Two tablets per day (40mg doxycycline per day, or 0.67mg/kg/day in a 60kg individual; expressed as the salt, the dosage is 46mg doxycycline hyclate per day, or 0.77mg/kg/day). The product is

labeled for up to nine months of continuous use per treatment episode. The maximum number of treatment episodes that a given patient may undergo is unclear, but is unlikely to be more than three or four (according to the clinical reviewer).

Previous clinical experience: Please see the original pharmacology summary of NDA 50-744.

Background and product history: An essentially identical product, Periostat capsules, was approved under NDA 50-744. The sponsor wishes to be able to market a tablet formulation of Periostat, and NDA 50-783 was submitted to that end. The formulations and proposed usage of the two products are identical, with the exception that the tablets contain { } (a film coating agent) in lieu of a hard gelatin capsule.

Studies reviewed within this submission: None. Please see the Pharmacology reviews of NDA 50-744 for evaluation of applicable data.

Studies not reviewed within this submission: None.

OVERALL SUMMARY AND EVALUATION:

Safety Evaluation: The proposed exposure to doxycycline is identical to that approved under NDA 50-744; please see the Pharmacology reviews of NDA 50-744 for evaluation of applicable data. The only difference between the tablet and capsule formulations is that the tablets contain { } (a film coating agent) in lieu of a hard gelatin capsule. The formulation of { } is:

<u>Ingredient</u>	<u>Amount (% w/w)</u>

The daily exposure to these compounds resulting from use of Periostat tablets (two tablets per day, or a total of { } would be:

<u>Ingredient</u>	<u>Daily Exposure (mg)</u>

All of the components of { } are listed in the CDER Inactive Ingredient Guide as having been excipients in drug products that were approved for oral use, as are other formulations of { }
 { } is a component of many foods, including dairy products. { }
 { } is GRAS as a direct food additive (21 CFR 172.874). { }
 { } is listed as a diluent in color additive mixtures for drug use (21 CFR 73.1575). { }
 { } is GRAS as a direct food additive (21 CFR 184.1901 and 21 CFR 582.1901). These exposures are acceptable.

Clinical relevance of safety issues: None

Other clinically relevant issues: None

Conclusions: The proposed exposure to the drug product is safe.

Communication review:

- Labeling review (NDA):

Labeling: The submitted draft label, which duplicates the currently approved label for Periostat capsules with respect to the warnings, pregnancy category and carcinogenesis sections, is acceptable to this reviewer.

RECOMMENDATIONS:

Internal comments: NDA 50-783 is approvable in regard to pharmacologic and toxicologic concerns.

External Recommendations (to sponsor): None

Draft letter Content for Sponsor: None

Future development or NDA issues: The sponsor has committed (under NDA 50-744) to conduct a two-year carcinogenesis bioassay with doxycycline hyclate in rats, and to submit the data when they become available. The most recent annual report submitted to NDA 50-783 indicated that the in-life phase of the bioassay had been completed and the report is in preparation. When those data are submitted and reviewed, the labels of NDA 50-744 and NDA 50-783 will be updated.

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ON ORIGINAL

Table 6
Summary of Bioavailability (BA) Results: Statistics for Pharmacokinetic Parameters by Treatment and Gender

