CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-795

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**50-795**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**4/9/04**
PRODUCT:	Doryx (coated doxycycline hyclate pellets) tablets, 75 and 100 mg
INTENDED CLINICAL POPULATION:	Patients with susceptible infections
SPONSOR:	**F. H. Faulding & Co.**
DOCUMENTS REVIEWED:	**Vol. 1.1, 1.7**
REVIEW DIVISION:	**Division of Anti-Infective Drug Products (HFD-520)**
PHARM/TOX REVIEWER:	**Amy C. Nostrandt, D.V.M., Ph.D.**
PHARM/TOX SUPERVISOR:	**Robert E. Osterberg, R.Ph., Ph.D., Fellow-A.T.S.**
DIVISION DIRECTOR:	**Janice Soreth, M.D.**
PROJECT MANAGER:	**Judit Milstein**

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From a pharmacology/toxicology standpoint, the application is approvable.

B. Recommendation for nonclinical studies

A battery of genetic toxicology tests for doxycycline is recommended to provide complete information for the label.

C. Recommendations on labeling

The pharmacology/toxicology sections of the proposed labeling are consistent with or identical to those for Doryx® capsules and Vibramycin® and are acceptable. However, there are no genetic toxicology data provided for doxycycline. Inclusion of data specific to this drug substance would make the label more complete.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The current drug product is a new formulation of a previously approved drug substance. The drug substance is found in the same strengths, 75 mg and 100 mg, in the approved formulation, Doryx® capsules. The proposed indications for the current drug product are the same as for the approved drug product. All excipients found in the new drug product formulation are found in approved drug products at levels as high or higher than those proposed. No new nonclinical studies were provided. Information provided by the sponsor is summarized in the review.

B. Pharmacologic activity

Doxycycline is a semi-synthetic tetracycline antibiotic with bacteriostatic activity against a wide range of Gram-negative and Gram-positive organisms. Doxycycline is thought to act via inhibition of protein synthesis.

C. Nonclinical safety issues relevant to clinical use

Safety issues associated with doxycycline are well-known following a long history of clinical use. Clinical adverse events that have been associated with this drug class include gastrointestinal effects, rashes and hypersensitivity reactions, benign intracranial hypertension, hematology effects, increase in BUN, depression of plasma prothrombin activity, and photosensitivity. Reproductive and developmental effects include embryotoxicity, permanent discoloration of teeth when used during tooth development, enamel hypoplasia, alteration of skeletal development, fetal

malformations in humans (Pregnancy Category D), and secretion in human milk. There have been positive findings for genetic toxicity in mammalian in vitro tests with drugs of this class.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

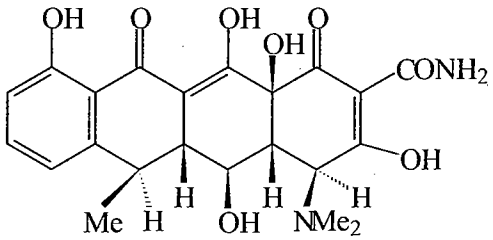
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 50-795
Review number: 1
Sequence number/date/type of submission: Original submission, letter date April 5, 2004
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: F. H. Faulding & Co. t/a Mayne Pharma International
Manufacturer for drug substance: [redacted]

Reviewer name:	**Amy C. Nostrandt, D.V.M., Ph.D.**
Division name:	**Division of Anti-Infective Drug Products**
HFD #:	**520**
Review completion date:	**September 8, 2004**

Drug:

Trade name: Doryx (coated doxycycline hyclate pellets) tablets, 75 and 100 mg
Generic name: Doxycycline hyclate
Code name: FP225, WC2031
Chemical name: Hydrochloride hemiethanol hemihydrate of (4S,4aR,5S,5a,6R,12aS)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide
CAS registry number: 24390-14-5
Molecular formula/molecular weight: $C_{22}H_{24}O_8$,HCl, ½C_2H_6O, ½H_2O
MW = 512.9
Structure:



HCl,1/2C_2H_5OH,1/2H_2O

Relevant INDs/NDAs/DMFs:

IND 66,553 for Doryx® (coated doxycycline hyclate pellets) tablets
NDA 50-582 for Doryx® (coated doxycycline hyclate pellets) capsules, 75 mg and 100 mg
ANDA 62-653 for Doryx® (coated doxycycline hyclate pellets) capsules, 100 mg

Drug class: Semi-synthetic tetracycline antimicrobial

Intended clinical population: Patients with susceptible infections as described in the current label for Doryx® (coated doxycycline hyclate pellets) Capsules, 75 and 100 mg.

