CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-795

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA 50-795
Submission Number	000
Submission Code	N
Letter Date	4/5/04
Stamp Date	4/7/04
Reviewer Name	Charles Cooper, M.D.
Review Completion Date	9/16/04
Established Name	Doxycycline Hyclate
(Proposed) Trade Name	Doryx Tablets
Therapeutic Class	Tetracycline Antibiotic
Applicant	Warner Chilcott
Priority Designation	S
Formulation	Tablets
Dosing Regimen	75 and 100 mg
Indication	Multiple antimicrobial indications
Intended Population	Patients with certain infections

Table of Contents

1 EXECUTIVE SUMMARY

Doryx (coated doxycycline hyclate pellets) Capsules, 100 mg was originally submitted for approval by F H Faulding and Co. LTD on September 1, 1983 and was approved by the Agency on July 22, 1985. Supplement (S-015) to NDA 50-582, which provided for a 75 mg strength capsule, was filed on April 4, 2001 by Warner Chilcott on behalf of F H Faulding and Co LTD and was approved by the FDA on August 31, 2001.

This NDA is seeking approval of a new formulation of doxycycline hyclate, coated-pellet tablets. The new formulation is proposed to be the same strength as the already approved capsule formulation (75 and 100 mg). In support of this NDA, the applicant, Warner Chilcott, has submitted two pharmacokinetic studies demonstrating bioequivalence to the already approved capsule formulation.

The applicant has indicated that they intend to change their marketed product from the capsule to the tablet formulation as a way of attempting to reduce the risk of retention pill esophagitis. Esophagitis and esophageal ulceration are well described rare adverse events that are listed in the approved Doryx label (PATIENT INFORMATION and ADVERSE REACTIONS) and may occur after administration of either a capsule or tablet form of doxycycline. No information regarding this adverse event was submitted as part of this review.

1.1 Recommendation on Approvability

It is recommended that this product be approved.

1.2 Recommendation on Post-marketing Actions

No post-marketing actions are recommended for this product.

1.3 Summary of Clinical Findings

There were no clinical data submitted for this NDA. Bioequivalence studies were submitted and demonstrated that the new Doryx Tablet formulation was equivalent to the already approved Doryx Capsule formulation.

1.4 Product Information

- This New Drug Application for Doryx (coated doxycycline hyclate pellets) Tablets, 75 mg and 100 mg provides for a new formulation of an already marketed product, Doryx Capsules. Doryx (coated doxycycline hyclate pellets) Capsules, 100 mg was originally submitted for approval by F H Faulding and Co. LTD on September 1, 1983 and was approved by the Agency on July 22, 1985. Supplement (S-015) to NDA 50-582, which provided for a 75 mg strength capsule, was filed on April 4, 2001 by Warner Chilcott on behalf of F H Faulding and Co LTD and was approved by the FDA on August 31, 2001.

- No new clinical efficacy data were submitted for review as part of this application.

- In support of the new tablet dosage form, the applicant provided the following information:

    - information on the chemistry and manufacturing controls of the tablets
    - the results of single and multiple dose bioequivalence study (Doryx Tablets, 100 mg compared to the approved Doryx Capsules, 100mg)
    - the results of a single-dose-effect-of-food study with Doryx 100 mg Tablets
    - dissolution testing results

1.5 State of Armamentarium For Indication(s)

Doxycycline is an antibiotic that has been marketed in the United States in several formulations (capsule, tablet, oral suspension, and injectable formulations). The indications for the proposed product are the same as for the already approved formulations of doxycycline.

1.6 Availability of Proposed Product in the U.S.

The proposed product provides for a new tablet formulation of doxycycline hyclate.

1.7 Important Issues with Pharmacologically Related Products

N/A

1.8 Pre-submission Regulatory Activity

N/A

1.9 Other Relevant Background Information

N/A

2 Significant Findings from Other Review Disciplines

N/A

3 Data Sources, Review Strategy, and Data Integrity

3.1 Sources of Clinical Data

There were no clinical studies submitted for this NDA for the purposes of evaluating efficacy or safety. There were two pharmacokinetic studies (PR-01402 and PR-10303) that were conducted to demonstrate equivalence between the approved capsule formulation of Doryx and the new tablet formulation which is the subject of this NDA. Both studies were single-center, non-blinded, 2-treatment, 2-sequence, 2-period, randomized crossover studies.

