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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
50-783**

Medical Review(s)

Dental Officer's Original Review of NDA 50-783

Drug: Periostat® (doxycycline hyclate) Tablets, 20 mg.

Sponsor: CollaGenex Pharmaceuticals, Inc.
41 University Drive
Newtown, PA 18940

Proposed Indication: Periostat® is indicated as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Submission Date: April 3, 2000

Received Date: April 10, 2000

Review Date: January 10, 2001

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

Project Manager: CDR Frank Cross

Materials Utilized in Review:

NDA 50-783, Vols. 1.1, Minor Amendment (4/19/2000), Minor Amendment (7/27/2000), Minor Amendment (11/6/2000)

Background and Regulatory History:

Periodontal disease is a pathogenic cascade which occurs at the supporting structures of the teeth and which, if untreated, results in the loss of connective tissue attachment, alveolar bone, and ultimately the teeth. Periodontal disease is a multifactorial process, the etiology of which may include the presence of dental plaque, microorganisms, occlusal trauma, nutritional deficiencies, and endocrinologic and hematologic influences. Some success in treating the disease or in slowing its progress has been achieved through several therapies, including surgical removal of diseased tissue, reduction of pathogens in the mouth, and reduction of the inflammatory response associated with periodontal destruction.

The most common treatment for periodontal disease is subgingival debridement combined with scaling and root planing (S/RP) and plaque control. As the pocket deepens, however, scaling and root planing may become less effective and a significant amount of bacteria may remain, exacerbating the tissue destruction that accompanies periodontal disease. Use of an agent that reduces inflammation may help to break the cycle of further bacterial accumulation by maintaining or reducing the depth of the gingival pocket (which traps the bacteria), thereby making the pocket more accessible for

cleansing. This has caused clinicians and researchers to investigate the use of host modulating drugs as both adjuncts to S/RP and as stand-alone products in the treatment of periodontitis.

Periostat® is a formulation of the antibiotic doxycycline hyclate. Doxycycline has anti-inflammatory as well as antibiotic properties and Periostat® contains a dose of doxycycline that is substantially below the recommended anti-microbial dose (20 mg versus 100 mg). NDA 50-744 for Periostat® (doxycycline hyclate) Capsules, 20 mg. was approved on September 30, 1998. In the current submission the Sponsor seeks FDA approval for a tablet formulation of the already approved product. The Sponsor has committed to discontinue marketing of the capsule formulation after the tablet formulation has been approved.

To date, the Agency has approved three related products. Actisite®, which is a tetracycline impregnated ethylene/vinyl acetate monofilament fiber, was approved on March 25, 1994, as an adjunct to scaling and root planing for reduction of pocket depth and bleeding on probing in patients with adult periodontitis. PerioChip®, which is a bioresorbable gelatin chip containing chlorhexidine gluconate was approved on November 25, 1997, as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis. On January 30, 1998 FDA approved Atridox™, 10% doxycycline (8.5% w/w) in a bioabsorbable polymer as a stand-alone therapy in the treatment of chronic adult periodontitis.

IND [redacted] for Periostat® (doxycycline hyclate) Capsules, 20 mg. was originally filed on March 6, 1986. The 10-month target date for this submission is February 3, 2001.

Chemistry, Manufacturing and Controls Summary:

Periostat® is a 20 mg tablet formulation of doxycycline hyclate for oral administration. Doxycycline is synthetically derived from oxytetracycline, with an empirical formula of $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$ and a molecular weight of 1025.89. The chemical designation for doxycycline is 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, compound with ethyl alcohol (2:1), monohydrate.

Doxycycline hyclate is a yellow to light-yellow crystalline powder, which is soluble in water. Inert ingredients in the formulation are: magnesium stearate; and microcrystalline cellulose. Each tablet contains doxycycline hyclate equivalent to 20 mg of doxycycline.

See Dr. Vidra's CMC review.