Clinical formulation:

Ingredient	100 mg tablet mg/tablet	75 mg tablet mg/tablet
doxycycline hyclate, USP		
(based on average potency of 860 µg/mg)		
lactose monohydrate (450 M), NF		
cellulose microcrystalline (PH 101), NF		
sodium lauryl sulfate, NF		
sodium chloride, USP		
USP		
talc , USP		
), NF		
, NF		
lactose anhydrous), NF		
starch (corn starch,), NF		
crospovidone , NF		
magnesium stearate , NF		
USP		

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: No new nonclinical studies were submitted. Summary data as provided by the sponsor are presented in the appropriate sections below. The sponsor also provided references, most of which were review articles. Information from them is referenced below when not already covered in the sponsor's summary or approved labeling for Doryx® capsules and Vibramycin®.

Studies not reviewed within this submission: None

The sponsor's new drug product is a new, coated, delayed-release tablet formulation of doxycycline hyclate (coated doxycycline hyclate pellets). The intention is to delay drug release until the drug reaches the small intestine by means of the pH-dependent coating. The strengths, 75 mg and 100 mg, are found in the approved formulation of the same drug substance, Doryx® capsules.

All excipients found in the new drug product formulation are found in approved drug products administered by the oral route at levels as high or higher than those proposed.

The sponsor stated in their briefing for a pre-NDA meeting on August 25, 2003, that they would provide a risk-benefit analysis of the new excipients present in the proposed formulation. Information was provided in an amendment to the NDA:

- The drug product contains —— lactose monohydrate, — mg anhydrous lactose per 100 mg tablet. The sponsor states that —— of lactose is the threshold value that may cause symptoms in intolerant individuals.
- The drug product contains microcrystalline cellulose. In a 90-day gavage study in rats cited by the sponsor, the NOAEL for >5000 mg/kg/day, but the data were not provided. The sponsor states that 14.6 mg per tablet would not be expected to produce any toxicity.
- Sodium lauryl sulfate was reported to cause gastrointestinal irritation in gavage studies in rats; the NOEL was reported to be 100 mg/kg (HED = 17 mg/kg). This excipient was reported to be negative for mutagenicity (studies not specified). The sponsor states that the substance present at —— /tablet is unlikely to be associated with gastrointestinal irritation.
- The low amount of NaCl was considered to be unlikely to be associated with toxicity.
- ——
- ——
- ——— has been used as a food additive with an Acceptable Daily Intake (ADI) of up to 20 mg/kg/day, as determined by the FAO/WHO committee on food additives. Signs of toxicity include central nervous system depression, convulsions, increased respiratory rate, and blocked nerve conduction. The LD_{50} in rats was reported to be approximately 7 mL/kg PO, with signs of toxicity related to the central nervous system (CNS). The LD_{50} in the cat was approximately 3.5 mL/kg PO, again with CNS signs. At a dose of 0.25 mL/kg/day for 8 weeks (7% LD_{50}), weakness, ataxia, and depression were evident after 4-5 doses, but all animals survived and recovered. Additional studies to investigate neurotoxicity revealed effects seen at HED>30 mg/kg in rats and rabbits IP or IV. The sponsor states that the compound is likely to be hydrolyzed to citric acid and ethanol in the gastrointestinal tract prior to absorption and that its presence at ——— is not likely to result in toxicity.
- Corn starch is not expected to cause toxicity, unless individuals are hypersensitive.
- Crospovidone resulted in no signs of toxicity in short term toxicology studies.
- Magnesium stearate has been shown to be nontoxic, but large quantities may have a laxative effect. The sponsor states that the NOEL in a rat feeding study was 2500 mg/kg/day.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Doxycycline is bacteriostatic at clinically tolerated concentrations. The sponsor states that it is effective against a wide range of prokaryotic organisms, including aerobic and anaerobic Gram-positive and Gram-negative bacteria, rickettsiae, chamydiae,

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2.6.2.2 Primary pharmacodynamics

Doxycycline and other members of the tetracycline class of antibiotics act by inhibition of prokaryotic protein synthesis. The drug binds to the 30S subunit of the ribosome, inhibiting the formation of the tRNA-aminoacyl-mRNA-ribosome complex, thus preventing translation of mRNA.

2.6.2.3 Secondary pharmacodynamics

Tetracycline penetration into susceptible organisms consists of two phases: The drug adsorbs to the bacterial plasma membrane, then is actively transported into the cell. Chelation of metal ions may be involved in antibacterial mechanisms (Vet. Hum. Toxicol. 30(5):431-443, 1988).

