CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 50-781

PHARMACOLOGY REVIEW(S)

NDA 50-781

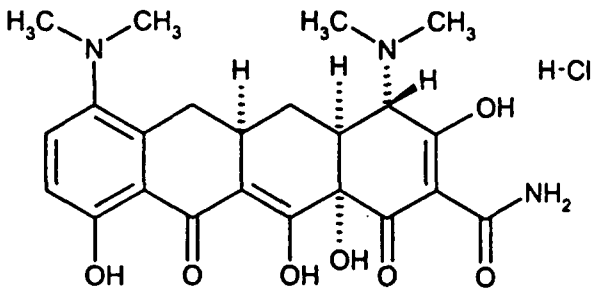
SEP 18 2000

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Minocycline; 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 50-781
Serial number of submission: 000
Letter date of submission: 16-FEB-2000
Center receipt date: 17-FEB-2000
Information to sponsor: Yes (—) No (X)
Sponsor (or agent): OraPharma, Inc.
Manufacturer of drug substance: ——

Drug:

Code name: CL 59,806
Generic name: Minocycline HCl
Trade name: Minocycline PTS 1mg
Chemical name: 7-Dimethylamino-6-demethyl-6-deoxytetracycline HCl
CAS registry number: 13614-98-7
Molecular formula/Molecular weight: $C_{23}H_{27}N_3O_7 \cdot HCl/493.94$
Structure:



Relevant INDs/NDAs/DMFs: IND —— ; NDA 50-315

Drug class: Antibiotic

Indication: Treatment of periodontitis

Clinical formulation: Each unit dose dispenser contains approximately 1mg of minocycline HCl and approximately —— of poly(glycolide-co-dl-lactide).

Route of administration: The product, a dry powder, is placed into periodontal pockets with a special syringe which is packaged with the product.

Proposed clinical protocol or use: The product is intended to be placed into periodontal pockets of 5mm depth or greater. The patients are to return to the clinic at intervals of four months for re-treatment of all pockets ≥ 5mm in depth at that time. The maximum number of dosage units used per treatment episode may be approximately —— (containing a total of —— of minocycline HCl), but would usually be much less. 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: Minocycline HCl, first approved in the US in 1971 under NDA 50-315, has been extensively used in the US as an orally or intravenously administered broad spectrum antibiotic for several decades. The approved labeling for Minocin (formerly Lederle, now Wyeth-Ayerst) calls for 200mg initially, followed by 100mg every 12 hours for up to 8 weeks. The "indications and usage" portion of the label mentions that minocycline may be a useful adjunctive therapy for severe acne, implying that the FDA has sanctioned chronic exposure to the drug, although acne is not mentioned under the "dosage and administration" section of the label.

Background and product history: The division, working in concert with personnel at the office level, agreed with the sponsor long ago that, in view of the extensive clinical database available to support the safety of minocycline with respect to systemic toxicity, and with the product with respect to local toxicity, that nonclinical data needed to support a NDA for the product could be limited to a suitable battery of genetic toxicology studies. Note that the clinical database for minocycline includes exposure at much higher levels and for much longer periods than proposed under NDA 50-781, and that minocycline bears the tetracycline class labeling for pregnancy category.

Studies reviewed within this submission:

1. CL 59,806 (Minocycline): Dermal sensitization study of a microcapsule formulation in the guinea pig. Study No. 87226.

2. A local tolerance study of minocycline hydrochloride (CL 59,806) applied topically to the gingiva of dogs daily for five days. Study No. 87228.

3. Bacterial reverse mutation assay. Study No. AA13KR.502.BTL.

4. *In vitro* mammalian cell gene mutation test (L5178Y/TK$^{+/-}$ mouse lymphoma assay. Study No. AA13KR.704.BTL.

5. *In vitro* mammalian chromosome aberration test. Study No. AA13KR.331.BTL.

6. Mammalian erythrocyte micronucleus test. Study No. AA13KR.123.BTL.

Studies <u>not</u> reviewed within this submission:

1. *In vivo* evaluation of minocycline periodontal formulations. This was a nonclinical study performed early in the development of the product in which the product was placed within periodontal defects of dogs and the minocycline concentration of the gingival crivicular fluid was measured. It was not reviewed here because the data are completely obsolete in light of data derived in clinical studies.

PHARMACOLOGY:

Mechanism of action: Inhibition of bacteria protein synthesis, resulting in bacterial stasis.
Drug activity related to Proposed Indication: Antibacterial
Ancillary pharmacology studies: See original summary of NDA 50-315.
Summary of pharmacology: See original summary of NDA 50-315.