Parameter	Treatment	Statistic	Per Protocol			Intent-to-Treat			
			Males	Females	Total	Males	Females	Total	
AUC 0-inf	F	N	9	10	19	9	10	19	
		Arithmetic Mean	4883	5557	5238	4883	5557	5238	
		Geometric Mean	4568	5359	4969	4568	5359	4969	
		Coefficient of Variation (%)	41.5	29.7	34.7	41.5	29.7	34.7	
	T	N	9	10	19	9	11	20	
		Arithmetic Mean	5671	5984	5836	5671	5949	5824	
		Geometric Mean	5259	5700	5487	5259	5691	5493	
		Coefficient of Variation (%)	45.6	32.7	38.0	45.6	31.2	37.1	
	AUC 0-t	F	N	9	10	19	9	10	19
			Arithmetic Mean	4055	4392	4232	4055	4392	4232
			Geometric Mean	3713	4286	4004	3713	4286	4004
			Coefficient of Variation (%)	46.1	23.5	34.4	46.1	23.5	34.4
T		N	9	10	19	9	11	20	
		Arithmetic Mean	5069	5089	5079	5069	5091	5081	
		Geometric Mean	4616	4748	4685	4616	4780	4706	
		Coefficient of Variation (%)	50.3	38.3	43.0	50.3	36.3	41.9	
Cmax		F	N	9	10	19	9	10	19
			Arithmetic Mean	243.6	297.2	271.8	243.6	297.2	271.8
			Geometric Mean	225.8	292.6	258.8	225.8	292.6	258.8
			Coefficient of Variation (%)	42.5	19.0	31.1	42.5	19.0	31.1
	T	N	9	10	19	9	11	20	
		Arithmetic Mean	308.3	410.0	361.8	308.3	417.2	368.2	
		Geometric Mean	294.1	403.2	347.2	294.1	410.4	353.2	
		Coefficient of Variation (%)	33.8	18.0	28.0	33.8	17.7	27.9	
	tmax	F	N	9	10	19	9	10	19
			Arithmetic Mean	3.22	3.55	3.39	3.22	3.55	3.39
			Geometric Mean	2.70	3.33	3.01	2.70	3.33	3.01
			Coefficient of Variation (%)	65.9	35.4	49.5	65.9	35.4	49.5
T		N	9	10	19	9	11	20	
		Arithmetic Mean	1.33	1.45	1.39	1.33	1.41	1.38	
		Geometric Mean	1.27	1.39	1.33	1.27	1.35	1.31	
		Coefficient of Variation (%)	37.5	30.2	32.9	37.5	31.0	33.1	

Table 6
Summary of Bioavailability (BA) Results: Statistics for Pharmacokinetic Parameters by Treatment and Gender

Parameter	Treatment	Statistic	Per Protocol			Intent-to-Treat		
			Males	Females	Total	Males	Females	Total
t _{1/2}	F	N	9	10	19	9	10	19
		Arithmetic Mean	21.38	19.37	20.32	21.38	19.37	20.32
		Geometric Mean	20.71	18.25	19.38	20.71	18.25	19.38
	Coefficient of Variation (%)	26.1	38.3	32.0	26.1	38.3	32.0	
	T	N	9	10	19	9	11	20
		Arithmetic Mean	18.70	17.48	18.06	18.70	17.20	17.88
Geometric Mean		18.18	16.81	17.44	18.18	16.57	17.28	
Coefficient of Variation (%)	25.2	29.5	26.9	25.2	28.9	26.8		
lambda _z	F	N	9	10	19	9	10	19
		Arithmetic Mean	0.0346	0.0401	0.0375	0.0346	0.0401	0.0375
		Geometric Mean	0.0335	0.0380	0.0358	0.0335	0.0380	0.0358
	Coefficient of Variation (%)	27.2	32.4	30.6	27.2	32.4	30.6	
	T	N	9	10	19	9	11	20
		Arithmetic Mean	0.0392	0.0429	0.0412	0.0392	0.0434	0.0415
Geometric Mean		0.0381	0.0412	0.0397	0.0381	0.0418	0.0401	
Coefficient of Variation (%)	25.2	28.9	27.1	25.2	27.4	26.4		

5. DISCUSSION AND CONCLUSIONS

The objectives of this study were to test for bioequivalence between the currently-marketed doxycycline hyclate 20 mg capsule and a doxycycline hyclate 20 mg tablet; and to evaluate possible food effects in the pharmacokinetic profile of doxycycline hyclate 20 mg tablets.

The capsule and tablet formulations of doxycycline are bioequivalent since the 90% confidence interval for the ratio of means for both AUC and C_{max} fell within 80%-125%. The least squares mean was close to 100%, which indicates a high level of bioequivalence.