2.6.2.4 Safety pharmacology

Neurological effects: No data were reported. However, Goodman and Gilman's The Pharmacological Basis of Therapeutics (10th ed., New York: McGraw-Hill, 2001) and the approved labeling for other doxycycline products indicate that tetracyclines may cause increased intracranial pressure and tense bulging of the fontanel (pseudotumor cerebri) in young infants, which reverses upon discontinuation of therapy. Increased pressure may occur rarely in older individuals, as well.

Cardiovascular effects: In dogs administered 10 mg/kg IV rapidly, doxycycline resulted in low ventricular and arterial pressures and bradycardia. These effects were dose-dependent and more pronounced at 30 mg/kg. ECG abnormalities included single extrasystoles, slight ST depression, negative T wave, and extension of the PQ segment.

In cats, rapid IV injections of 8 mg/kg doxycycline resulted in pronounced decrease of blood pressure in 4 of 10 anesthetized cats. The NOEL for this effect was 4 mg/kg by rapid injection, or 8 mg/kg administered over a 2 minute period.

Pulmonary effects: No data were reported.

Renal effects: In rats and dogs, ——— was a degradation product of tetracycline that was found to induce renal cortical tubular necrosis. Morphological studies in dogs revealed hydropic degeneration of proximal tubule cells after long-term treatment with therapeutic doses of tetracycline.

Dogs administered high doses of tetracyclines exhibited decreased inulin and PAH clearance, with unchanged renal plasma flow. The sponsor states that these findings are suggestive of tubular obstruction.

The sponsor states that doxycycline has been reported to have fewer renal side effects than other tetracyclines, but that there may be an association between doxycycline and renal failure.

Gastrointestinal effects: No nonclinical data were reported. The sponsor does state in section 5.5 of the NDA that tetracyclines may produce gastrointestinal irritation in some human patients, including nausea, vomiting, diarrhea, esophageal ulcers, and association with pancreatitis, in addition to varying degrees of gastrointestinal discomfort. This information is reflected in proposed and approved labeling.

Hepatic effects: In mice, an IV bolus dose of 25-50 mg/kg of tetracycline resulted in increased serum transaminases, alkaline phosphatase, urea, and total and conjugated bilirubin. Serum cholesterol was decreased. Triglycerides were increased transiently, followed by a decrease. Liver cholesterol and triglycerides were increased. Females appeared to be more susceptible. Doxycycline was stated to be less hepatotoxic than tetracycline in mice

The sponsor states in section 5.5 of the NDA that hepatic effects have been documented in human patients. Vacuolation and increased fat content of the liver have been reported following large doses of tetracycline. Jaundice, followed by azotemia, acidosis, and irreversible shock may also occur. The sponsor states that pregnant women appear to be particularly susceptible to severe hepatic damage from tetracycline.

Other: Tetracycline may cause permanent discoloration of the teeth in pediatric patients or in the developing fetus. Tetracycline deposition in the developing skeleton may depress bone growth.

2.6.2.5 Pharmacodynamic drug interactions

No nonclinical data were reported.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

No nonclinical studies were provided by the sponsor.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The following information is from the sponsor's summary and a submitted review article of human and animal pharmacokinetics of doxycycline (Vet. Hum. Toxicol. 30(5):431-443, 1988).

2.6.4.2 Methods of Analysis

Data were not presented in the pharmacology/toxicology section.

2.6.4.3 Absorption

Doxycycline is reported to be well absorbed by the oral route due to its high lipophilicity. Food does not interfere with absorption. Absorption occurs primarily in the duodenum in dogs by a carrier-independent and non-saturable process. Metallic ions

decrease the bioavailability of tetracyclines, with doxycycline being one of the less affected members of this drug class.

2.6.4.4 Distribution

High lipophilicity results in a high degree of tissue penetration by doxycycline and a large volume of distribution. Plasma protein binding was reported to be 80-95%. Doxycycline distributes into most fluids and tissues. Concentrations in synovial fluid and mucosa of the maxillary sinus are stated to be similar to those in plasma.

Tetracyclines as a class were reported to be concentrated in liver, excreted in bile and to undergo reabsorption in the intestine. Reabsorption also takes place in the renal tubules. The sponsor states that doxycycline is stored in the reticuloendothelial cells of the liver, spleen and bone marrow, and in dentine and enamel of unerupted teeth.

The sponsor states that doxycycline crosses the placenta and enters the fetal circulation and amniotic fluid. Umbilical cord plasma concentration approaches 60% and amniotic fluid concentrations approach. 20% of the maternal circulating concentration. High concentrations of the tetracyclines are found in milk.