SAFETY PHARMACOLOGY: See original summary of NDA 50-315.

CLINICAL PHARMACOKINETICS:

PK parameters: $T_{1/2} \approx 16$; $T_{max} \approx 2.1$ hours.
Absorption: Oral absorption almost complete. May be decreased by metal ions, but less affected than most other tetracyclines.
Distribution: Widely distributed; highest levels in liver, kidneys, GI tract, thyroid, brain, fat.
Metabolism: Approximately 80% of dose excreted unchanged; metabolites include 9-hydroxy-minocycline and 4 or 7 position demethylated forms of minocycline.
Elimination: Within 216 hours, 60%-80% of administered dose was eliminated in feces and 2%-9% eliminated in urine.

Summary: Well absorbed orally, widely distributed, primarily eliminated unchanged in feces.

TOXICOLOGY:

General Comments: As noted above, per agreement with sponsor, nonclinical data needed to support a NDA are limited to genetic toxicology (to update label).

1. GENETIC TOXICOLOGY:

1.1 Study Title: Bacterial reverse mutation assay
Study No: AA13KR.502.BTL
Study Type: Bacterial reverse mutation assay
Volume # and Page #: Vol. 10, page 61
Conducting Laboratory: [redacted]
Date of Study Initiation/completion: 04-MAR-1999/27-MAY-1999
GLP Compliance: Yes
QA- Reports Yes (X) No ( ):
Drug Lot Number: 98043
Study Endpoint: Assessment of potential to induce point mutations through comparison (between test and control materials) of numbers of colonies that grow in medium that is devoid of a formerly essential nutrient (reversion of former auxotrophs to wild phenotype).

Methodology:
- Strains/Species/Cell line: S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and E. coli strain WP2uvrA
- Dose Selection Criteria:
  - Basis of dose selection: Per ICH guidelines
  - Range finding studies: Satisfactory, from 0 to 5000µg per plate
- Test Agent Stability: Not addressed
- Metabolic Activation System: Aroclor 1254-induced rat liver S9
- Controls:
  - Vehicle: Sterile distilled water
  - Negative Controls: Vehicle
  - Positive Controls: 2-aminoanthracene for all experiments involving S9. In absence of S9, 2-nitrofluorene for TA98, sodium azide for TA100 and TA1535, 9-aminoacridine for TA1537, and methyl methanesulfonate for WP2uvrA
  - Comments: Satisfactory
- Exposure Conditions:
  - Doses used in definitive study: 0 to 7.5µg/plate
  - Study design: Plate assay
- Analysis:
  - No. slides/plates/replicates/animals analyzed: 2/strain
  - Counting method: hand or machine
  - Cytotoxic endpoints: Greater than 50% reduction in mean number of revertants compared to negative control or reduction in background lawn
- Criteria for Positive Results: Dose-related increase in mean number of revertants per plate of at least one strain

Results:
- Study Validity: Satisfactory
- Study Outcome: Negative. This study provided no evidence that the test material was mutagenic.

Reviewer's Comment: As anticipated, the tester bacteria exhibited very little tolerance to minocycline. In the instance of this drug substance, I consider

the assay in L5178Y cells, reviewed below, to be a more definitive test for potential to induce point mutations than was the Ames assay.

Summary: No significant increase in the reverse mutation rate was observed at any concentration of test material, in either the presence or absence of S9. Appropriate responses were induced by the positive control substances.

1.2 Study Title: *In vitro* mammalian cell gene mutation test (L5178Y/TK mouse lymphoma assay)
Study No: AA13KR.704.BTL
Study Type: In vitro mammalian point mutation
Volume # and Page #: Vol. 10, page 114
Conducting Laboratory:
Date of Study Initiation/completion: 24-JUN-1999/20-SEP-1999
GLP Compliance: Yes
QA- Reports Yes (X) No ( ):
Drug Lot Number: 98043
Study Endpoint: Growth in medium containing trifluorothymidine (TFT), indicating mutation from tk^+tk^+ to tk^-tk^-