3.2 Tables of Clinical Studies

Study	No. of Subjects	Objective
PR-01402	24 healthy males (ages 18-45)	Compare oral bioavailability of Doryx 100 mg tablets to Doryx 100 mg capsules following multiple-dose administration under fasting conditions to healthy volunteers
PR-08302	18 healthy males (ages 18-45)	Assess the effect of food on doxycycline bioavailability following oral administration of a single dose of Doryx tablets

3.3 Review Strategy

Study reports for both studies were reviewed. Since no efficacy data were collected, review focused on safety data collected during the two studies.

3.4 Data Quality and Integrity

Both studies were conducted at a single clinical center in ——— . Both studies were performed by the same principal investigator and co-investigator at ——— . Audit certificates were provided indicating that the clinical data, bioanalytical laboratory results, and final study reports were audited.

The Division of Scientific Investigations inspected the clinical center where this study was conducted and the laboratory where serum concentrations of doxycycline were assayed. The report from DSI recommended that data from 5 subjects be excluded from the bioequivalence determination. The doxycycline hyclate tablets were still demonstrated to be bioequivalent to the doxycycline hyclate capsules despite exclusion of these five subjects. (See Clinical Pharmacology and Biopharmaceutics review for details.)

3.5 Compliance with Good Clinical Practices

The sponsor stated that both pharmacokinetic studies were conducted in accordance with Good Clinical Practices. The studies were approved by the ———

3.6 Financial Disclosures

The investigators reported that they had no significant financial or equity interests in the sponsor company for these studies.

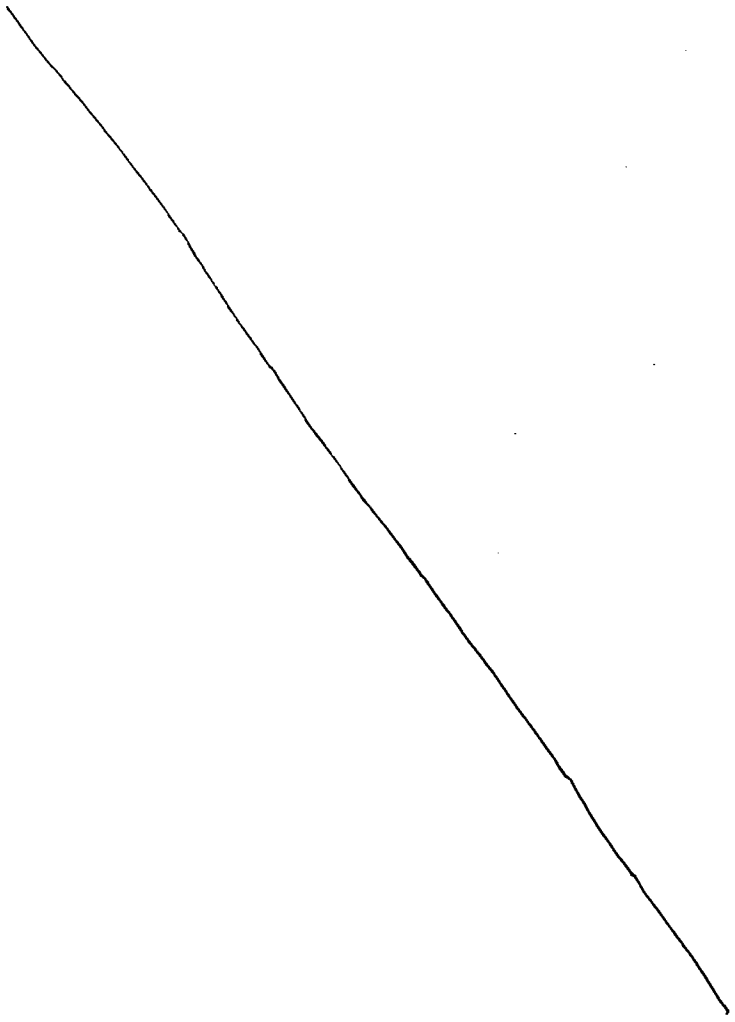
4 CLINICAL PHARMACOLOGY

The primary objective of studies PR-01402 and PR-10303 was to demonstrate bioequivalence to the approved capsule formulation of doxycycline hyclate.