AUC and C_{max} were higher, and t_{1/2} was shorter in females than males. These gender differences appear to be more marked for the fasted capsule condition compared to the fasted tablet condition as summarized in the following Table 7:

Table 7: Summary of Gender Analysis

Study	Entity	Parameter	Male (M)	Female (F)	Comments
Bioequivalence	Fasted Capsule	AUC _{0-∞}	4925 ng.h/mL	6025 ng.h/mL	F22.3%>M
	Fasted Tablet	AUC _{0-∞}	5259 ng.h/mL	5700 ng.h/mL	F8.4%>M
	Fasted Capsule	C _{max}	243.6 ng/mL	418.1 ng/mL	F71.6%>M
	Fasted Tablet	C _{max}	294.1 ng/mL	403.2 ng/mL	F37.1%>M
	Fasted Capsule	t _{1/2}	22.0 hr	16.7 hr	M31.7%>F
	Fasted Tablet	t _{1/2}	18.7 hr	17.5 hr	M6.9%>F
	Bioavailability (Food Effect)	Fed Tablet	AUC _{0-∞}	4568 ng.h/mL	5359 ng.h/mL
Fasted Tablet		AUC _{0-∞}	5259 ng.h/mL	5700 ng.h/mL	F8.4%>M
Fed Tablet		C _{max}	225.8 ng/mL	292.6 ng/mL	F29.6%>M
Fasted Tablet		C _{max}	294.1 ng/mL	403.2 ng/mL	F37.1%>M
Fed Tablet		t _{1/2}	21.4 hr	19.4 hr	M10.3%>F
Fasted Tablet		t _{1/2}	18.7 hr	17.5 hr	M6.9%>F
Fed Tablet		t _{max}	3.22 hr	3.55 hr	F10.3%>M
Fasted Tablet		t _{max}	1.33 hr	1.45 hr	F9.0%>M

There is a food effect since the 90% lower confidence limit for the ratio of means (fed to fasted) for AUC fell below 80% and the 90% lower confidence limit for the ratio of means (fed to fasted) for C_{max} fell below 70%. The AUC and C_{max} were lower and the t_{max} was higher in the fed state, indicating that food decreases the rate and extent of absorption and delays the time at which maximal concentrations are reached.

Female subjects had a higher AUC and maximum concentration (C_{max}), a longer t_{max}, and a shorter t_{1/2} than males. Gender differences in AUC and t_{1/2} appear to be more marked for the fed tablet condition compared to the fasted tablet condition. Conversely, for C_{max},

a more marked gender difference is seen in the fasted tablet condition compared to the fed tablet condition (Table 7).

Final Conclusions

The capsule and tablet formulations of doxycycline are bioequivalent since the 90% confidence interval for the ratio of means for both AUC and C_{max} fell within 80%-125%. There is a food effect since the 90% lower confidence limit for the ratio of means (fed to fasted) for AUC fell below 80% and the 90% lower confidence limit for the ratio of means (fed to fasted) for C_{max} fell below 70%. Food decreases the rate and extent of absorption and delays the time at which maximal concentrations are reached.

6. COMMENTS:

- ❖ The sponsor discussed differences in pharmacokinetic parameters between males and females in several places. However, in their demographic distribution table, they did not report individual or mean weight of the male and female patients. Given that mean female weight is 1/3rd less than mean male weight, a weight normalized analysis of the individual pharmacokinetic parameters could have eliminated the observed differences in pharmacokinetic parameters between male and female subpopulation and rendered the following comments redundant.
- ❖ In both bioequivalence and food effect bioavailability studies, it was found that AUC and C_{max} were higher, and $t_{1/2}$ was shorter in females than males. It is an apparent anomaly to the conventional relationship between AUC and $t_{1/2}$ which should be proportional to each other.
- ❖ Though AUC and C_{max} were higher in females than males, the extent of the difference does not call for recommendation for any dose adjustment.
- ❖ Comments pertaining to gender differences in the subheading *Gender* under **Clinical Pharmacology** labeling should be eliminated.