Methodology:
- Strains/Species/Cell line: tk^+tk^+ 3.7.2.C mouse lymphoma L5178Y cells
- Dose Selection Criteria: Cytotoxicity
  - Basis of dose selection: Cytotoxicity in range-finding studies
  - Range finding studies: Examined concentrations of minocycline in culture medium ranging from 0 to 5000µg/mL, with and without S9
- Test Agent Stability: Not addressed
- Metabolic Activation System: Aroclor 1254-induced S9 (supernatant of the post-mitochondrial 9000 g fraction from adult male Sprague-Dawley rats)
- Controls:
  - Vehicle: Sterile distilled water
  - Negative Controls: Vehicle
  - Positive Controls: Methyl methanesulphonate in absence of S9; 7,12-dimethyl-benz(a)anthracene in presence of S9
  - Comments: Controls were adequate
- Exposure Conditions:
  - Incubation times: 4 hour exposure with and without S9; negative results in absence of S9 were repeated in a 24 hour exposure
  - Doses used in definitive study: 0, 5, 10, 15, 20, 30, 40, and 50µg/mL in presence of S9; 0, 2.5, 5, 6, and 7µg/mL in absence of S9.
  - Study design: Following the exposure period, the cells were washed and grown for 10 to 14 days with and without TFT
- Analysis:
  - Cytotoxic endpoints: Reduced cell count in absence of TFT
  - Genetic toxicity endpoints: Increased numbers of cells that grew in presence of TFT

Results:
- Study Validity: Acceptable
- Study Outcome: Negative; minocycline did not increase the incidence of cell survival (colony formation) in medium that contained TFT in either the presence or absence of S9. Appropriate results were obtained with the controls.

Summary: The mean mutation frequency of cells exposed to the test substance did not differ significantly from the negative controls. Significant differences were obtained with the positive controls. These data provide no evidence that the test substance is mutagenic.

1.3 Study Title: *In vitro* mammalian chromosomal aberration test
Study No: AA13KR.331.BTL
Study Type: *In vitro* mammalian chromosomal aberration test
Volume # and Page #: Vol. 10, page 150
Conducting Laboratory: [redacted]
Date of Study Initiation/completion: 26-FEB-1999/21-JUN-1999
GLP Compliance: Yes
QA- Reports Yes (X) No ( ):
Drug Lot Number: 98043

Methodology:
- Strains/Species/Cell line: CHO-K_1 cells
- Dose Selection Criteria:
  - Basis of dose selection: Cytotoxicity
  - Range finding studies: Yes, over range of 0 to 5000µg/mL
- Test Agent Stability: Not addressed
- Metabolic Activation System: Aroclor 1254-induced S9 (supernatant of the post-mitochondrial 9000 g fraction from adult male Sprague-Dawley rats)
- Controls:
  - Vehicle: Sterile distilled water
  - Negative Controls: Vehicle
  - Positive Controls: Mitomycin C in absence of S9; cyclophosphamide in presence of S9
  - Comments: Controls satisfactory
- Exposure Conditions:
  - Incubation and sampling times: 4 hour exposure with and without S9 (16 hour recovery period); plus 20 hour exposure studies in absence of S9 only
  - Doses used in definitive study: 0, 32, 63, 125, 250, 500, 750, and 1000µg/mL in presence of S9; 0, 125, 250, 500, 750, 1000, and 1250µg/mL with 4 hour exposure and 7, 13, 25, 50, 75, 150, and 300µg/mL in absence of S9.
- Analysis:
  - No. slides/plates/replicates/animals analyzed: 2
  - Cytotoxic endpoints: Reduced cell survival
  - Genetic toxicity endpoints/results: Microscopic examination for chromosome anomalies
- Criteria for Positive Results: Percentage of cells with aberrations must be statistically significantly higher than negative controls (p 0.05, Fisher's exact test)

Results:
- Study Validity: Satisfactory
- Study Outcome: Negative

Summary: Exposure to minocycline did not increase the frequency of occurrence of chromosomal aberrations, either with or without metabolic activation. The positive control compounds did significantly increase the incidence of chromosomal aberrations. This study provided no evidence that minocycline was clastogenic.

1.4 Study Title: Mammalian erythrocyte micronucleus test
Study No: AA13KR.123.BTL
Study Type: Mammalian erythrocyte micronucleus test
Volume # and Page #: Vol. 10, page 189
Conducting Laboratory: [redacted]
Date of Study Initiation/completion: 25-FEB-1999/28-MAY-1999
GLP Compliance: Yes
QA- Reports Yes (X) No ( ):
Drug Lot Number: 98043