The sponsor includes among the references the doxycycline summary report by the EMEA committee for veterinary medicinal products (October 1997). It states that doxycycline is rapidly and well absorbed from the gastrointestinal tract, with a longer half-life (15-22 hours) and is more lipid-soluble than other tetracyclines. Doxycycline is widely distributed with the highest levels achieved in kidney, liver, bone and dentine.

2.6.4.5 Metabolism

The doxycycline summary report by the EMEA committee for veterinary medicinal products (October 1997) states that doxycycline may be metabolized up to 40% and is mostly excreted in feces via bile and intestinal secretion. In contrast, other references indicate that doxycycline does not undergo extensive metabolism (Vet. Hum. Toxicol. 30(5):431-443, 1988), but that 4-epidoxycycline forms spontaneously in acidic media and has been mistaken for a metabolite.

2.6.4.6 Excretion

Unlike the other tetracyclines, the primary route of elimination of doxycycline is not the renal route. Instead, it is stated to be excreted in feces mostly as an inactive conjugate or a chelate. Due to intestinal reabsorption, doxycycline has a long elimination half-life.

According to a reference provided by the sponsor (Vet. Hum. Toxicol. 30(5):431-443, 1988), renal elimination accounts for 25% of doxycycline excretion in dogs and 40-55% of doxycycline excretion in man. Doxycycline is reabsorbed in the distal tubules and collecting tubules. It does not accumulate when glomerular filtration rate is compromised; compensation is probably by intestinal secretion. The second route of elimination is biliary excretion. The majority of doxycycline is excreted via a third route, diffusion into the small intestine. Enterohepatic re-circulation has been demonstrated with tetracycline in rats.

2.6.4.7 Pharmacokinetic drug interactions

No new nonclinical data were submitted

2.6.4.8 Other Pharmacokinetic Studies

None

2.6.4.9 Discussion and Conclusions

The pharmacokinetics of doxycycline have been investigated and described in humans. Detailed studies in animals were not provided.

2.6.4.10 Tables and figures to include comparative TK summary

None

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

No nonclinical studies were provided by the sponsor.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Safety issues associated with doxycycline are well-known following a long history of clinical use. Adverse events that have been associated with this drug class in nonclinical and clinical studies include gastrointestinal effects, rashes and hypersensitivity reactions, benign intracranial hypertension, hematology effects, increase in BUN, depression of plasma prothrombin activity, and photosensitivity. Reproductive and developmental effects include embryotoxicity, permanent discoloration of teeth when used during tooth development, enamel hypoplasia, alteration of skeletal development, fetal malformations in humans (Pregnancy Category D), and secretion in human milk. There have been positive findings for genetic toxicity in mammalian in vitro tests with drugs of this class.

2.6.6.2 Single-dose toxicity

LD_{50} values in mg/kg were provided as follows:

Species	Oral	Intravenous	Intraperitoneal
Mouse	1007 – 1900	204-223	204
Rat	> 2000	---	281
Guinea pig	---	---	175
Dog	> 500	---	---

Human equivalent doses in mg/kg for oral LD_{50} values in the mouse, rat, and dog are 84-158 mg/kg, > 333 mg/kg, and > 250 mg/kg, respectively. For a 60 kg human, the lowest total acute oral LD_{50} dose would be 15 g.

2.6.6.3 Repeat-dose toxicity

In a rodent (species not named) pediatric study of doxycycline, there was no evidence of increased toxicity in newborn animals relative to adults.

In a 90-day study in dogs, biliary hepatic dysfunction was observed at a dose of 250 mg/kg PO for more than 2 weeks. This effect was reversible in 21 days.

Chronic toxicology studies in the rat, dog, and monkey have demonstrated characteristic tetracycline effects of bone, teeth, and thyroid staining. These findings were not reversible.

The doxycycline summary report by the EMEA committee for veterinary medicinal products (October 1997) describes repeated dose studies in rats, hamsters, minipigs, dogs and monkeys. Hepatotoxicity was considered to be idiosyncratic in dogs with a NOEL of 25 mg/kg in 1-mo. study (HED = 12.5 mg/kg), and was reversible.

The approved label for Doryx® (coated doxycycline hyclate pellets) Capsules, 75 and 100 mg, states that the anti-anabolic action of drugs of this class may cause an increase in BUN. The label also indicates in the Precautions section that tetracyclines have been shown to depress plasma prothrombin activity, which may necessitate anticoagulant dosage adjustment for patients on anticoagulant therapy. The Adverse Reactions section of the label describes other clinical adverse events that have been associated with this drug class, including gastrointestinal effects, including antibiotic-associated diarrhea and pseudomembranous colitis, rashes and hypersensitivity reactions, benign intracranial hypertension, and effects on blood (hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia).