7. LABELING COMMENTS:

Following modifications have been proposed in the "Clinical Pharmacology" section of the labeling. "Strikeout" means suggested deletions and "Shading" suggests insertion of new text.

Pharmacokinetics

The pharmacokinetics of doxycycline following oral administration of Periostat® were investigated in 4 volunteer studies involving 107 adults. Additionally, doxycycline pharmacokinetics have been characterized in numerous scientific publications.² Pharmacokinetic parameters for Periostat® following single oral doses and at steady-state in healthy subjects are presented as follows:

DRAFT

Genders

DRAFT

/s/

Tapash Ghosh
1/16/01 12:16:40 PM
BIOPHARMACEUTICS

Dennis Bashaw
1/16/01 04:23:25 PM
BIOPHARMACEUTICS



CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
50-783**

Chemistry Review(s)

DEC 27 2000

Division of Dermatological and Dental Drug Products, HFD-540

DMF: [redacted] Type II

Title: Doxycycline Hyclate

- 1. CHEM REVIEW No. 1
- 2. REVIEW DATE: 12-Dec-00

3. ITEM REVIEWED:

A. IDENTIFICATION

USAN: Doxycycline hyclate
 Ingredient Dictionary Name: Doxycycline hydrochloride hemihydrate hemiethanolate.
 Tradename: PerioStat
 Manufacturer's Code: MA51
 Chemical Name: [4S-(4 α ,4 α ,5 α ,5 α ,6 α ,12 α)]-4-(Dimethylamino)-,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12-12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrate.
 CAS Number: 24390-14-5

B. LOCATION IN DMF

<u>Type of Submission</u>	<u>Date of Submission</u>	<u>Location of Information</u>
DMF Amendment	18-Feb-00	Vol.6.1, dated 2/18/00
DMF Amendment	02-Jun-99	Vol.6.1, dated 6/2/99

4. PREVIOUS DOCUMENTS

<u>Type of Document</u>	<u>Date of Document</u>	<u>Comment</u>
AADA 62-839 / S-008	08-Aug-96	Adequate Review

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
 ADDRESS:

REPRESENTATIVE or U.S. AGENT (if applicable):

NAME:
 ADDRESS:

6. DMF REFERENCED FOR:

NDA/ANDA/SUPPLEMENT/IND: NDA 50-783
 PRIMARY DMF (as needed):
 APPLICANT NAME: CollaGenex Pharmaceuticals
 LOA DATE: 06-Mar-00
 DRUG PRODUCT NAME: PerioStat
 DOSAGE FORM: Tablet CODE: 500
 STRENGTH: 20 mg
 ROUTE OF ADMINISTRATION: Oral CODE: 001

7. **SUPPORTING DOCUMENTS:** AADA 62-839/S-008, Dtd. 8/8/96
8. **CURRENT STATUS OF DMF:**
DATE OF LAST UPDATE OF DMF: 14-Jul-00
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S HAVE BEEN PROVIDED: 07-Jul-00
10. **CONSULTS:** Not Applicable
11. **COMMENTS:**
The 6/2/99 & 2/18/00 amendments were reviewed. The former amendment referenced a quality system related to doxycycline hyclate manufacturing. The latter reviewed [redacted] as an additional supplier of [redacted]. Both amendments were adequate, however, the latter has an IR.

12. **CONCLUSIONS:**
This review of DMF [redacted] found both the 6/2/99 and 2/18/00 amendments to be ADEQUATE.

However, there is an Informational Request in the 2/18/00 amendment for comparative physical studies to be conducted on the doxycycline hyclate synthesized by each of the [redacted] and [redacted].