Methodology:
- Strains/Species/Cell line: ICR mice
- Dose Selection Criteria:
- Basis of dose selection: Acute toxicity study performed over dosage range of 0 to 2000mg/kg; 125mg/kg established as highest tolerated dose
- Test Agent Stability: Not addressed
- Metabolic Activation System: NA
- Controls:
  - Vehicle: Sterile distilled water
  - Negative Controls: Vehicle
  - Positive Controls: Cyclophosphamide (50mg/kg)
  - Comments: Satisfactory
- Exposure Conditions:
  - Doses used in definitive study: 0, 32, 63, 125mg/kg
  - Study design: 5 animals per gender from each treatment and control group were sacrificed at 24 hours post-dosing; in addition, 5 animals per gender that received either vehicle or 125mg/kg minocycline were sacrificed 48 hours after dosing
- Analysis:
  - No. slides/plates/replicates/animals analyzed: 5/gender/group
  - Cytotoxic endpoints: NA
  - Genetic toxicity endpoints/results: Bone marrow smears were processed and examined for the number of micronucleated cells per 2000 polychromatic cells examined; the ratios of polychromatic to normochromatic erythrocytes were recorded.
- Criteria for Positive Results: Statistically significantly greater incidence of micronucleated polychromatic erythrocytes relative to negative controls (p 0.05, Kastenbaum-Bowman tables)

Results:
- Study Validity: Satisfactory
- Study Outcome: Negative

Summary: Minocycline did not increase the incidence of micronucleated polychromatic erythrocytes. A significant increase in the occurrence of micronucleated polychromatic erythrocytes was observed in smears from positive control animals. These data provide no evidence that the test substance is clastogenic.

2. SPECIAL TOXICOLOGY STUDIES:

2.1 Study Title: CL 59,806 (Minocycline): Dermal sensitization study of a microcapsule formulation in the guinea pig
Study No: 87226
Vol #, and page #: Vol. 10, page 1
Conducting laboratory and location: [redacted]
Date of study initiation: 20-OCT-1987/23-MAR-1988
GLP compliance: Yes
QA- Reports Yes (X) No ( ):

Methods: A "microcapsule formulation of CL 59,806", consisting of minocycline and poly(glycolide-co-dl-lactide) (apparently the current drug product) was assayed for dermal sensitization in a guinea pig maximization study. Three groups of Hartley guinea pigs (5/gender/group) were studied; one group received vehicle (sterile distilled water), one group received the drug product, and one received 0.2% dinitrochlorobenzene (DNCB, positive control), with or without Freund's complete adjuvant. The materials were applied to shaved skin under an occlusive dressing for 48 hours on "induction" day 0 and again on day 7. "Challenge" applications of either 0.05% DNCB or the drug product were administered with occlusion for 24 hours to naive sites on the same animals on study day 21. The application sites were scored for erythema, eschar, and edema at 24 and 48 hours post application.

Drug lot#: 6793B131
Results: No skin reactions or other signs of toxicity were observed in animals that were induced with either the drug product or the negative control (vehicle). Four of 5 male and 4 of 5 female animals induced with DNCB exhibited slight skin reactions.
Summary: These data indicate that the drug product was non-sensitizing under the conditions of this study.
Key finding(s): The drug product was non-sensitizing.

2.2 Study Title: A local tolerance study of minocycline hydrochloride (CL 59,806) applied topically to the gingiva of dogs daily for five days
Study No: 87228
Vol #, and page #: Vol. 10, page 40
Conducting laboratory and location: [redacted]
Date of study initiation: 15-OCT-1987/23-MAR-1988
GLP compliance: Yes
QA- Reports Yes (X) No ( ):

Methods: A minocycline and poly(glycolide-co-dl-lactide) formulation (apparently the current drug product) was assayed for potential to cause irritation of the oral tissues. Approximately 150mg of the material was applied daily to the gingiva of 2 male and 2 female beagle dogs for 5 consecutive days. An additional animal of each sex received "vehicle" (poly(glycolide-co-dl-lactide) alone). Application consisted of pulling out the lip, pouring the material into the space between the lip and gingiva, and then holding the lip against the gingiva for 1 minute. Some of the treatment sites were abraded with a hard brush prior to the first treatment. The treatment sites were examined daily for signs of irritation (erythema, edema, etc.).
Drug lot#: 6793B-132

Results: No irritation or other signs of toxicity were observed, and healing of the induced lesions was not delayed by the drug product.
Summary: These data indicate that the drug product was well tolerated under the conditions of this study. It should be noted that the product is intended to be placed into a periodontal pocket (the space between the tooth and gum), and not between the gum and the buccal surface, as in this study, so the data may not be directly relevant to the proposed clinical use. However, the data do pertain to accidental placement of the drug product into the oral cavity outside the periodontal pocket.

OVERALL SUMMARY AND EVALUATION:

Safety Evaluation: The proposed exposure to minocycline HCl, 100mg or less, released over several days on three or four occasions at intervals of four months, is much lower than the exposure permitted under the approved label for Minocin, which allows for 200mg or more per day, administered for up to eight weeks (or longer, if used for acne). The level and duration of the proposed exposure to minocycline has been documented to be safe. A battery of genetic toxicology studies conducted with minocycline yielded negative results. Tetracyclines as a class have been associated with teratogenic events, and have class labeling to address this fact. Use of the product would not involve chronic exposure to minocycline HCl.