4.1 Pharmacokinetics

The pharmacokinetic data submitted by the sponsor have been reviewed by the assigned biopharmaceutics reviewer. The biopharmaceutics reviewer has recommended approval of the proposed Doryx® tablets, based on bioequivalence to the approved Doryx® capsules.

As part of his review, the biopharmaceutics reviewer has recommended changes to the proposed label describing the ——— Doryx® tablets.



4.2 Pharmacodynamics

N/A

4.3 Exposure-Response Relationships

N/A

5 INTEGRATED REVIEW OF EFFICACY

N/A – The approval of this NDA is based on the demonstration of bioequivalence between the proposed tablet formulation of doxycycline hyclate and the approved capsule formulation of doxycycline hyclate. There were no efficacy studies performed for submission of this NDA.

6 INTEGRATED REVIEW OF SAFETY

6.1 Methods and Findings

The safety data reported in the study reports for studies PR-01402 and PR-10303 were reviewed.

6.1.1 Deaths

There were no deaths.

6.1.2 Other Serious Adverse Events

There were no serious adverse events.

6.1.3 Dropouts and Other Significant Adverse Events

There were no dropouts or other significant adverse events.

6.1.3.1 Other Significant Adverse Events

There were no significant adverse events.

6.1.3.2 Adverse Event Categorization and Preferred Terms

Between the two studies there were a total of 20 adverse events reported by 9 of the 42 patients. The reported adverse events were typical and consistent with the safety profile generated from the original approval of Doryx and included such adverse events as headaches and nausea. The only adverse events which required countermeasures were unlikely to have been caused by the study drug and include bronchitis in one patient, and cough/nasal congestion in another patient.

6.1.3.3 Incidence of Common Adverse Events

N/A

6.1.3.4 Common Adverse Event Tables

NA

6.1.3.5 Identifying Common and Drug-Related Adverse Events

NA

6.1.3.6 Additional Analyses and Explorations

NA

6.1.4 Less Common Adverse Events

NA

6.1.5 Laboratory Findings

There were no clinically significant changes in the measured laboratories.

6.1.5.1 Overview of Laboratory Testing in the Development Program

Blood and urine samples were collected at the screening visit for clinical laboratory evaluations which included hematology, clinical chemistry, urinalysis, serology, and a urine drug screen. At study exit, blood and urine samples were collected for hematology and clinical chemistry testing, and urinalysis.

6.1.5.2 Selection of Studies and Analyses for Drug-Control Comparisons of laboratory Values

NA

6.1.5.3 Standard Analyses and Explorations of Laboratory Data

NA

6.1.5.4 Additional Analyses and Explorations

NA

6.1.5.5 Special Assessments

NA

6.1.6 Vital Signs

NA

6.1.6.1 Extent of Vital Signs Testing in the Development Program

Vital signs (blood pressure and heart rate) were measured prior to dosing and upon completion of the study drug. There were no clinically significant changes in the measured vital signs.

6.1.6.2 Selection of Studies and Analyses for Overall Drug-Control Comparison

NA

6.1.6.3 Analyses and Explorations of Vital Signs Data

NA

6.1.6.4 Additional Analyses and Explorations

6.1.7 Electrocardiograms (ECGs)
NA

6.1.8 Immunogenicity
NA

6.1.9 Human Carcinogenicity
NA

6.1.10 Special Safety Studies
NA

6.1.11 Withdrawal Phenomena / Abuse Potential
NA

6.1.12 Human Reproduction and Pregnancy Data
NA

6.1.13 Overdose Experience
NA

6.1.14 Post-marketing Experience
NA

6.2 Adequacy of Patient Exposure and Safety Assessments
NA

6.3 Summary of Selected Drug-Related Adverse Events
NA

6.4 General Methodology
NA

6.5 Safety Conclusions
The small amount of safety data contained in this NDA is consistent with that described in the original NDA.