[redacted] 12/12/00
James D. Vidra, Ph.D.
Review Chemist
HFD-830/HFD-540

[redacted] 2/27/00
Wilson H. DeCamp, Ph.D.
Chemistry Team Leader
HFD-830/HFD-540

cc:

DMF [redacted] (2copies)
HFD-540/Div File NDA 50-783
HFD-540/ProjMgr/Cross
HFD-540/ChmTL/DeCamp
R/D Init by JD Vidra

File: Dm [redacted]

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information

DMF [redacted]

8. **CURRENT STATUS OF DMF:**
DATE OF LAST UPDATE OF DMF: 22-Dec-00
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S HAVE
BEEN PROVIDED: 22-Feb-00
9. **CONSULTS:** Not Applicable
10. **COMMENTS:**
Two Amendment 90s on [redacted] were reviewed and found ADEQUATE.
11. **CONCLUSIONS:** ADEQUATE.

[redacted] /S/ 1/4/01
James D. Vidra, Ph.D.
Review Chemist, HFD-830/HFD-540

[redacted] /S/ 1/12/01
Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, HFD 830/HFD-540

Attachments (3)

cc:

DMF [redacted] (2 copies)
HFD-540/Division File for NDA 50-783/000
HFD-540/Chm/Vidra
HFD-540/PM/Cross
HFD-540/ChmTL/DeCamp
R/D Init by: Vidra
File: DMF [redacted]

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commercial

information

7. SUPPORTING DOCUMENTS: None

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: January 21, 2000

DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S HAVE BEEN PROVIDED: January 21, 2000

9. CONSULTS: Not Applicable

10. COMMENTS: ADEQUATE for [redacted]

11. CONCLUSIONS: ADEQUATE

[Signature] 1/10/01
James D. Vidra, Ph.D.
Review Chemist, HFD-540/HFD-830

[Signature] 1/10/01
Wilson H. DeCamp, Ph.D.
Review Chemist, HFD-540/HFD-830

Attachments (3)

- Cc: DMF [redacted] (2 copies)
- HFD-540/DivFile NDA 50-783
- HFD-540/PrjMgt/Cross
- HFD-540/Chm/Vidra
- HFD-540/ChmTL/DeCamp

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information

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

NDA #: 50-783/000 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 12-Jan-01

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	31-Mar-00	04-Apr-00	10-Apr-00
Amendment BC	17-Apr-00	18-Apr-00	02-May-00
Amendment XR	20-Apr-00	21-Apr-00	NAI on 09-May-00
Amendment BC	24-Apr-00	25-Apr-00	01-May-00
Amendment BC	11-Oct-00	12-Oct-00	18-Oct-00
Amendment BC	19-Dec-00	20-Dec-00	29-Dec-00
Amendment BC	05-Jan-01	09-Jan-01	09-Jan-01
Amendment BC	10-Jan-01	11-Jan-01	11-Jan-01

NAME & ADDRESS OF APPLICANT:

CollaGenex Pharmaceuticals, Inc.
41 University Drive
Newtown, Pennsylvania 18940
ATTN: Christopher Powala
Senior Director
Drug Development &
Regulatory Affairs
Telephone No. (215) 579-7388
Fax No. (215) 579-8577

DRUG PRODUCT NAME

<u>Proprietary:</u>	PerioStat
<u>Nonproprietary/USAN:</u>	Doxycycline Hyclate
<u>Code Names/#s:</u>	Doxycycline Hydrochloride Hemihydrate hemeiethanolate
<u>Chemical Type/</u>	Antibiotic
<u>Therapeutic Classes:</u>	3S

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!

PHARMACOLOGICAL CATEGORY/INDICATION: Treatment of Adult Periodontitis

<u>DOSAGE FORM:</u>	Tablet
<u>STRENGTHS:</u>	20 mg
<u>ROUTE OF ADMINISTRATION:</u>	Oral
<u>DISPENSED:</u>	Rx <u>X</u> OTC <u> </u>

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,

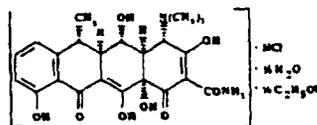
MOL.WT:

4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacencarboxamide monohydrochloride with ethyl alcohol (2:1) monohydrate.