Pharmacology and Toxicology Summary:

Dr. See concludes in his review that the substitution of the film-coating agent, [redacted] in lieu of the hard gelatin capsule in the tablet formulation presents no safety issues.

Further, he notes that the Pharm./Tox. sections of the draft labeling submitted for NDA 50-783 are identical to the approved labeling for NDA 50-744, and is acceptable.

Dr. See notes that, "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."

See Dr. See's review.

Pharmacokinetics Summary:

The clinical pharmacology study that was submitted in NDA 50-783 was designed to test the bioequivalence of two formulations of doxycycline hyclate, the currently marketed 20 mg capsule and a 20 mg tablet. In addition, the study was designed to determine if the ingestion of a high-fat, high-calorie meal immediately before the administration of a single 20 mg oral dose of doxycycline hyclate would alter the absorption and distribution of doxycycline in healthy adult subjects.

This was a randomized, single-dose, three-treatment, three-period, six-sequence crossover study in healthy adults (9 men and 11 women) age 18-40 years. It was the conclusion of the biopharmaceutics reviewer that the capsule and tablet formulations are bioequivalent since the 90% confidence interval for the ratio of means for both AUC and C_{max} fell within 80% - 125% of the least square mean. Further, 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 the C_{max} fell below 70% of the least square mean. Food decreases the rate and extent of absorption and delays the time at which maximal concentrations are reached. He recommends approval with labeling changes.

See Dr. Ghosh's Biopharmaceutics review.

Microbiology Summary:

The microbiology reviewer notes that his review is not comprehensive since this application is for a change in dosage form and refers to his 4/1/98 review of NDA 50-744. He notes that he is not aware of anything in the literature to suggest that use of the capsule formulation of this product has been associated with permanent increases in tetracycline-resistance of the pathogens associated with periodontal disease or other bacteria in patients who have been treated with that product. He recommends approval with no changes in the microbiology section of the original NDA, 50-744.

See Dr. Marsik's Microbiology Review.

Clinical Review:

As mentioned above, the clinical data in this application consisted of that from a single bioequivalence study. This reviewer concurs that the design of the bioequivalence study, including the inclusion and exclusion criteria, was appropriate to address the questions being asked. That study has been reviewed in depth by the biopharmaceutics reviewer.

The reader is referred to Dr. Gilkes' clinical review of NDA 50-744, the approved capsule formulation of this product for a review of the safety and efficacy studies that supported the approval of the original NDA.

Safety:

Only 2 of the 20 subjects in the biopharmaceutics study reported in this NDA experienced adverse events and these were labeled and minor (sore throat, sinus congestion and headache). The Division agreed, prior to the submission of the NDA that it would not be necessary for the Sponsor to recalculate the values on the adverse event table to take these two patients into account. ✓

In addition, the Sponsor was asked to submit the annual frequency and trend analysis from the spontaneous reporting of adverse events that was part of the Annual Report that was submitted to NDA 50-744 in November of 1999. That report included 487 nonserious ADRs involving 322 patients. The Sponsor estimated that [redacted] patients had received Periostat® during the reporting period. Of these 487 ADRs, 181 were not labeled. Pruritus (15), dizziness (11), constipation (10), stomatitis (7), taste perversion (7), hypertension (7), dyspnea (7), somnolence (6), chest pain (5), gingivitis (5) and alopecia (5) were the most frequently reported non-labeled events.

From the total of 306 listed reactions reported during this period, of note is the fact that skin rash was more frequently reported than in the clinical trials (9% v. 4%) and the incidence of fungal infection was 6% v. 2%, with 74% of those ADRs involving vaginal candidiasis. The incidence of headache from the clinical trials was much greater than from the spontaneous reports (26% v. 4%).

The Sponsor also reported a single article published during the reporting period that concerned a patient who developed a gastric ulcer after receiving a 100 mg tablet BID of doxycycline for Lyme Disease.