7 ADDITIONAL CLINICAL ISSUES

NA

8 OVERALL ASSESSMENT

8.1 Conclusions on Available Data

The available data supports the conclusion that Doryx Tablets are bioequivalent to the approved Doryx Capsules.

8.2 Recommendation on Regulatory Action

Approval of the new formulation, Doryx Tablets, is recommended.

8.3 Recommendation on Post-Marketing Actions

No post-marketing actions are recommended.

8.4 Labeling Review

The proposed product label was reviewed and compared to both the already approved Doryx Capsule label as well as to Vibramycin, which is marketed by Pfizer. The proposed changes to the sponsor's label are shown in the line by line review in section 9.2. The proposed changes to the label are generally to make the Doryx label consistent with the currently approved Vibramycin label. There are no substantial differences and the content of the proposed label is acceptable, however, changes to the INDICATIONS AND USAGE section as well as the Geriatric Use subsection are recommended.

In the INDICATIONS AND USAGE section, an indication for anthrax is listed "to reduce the incidence or progression of disease following exposure to aerosolized Anthrax due to Bacillus anthracis." This is incorrect terminology and it is recommended that the statement in the label be consistent with what is contained in the other doxycycline product labels, which is:

Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.*

In addition, the proposed label is not consistent with CFR 201-57 (f)(10)(ii)(A) and CFR 201-57 (f)(10)(iii)(B), the standard language statement for use in the "Geriatric Use" subsection of the PRECAUTIONS section.

In accordance with the CFR, it is recommended that the label include the following wording:

"Clinical studies of doxycycline did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the

elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."

In addition to the changes outlined above, the "Geriatric Use" subsection should provide information about a drug's sodium content. Since Doryx Tablets contain a minimal amount of sodium, then the following statement would be acceptable for inclusion in the Geriatric Use Subsection:

"Doryx Tablets contain X mg (X mEq) of sodium per tablet."

8.5 Comments to Applicant

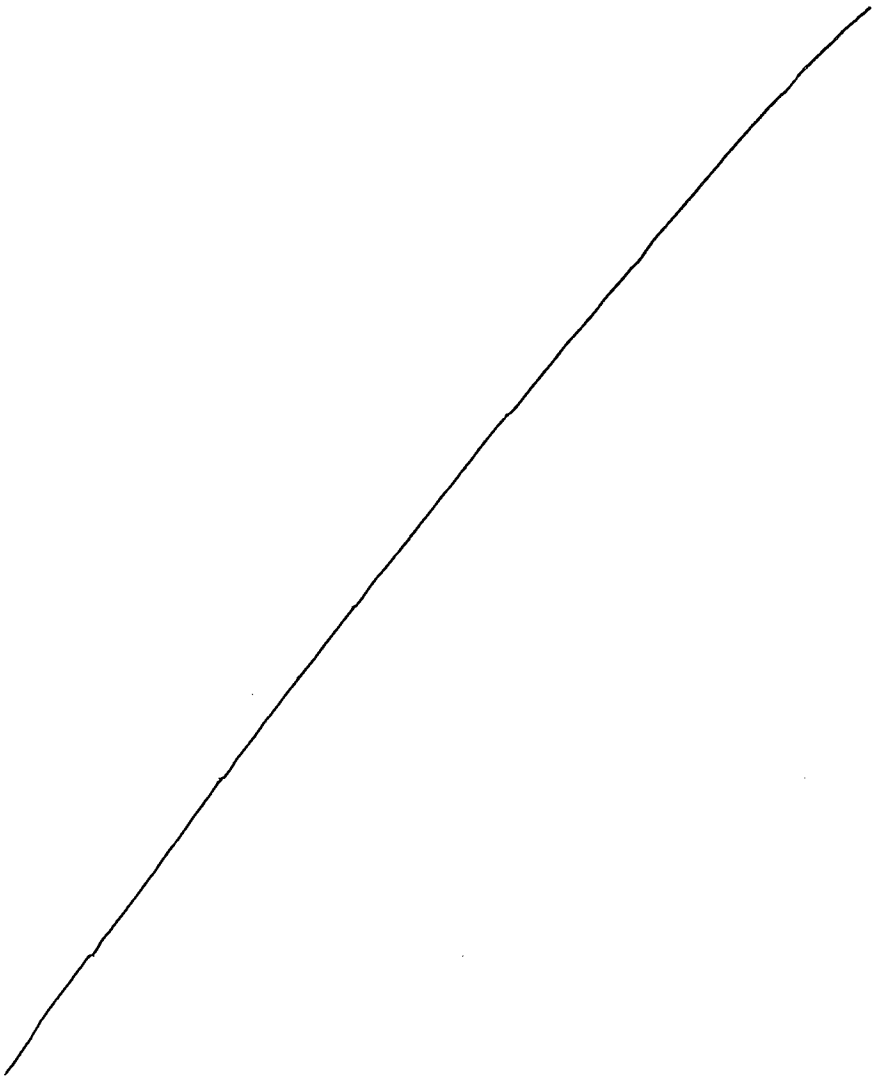
No comments to the applicant are recommended.