Molecular Weight: 1025.89

Molecular Formula: $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_5OH \cdot 1/2H_2O$

Structural Formula:



doxycycline hyclate

SUPPORTING DOCUMENTS:

Type / Number	Subject	Holder	Status	Review Date	Letter Date
Type II DMF [redacted]	[redacted]	[redacted]	Adequate	1/3/01	3/6/00
Type III DMF [redacted]			Adequate	4/20/00	2/22/00
Type III DMF [redacted]			Adequate	1/4/01	3/7/00
Type III DMF [redacted]			Adequate	12/19/00	3/17/00
Type III DMF [redacted]			Both Adequate	o 1g, 4/13/00 o 3g, 1/8/01	o 1g LOA on 2/14/00 o 3g LOA on 2/14/00
Type III DMF [redacted]			Adequate	9/21/99	3/21/00
Type IV DMF [redacted]			Adequate	2/28/00	8/23/00
NDA 50-744	PerioStat Capsules	CollaGenex Pharmaceuticals, Inc.	Approved	9/30/98	NA

REMARKS/COMMENTS:

The PerioStat Tablet is similar to the previously approved PerioStat Capsules (NDA 50-744 approved on 9/30/98) with respect to drug substance concentration and labeling. The clinical indication also remains the same, e.g., for the treatment of adult periodontitis. No additional clinical studies were conducted with the PerioStat Tablets, only bioequivalence studies to demonstrate equivalence with the previous PerioStat Capsules. Most of the tablet ingredients are similar to the capsule ingredients with the exception of the tablet film coating [redacted] which was reviewed in Type IV DMF [redacted] and found adequate. The major CMC factors to be reviewed in NDA 50-783 include the tablet film coating, the dissolution rate of the tablet (primarily a biopharmaceutical function), the length of stability data for the new drug product, additional product quality tests and the new container closure systems.

PerioStat (doxycycline hyclate) Tablet, 20 mg

The PerioStat Tablets will be sampled in a [redacted] Blister Card of eight tablets and commercialized in 120 cc white [redacted] square bottles containing 60 tablets and in 325 cc [redacted] bottles containing 1,000 tablets. Each of the two bottle also contains a desiccant, [redacted] and a child-resistant white plastic cap with liner.

The drug substance, doxycycline hyclate, was upgraded into a new DMF format from its previous AADA format involving many minor areas. A new supplier, [redacted] was identified that manufactured [redacted] is one of two possible starting materials used in the synthesis of doxycycline hyclate. Drug Master File # [redacted] was found adequate for these drug substance changes.

The two manufacturers and packager were prepared for inspection and found acceptable.

CONCLUSIONS & RECOMMENDATIONS:

NDA 50-783/000 is Recommended for Approval.

/s/

James D. Vidra, Ph.D.
Review Chemist

cc: Orig. NDA# 50-783
HFD-540/Division File
HFD-540/DO/Kelsey
HFD-540/PharmTox/See
HFD-540/ProjMan/Cross
HFD-540/Chem/Vidra
HFD-540/TeamLdr/DeCamp

filename: N50783.000

Redacted 29

pages of trade

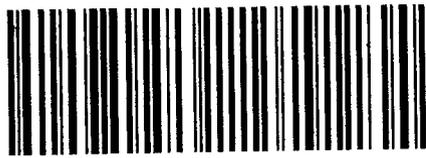
secret and/or

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commercial

information

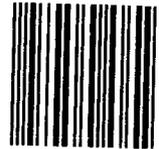
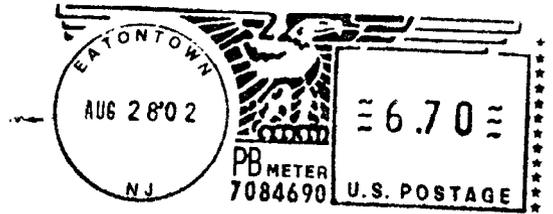
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