The only excipient in the product is poly(glycolide-co-dl-lactide). This material is a biodegradable polymer that is degraded to lactic acid and glycolic acid monomers. Similar polymers have been used extensively as absorbable suture materials; the only toxicity that has been associated with these suture materials has been localized inflammation and foreign-body reaction, which are associated with all suture materials. Lactic acid is an endogenous compound produced during anaerobic metabolism and is a component of many foods (such as dairy products). Lactic acid is GRAS as a direct food additive (21 CFR 184.1061, 21 CFR 582.1061). Glycolic acid (also known as hydroxyacetic acid) is listed as an indirect food additive (21 CFR 175.105), and the toxicology of glycolic acid has been described in some detail[1]. The oral LD_{50} values of glycolic acid in rats and mice are approximately 3000mg/kg and 2000mg/kg, respectively; an acute oral dose of 350mg/kg in rats caused no deaths. In cats that received sodium glycolate by mouth acutely, 100mg/kg was an apparent NOAEL, 250mg/kg was "toxic but not fatal" (details not given), and doses 500mg/kg generally resulted in death. Dogs administered 1000mg glycolic acid by mouth daily for 35 days (approximately 125mg/kg/day) apparently did not exhibit serious toxicity. In a developmental toxicity study in which pregnant rats were dosed on days 7-21 following impregnation, 150mg/kg/day was a NOAEL for both maternal and fetal toxicity. Glycolic Acid was not mutagenic in Ames tests and was not clastogenic in an *in vitro* chromosome aberration assay in CHO cells. Glycolic acid is a major metabolite of ethylene glycol, which the EPA regards as being without risk when ingested at a rate of 2mg/kg/day (IRIS database). The maximum exposure to poly(glycolide-co-dl-lactide) per treatment episode would be approximately 240mg, which would degrade to approximately 100mg of glycolate and 140mg of lactate over a period of days. These exposures are acceptable.

[redacted]

[1] Final report on the safety assessment of glycolic acid, ammonium, calcium, potassium and sodium glycolates, methyl, ethyl, propyl, and butyl clycolates, and lactic acid, ammonium, clacium, potassium, sodium, and TEA-lactates, methyl, ethyl, isopropyl, and butyl lactates, and lauryl, myristyl, and cetyl lactates. Cosmetic Ingredient Review Expert Panel, Wilma F. Bergfeld, MD (Panel Chairperson), Int J Toxicol 17(1):1-241 (1998).

[redacted]

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 following modifications of the draft labeling of NDA 50-781 are recommended:

1. "WARNINGS" section. Please change this section to read:

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 OR IN PREGNANT OR NURSING WOMEN UNLESS THE POTENTIAL BENEFITS ARE CONSIDERED TO OUTWEIGH THE POTENTIAL RISKS.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. If any tetracyclines are used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

2. Carcinogenesis, Mutagenesis, Impairment of Fertility. Please change this section to read:

Dietary administration of minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasia in rats and dogs. In addition, there has been evidence of oncogenic activity in rats in studies with a related antibiotic, oxytetracycline (i.e., adrenal and pituitary tumors). Minocycline demonstrated no potential to cause genetic toxicity in a battery of assays which included a bacterial reverse mutation assay (Ames test), an *in vitro* mammalian cell gene mutation test (L5178Y/TK$^{+/-}$ mouse lymphoma assay), an *in vitro* mammalian chromosome aberration test, and an *in vivo* micronucleus assay conducted in ICR mice.

Fertility and general reproduction studies have provided evidence that minocycline impairs fertility in male rats.

RECOMMENDATIONS:

Internal comments: NDA 50-781 is approvable in regard to pharmacologic and toxicologic concerns. Recommended changes in the product label are indicated above.
External Recommendations (to sponsor): None
Draft letter Content for Sponsor: See labeling comments, above.
Future development or NDA issues: None

/S/ 9/18/00

Norman A. See, Ph.D., R.Ph.
Reviewing Pharmacologist

cc:
NDA 50-781
Original Summary
HFD-540 Div. File
HFD-540/TL/JACOBS
HFD-540/PHARM/SEE
HFD-540/CSO/BHATT

Concurrence Only: 9/28/00 DFS
HFD-540/DD/WILKIN
HFD-540/TL/JACOBS 9/18/00 IN DFS