9 APPENDIX

9.1 Review of Individual Study Reports

NA

9.2 Line-by-line Labeling Review



Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile and excreted in the urine and feces at high concentrations and in a biologically active form.

Doxycycline is virtually completely absorbed after oral administration. Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 mcg/mL of doxycycline at 2 hours decreasing to 1.45 mcg/mL at 24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 mL/min). This percentage excretion may fall as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min). Studies have shown no significant difference in serum half-life of doxycycline (range 18-22 hours) in individuals with normal and severely impaired renal function.

The mean C_{max} and $AUC_{0-\infty}$ of doxycycline are reduced by 24% and 13%, respectively, following single dose administration of Doryx tablets with a high fat meal. The clinical significance of this decrease is unknown.

Hemodialysis does not alter serum half-life.

Results of animal studies indicate that tetracyclines cross the placenta and are found in fetal tissues.

Microbiology: The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including doxycycline, have a similar antimicrobial spectrum of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracycline is common.

Gram-Negative Bacteria

Neisseria gonorrhoeae
Calymmatobacterium granulomatis
Haemophilus ducreyi
Haemophilus influenzae
Yersinia pestis (formerly *Pasteurella pestis)*
Francisella tularensis (formerly *Pasteurella tularensis)*
Vibrio cholerae (formerly *Vibrio comma)*
Bartonella bacilliformis
Brucella species

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended:

Escherichia coli
Klebsiella species
Enterobacter aerogenes
Shigella species
Acinetobacter species (formerly *Mima* species *and Herellea* species)
Bacteroides species

Gram-Positive Bacteria
Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracycline, culture and susceptibility testing are recommended. Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracycline should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.
Streptococcus pyogenes
Streptococcus pneumoniae
Enterococcus group *(Streptococcus faecalis* and *Streptococcus faecium)*
Alpha-hemolytic streptococci (viridans group)
Other Microorganisms
Rickettsiae
Chlamydia psittaci
Chlamydia trachomatis
Mycoplasma pneumoniae
Ureaplasma urealyticum
Borrelia recurrentis
Treponema pallidum
Treponema pertenue
Clostridium species
Fusobacterium fusiforme
Actinomyces species
Bacillus anthracis
Propionibacterium acnes
Entamoeba species
Balantidium coli
Plasmodium falciparum
Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum* but not against the gametocytes of *P. falciparum.* The precise mechanism of action of the drug is not known.
Susceptibility Tests: Diffusion Techniques: Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such standard procedure[1] that has been recommended for use with diseks to test susceptibility of organisms to doxycycline uses the 30-mcg tetracycline-class disek or the 30-mcg doxycycline disek. Interpretation involves the correlation of the diameter obtained in the disk test with the minimum inhibitory concentration (MIC) for tetracycline or doxycycline, respectively.
Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30-mcg tetracycline-class disk or the 30-mcg-doxycycline disk should be interpreted according to the following criteria:

Zone Diameter (mm)		**Interpretation**
Tetracycline	doxycycline	
≥19	≥16	Susceptible
15-18	13-15	Intermediate
≤14	≤12	Resistant

12 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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