2.6.6.4 Genetic toxicology

The sponsor states that there is no evidence of genotoxic potential of doxycycline. However, this is because no tests for genetic toxicity of that drug substance have been performed.

The approved label for Doryx® (coated doxycycline hyclate pellets) Capsules, 75 and 100 mg, indicates that there have been positive findings for genetic toxicity in the mouse lymphoma assay and an assay in Chinese hamster lung cells in vitro. The Vibramycin® label indicates that these studies were performed to test tetracycline and/or oxytetracycline.

2.6.6.5 Carcinogenicity

No carcinogenicity data for doxycycline were provided.

2.6.6.6 Reproductive and developmental toxicology

Tetracylines, as a class, are known to cross the placenta and penetrate into fetal tissue. Toxic effects on the developing fetus include retardation of skeletal development. Embryotoxicity has also been noted in animals treated early in pregnancy.

Teratogenicity was not reported in developmental toxicity studies of doxycycline in rats, rabbits, and monkeys.

The sponsor describes a case-controlled study in humans which demonstrated a statistically significant association with total malformations and use of doxycycline in pregnancy. A small prospective study of pregnant women treated in the first trimester revealed no apparent effects on the offspring.

The sponsor references a CDER webpage (http://www.fda.gov/cder/drut/infopage/penG_doxy/doxypreg.htm) which states that doxycycline is excreted into breast milk. It states that there are concerns regarding staining of teeth, enamel hypoplasia, and depression of fetal bone growth. It also points out that tetracyclines are associated with fatty liver of pregnancy.

The sponsor states that doxycycline should not be used in pregnant patients or in children under 8 years of age.

These concerns are covered in the proposed labeling and in approved labeling for approved doxycycline drug products. The statement is made in the proposed labeling and that for Vibramycin® that tetracyclines form stable calcium complexes in bone-forming tissue and can alter bone growth, although this may be reversible on discontinuation of the drug.

The label states that the drug is included in Pregnancy Category D, based on a statistically significant association with fetal malformations in humans. The label also states that tetracyclines are secreted in human milk.

2.6.6.7 Local tolerance

No nonclinical data were described. The proposed label describes gastrointestinal irritation as a possible adverse effect associated with doxycycline.

2.6.6.8 Special toxicology studies

No nonclinical data were provided. The sponsor states in section 5.5 of the NDA that doxycycline may produce mild to severe phototoxic reactions in the skin of treated human patients exposed to sunlight ———— They state that this may be accompanied by onycholysis and pigmentation of the nails.

In human patients, skin reactions may follow use of tetracyclines. The sponsor's summary states that cross-sensitization among the various tetracyclines is very common.

Doxycycline inhibits chemotactic and phagocytic activity in neutrophils in vitro and in vivo, but may not be immunosuppressive at therapeutic doses. High concentrations may affect lymphocyte and IgG function. Slight decreases in humoral and cellular immune responses were seen in doxycycline-treated mice. (Vet. Hum. Toxicol. 30(5):431-443, 1988).

2.6.6.9 Discussion and Conclusions

The adverse events associated with nonclinical testing and clinical use of doxycycline are well known and have been described. The proposed labeling appears to cover these known events, however, genetic toxicology data for doxycycline are missing.

2.6.6.10 Tables and Figures

None

2.6.7 TOXICOLOGY TABULATED SUMMARY

No nonclinical studies were provided by the sponsor.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Adverse events have been previously described. There is extensive clinical experience with doxycycline.

Unresolved toxicology issues (if any): There is no genetic toxicology test data provided for doxycycline.

Recommendations: From a pharmacology/toxicology standpoint, the application is approvable. The following should be conveyed to the sponsor:

"Please provide data regarding the potential for genetic toxicity of doxycycline (see ICH S2A, S2B) for inclusion in the final labeling. This will ensure complete and accurate information in the label for this drug substance. Data may be provided from the peer-reviewed literature, or from original study reports."

Suggested labeling:

Signatures:

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

Deputy Division Director Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amy Nostrandt
9/20/04 03:48:30 PM
PHARMACOLOGIST
There is a request for the sponsor to provide genetic toxicity information for this drug substance at the end of the review.

Robert Osterberg
9/24/04 09:39:05 AM
PHARMACOLOGIST

Lillian Gavrilovich
9/24/04 05:29:06 PM
MEDICAL OFFICER