The Sponsor submitted Quarterly Safety Updates for NDA 50-744 on July 27, 2000 and November 6, 2000. There were 379 reports of which 169 were not labeled. The AE incidence rate during this period was less than 2 per 1,000 patients.

There were three serious adverse drug reactions reported during this period. Two, anaphylaxis and severe diarrhea were listed and one, severe epistaxis was not listed. There was limited information available about each of these events, but none were clearly related to Periostat®.

Reviewer's Comment: Based on the fact that the spontaneously reported ADRs were largely non-serious and in the case of the labeled events did not differ greatly from the percentages listed in the approved label, it is this reviewer's opinion that the existing adverse event labeling does not need to be revised.

Discussion:

The Sponsor has conducted a bioequivalence study in 20 patients and has shown the tablet formulation of Periostat to be bioequivalent to the previously approved capsule formulation. The sponsor had also conducted a food effects study as required by a Phase IV agreement to NDA 50-744, and has demonstrated a food effect as occurs with other drugs in the tetracycline class. The safety data collected during the pharmacokinetics study and the spontaneously reported adverse events reported in the most recent annual report for the capsule formulation do not raise concern and do not warrant a change in the adverse event labeling. Neither the Pharm/Tox nor the Microbiology reviewer had significant material to review in this application. The Sponsor has satisfied the CMC requirements and all disciplines have recommended approval. There were a number of minor changes to the label recommended by the reviewers.

Labeling Review:

The Sponsor made few changes to the label that is approved for the capsule formulation of Periostat®. These primarily concern the CMC and Clinical Pharmaceutics sections of the label. The Sponsor did include one new statement in the DOSAGE AND ADMINISTRATION section of the label as follows (italics = sponsor's proposed label, bold = change from approved labeling):

DOSAGE AND ADMINISTRATION

DRAFT LABELING

]

In addition, the following footnote is included at the end of the label:

Reviewer's Comments:

1. *The additional instructions to patients regarding dosing interval and relationship of dose to meal times is useful, but in this reviewer's opinion should be combined with the previous statement to make clear that efficacy beyond 9 months has not been established. The new section should read:*

"Periostat® 20 mg twice daily as an adjunct following scaling and root planing may be administered for up to 9 months. Periostat® should be taken twice daily at 12-hour intervals, usually in the morning and evening. It is recommended that if Periostat® is taken close to meal times, allow at least one hour prior to or two hours after meals. Safety beyond 12 months and efficacy beyond 9 months have not been established."

2. *The citation to Facts and Comparisons should be deleted. The statement is useful and does not require the citation as support.*
3. *The Pediatric Use: section should be revised to provide a specific age (8) up until which Periostat® is contraindicated. The rationale is that by the age of 8 the crowns of the anterior teeth, which are the ones of concern for staining, have completed the mineralization process and are therefore not susceptible to staining. The new statement should read:*

Financial Disclosure:

The Sponsor has provided the required certification (Form FDA 3454) regarding financial interests and arrangements of clinical investigators. The Sponsor has certified that the value of compensation to the investigator was not influenced by the outcome of the study. Further, no investigator had a proprietary interest in the product or a significant equity interest in the sponsor and no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Pediatric Waiver:

In accordance with the provisions of 21 CFR 54.4 the Sponsor requested a waiver of the requirement to submit data on the safety and efficacy of their drug product in a pediatric population. Adult periodontitis, as its name indicates, affects only adults, so no studies in children are possible and the waiver should be granted.

Recommendation:

NDA 50-783 for Periostat® (doxycycline hyclate tablets), 20 mg. is approvable with the labeling changes recommended above.

/S/

1/26/01

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

Original to NDA 50-783
HFD-540 Division File
HFD-540 Wilkin
HFD-540 Kelsey/Hyman/Gilkes
HFD-540 Cross
HFD-540 Jacobs/See
HFD-830 DeCamp/Vidra
HFD-725 Alesh/Rahman
HFD-880 Bashaw/Ghosh
HFD-520 Marsik