CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 50-795/S19

Trade Name: Doxteric

Generic Name: doxycycline Hyclate

Sponsor: Mayne Pharma International Pty Ltd.

Approval Date: December 19, 2014

Indications: For the treatment of rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, anthrax, including inhalational anthrax (post-exposure), alternate treatment for selected infections when penicillin is contraindicated, adjunctive therapy in acute intestinal amebiasis and severe acne and prophylaxis of malaria.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

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NDA 50-795/S19

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50795/S-19

SUPPLEMENT APPROVAL

Mayne Pharma International Pty Ltd
Attention: Susan Canady
Regulatory Affairs Specialist
1240 Sugg Parkway
Greenville, NC 27834

Dear Ms. Canady:

Please refer to your Supplemental New Drug Application (sNDA) dated August 25, 2014, received August 28, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DOXTERIC (doxycycline hyclate) Tablet 50 mg.

We acknowledge receipt of your amendments dated September 18, October 14, November 6 and 14, and December 19, 2014.

This "Prior Approval" supplemental new drug application provides for a new 50-mg strength tablet.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your December 19, 2014, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your November 6, 2014, submission containing final printed carton and container labels.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Naseya Minor, Regulatory Project Manager, at (301)796-0756.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

KATHERINE A LAESSIG
12/19/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S19

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DOXTERIC™ (doxycycline hyclate delayed-release tablets) safely and effectively. See full prescribing information for DOXTERIC.

DOXTERIC™ (doxycycline hyclate delayed-release tablets), Oral use.
Initial U.S. Approval: 1967

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline hyclate and other antibacterial drugs, DOXTERIC Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1)

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.5) 12/2014

----------INDICATIONS AND USAGE----------
DOXTERIC is a tetracycline-class antibacterial indicated for:
- Rickettsial infections (1.1)
- Sexually transmitted infections (1.2)
- Respiratory tract infections(1.3)
- Specific bacterial infections (1.4)
- Ophthalmic infections (1.5)
- Anthrax, including inhalational anthrax (post-exposure) (1.6)
- Alternative treatment for selected infections when penicillin is contraindicated (1.7)
- Adjunctive therapy in acute intestinal amebiasis and severe acne (1.8)
- Prophylaxis of malaria (1.9)

----------DOSAGE AND ADMINISTRATION----------
- Adults: the usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended. (2.1)
- For children above eight years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used. (2.1)

----------DOSAGE FORM AND STRENGTHS----------
Tablets: 50 mg

----------CONTRAINDICATIONS----------
Doxycycline is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines. (4)

----------WARNINGS AND PRECAUTIONS----------
- 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). (5.1)
- *Clostridium difficile*-associated diarrhea. Evaluate patients if diarrhea occurs. (5.2)
- Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Limit sun exposure. (5.3)
- Overgrowth of non-susceptible organisms, including fungi, may occur. Re-evaluate therapy if superinfection occurs. (5.4)

----------ADVERSE RECTIONS----------
Adverse reactions observed in patients receiving tetracyclines include anorexia, nausea, vomiting, diarrhea, rash, photosensitivity, urticarial, and hemolytic anemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mayne Pharma at 1-844-825-8500 or FDA at 1-800-FDA-1088 or www fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage (7.1)
- Avoid co-administration of tetracyclines with penicillin (7.2)
- Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron-containing preparations (7.3)
- Concurrent use of tetracycline may render oral contraceptives less effective (7.4)
- Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline (7.5)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy Category D (8.1)
- Tetracyclines are excreted in human milk, however, the extent of absorption of doxycycline in the breastfed infant is not known. Doxycycline use during nursing should be avoided if possible. (**8.3**)

See 17 for PATIENT COUNSELING INFORMATION

Revised: XX/XXXX

FULL PRESCRIBING INFORMATION: CONTENTS*

Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DOXTERIC and other antibacterial drugs, DOXTERIC should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Doxycycline is a tetracycline-class antibacterial indicated in the following conditions or diseases:

1.1 Rickettsial infections

Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by *Rickettsiae*.

1.2 Sexually transmitted infections

Uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis.*

Nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.

Granuloma inguinale caused by *Klebsiella granulomatis*.

Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*.

Chancroid caused by *Haemophilus ducreyi*.

1.3 Respiratory tract infections

Respiratory tract infections caused by *Mycoplasma pneumoniae*.

Psittacosis (ornithosis) caused by *Chlamydophila psittaci*.

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following microorganisms, when bacteriological testing indicates appropriate susceptibility

to the drug:
Respiratory tract infections caused by *Haemophilus influenzae*.
Respiratory tract infections caused by *Klebsiella* species.
Upper respiratory infections caused by *Streptococcus pneumoniae*.

1.4 Specific bacterial infections

Relapsing fever due to *Borrelia recurrentis*.
Plague due to *Yersinia pestis*.
Tularemia due to *Francisella tularensis*.
Cholera caused by *Vibrio cholerae*.
Campylobacter fetus infections caused by *Campylobacter fetus*.
Brucellosis due to *Brucella* species (in conjunction with streptomycin).
Bartonellosis due to *Bartonella bacilliformis*.

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:
Escherichia coli
Enterobacter aerogenes
Shigella species
Acinetobacter species
Urinary tract infections caused by *Klebsiella* species.

1.5 Ophthalmic infections

Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated as judged by immunofluorescence.
Inclusion conjunctivitis caused by *Chlamydia trachomatis*.

1.6 Anthrax including inhalational anthrax (post-exposure)

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

1.7 Alternative treatment for selected infections when penicillin is contraindicated

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections:
Syphilis caused by *Treponema pallidum*.
Yaws caused by *Treponema pallidum* subspecies *pertenue*.
Vincent's infection caused by *Fusobacterium fusiforme.*
Actinomycosis caused by *Actinomyces israelii*.
Infections caused by *Clostridium* species.

1.8 Adjunctive therapy for acute intestinal amebiasis and severe acne

In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.
In severe acne, doxycycline may be useful adjunctive therapy.

1.9 Prophylaxis of malaria

Doxycycline is indicated for the prophylaxis of malaria due to *Plasmodium falciparum* in short-term travelers (less than 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains [*see Dosage and Administration (2.2) and Patient Counseling Information (17)*].

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage and Administration

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours), followed by a maintenance dose of 100 mg daily. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For pediatric patients above eight years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline-class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration [*see Adverse Reactions (6.1)*].

If gastric irritation occurs, doxycycline may be given with food or milk [*see Clinical Pharmacology (12)*].

When used in streptococcal infections, therapy should be continued for 10 days.
Uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis*: 100 mg by mouth twice-a-day for 7 days.

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice-a-day for 7 days. As an alternative single visit dose, administer 300 mg stat followed in an hour by a second 300 mg dose.

Nongonococcal urethritis (NGU) caused by *U. urealyticum*: 100 mg by mouth twice-a-day for 7 days.

Syphilis – early: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice-a-day for 2 weeks.

Syphilis of more than one year's duration: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice-a-day for 4 weeks.

Acute epididymo-orchitis caused by *C. trachomatis*: 100 mg, by mouth, twice-a-day for at least 10 days.

2.2 For prophylaxis of malaria

For adults, the recommended dose is 100 mg daily. For children over 8 years of age, the recommended dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis should begin 1 or 2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area.

2.3 Inhalational anthrax (post-exposure)

ADULTS: 100 mg, of doxycycline, by mouth, twice-a-day for 60 days.

CHILDREN: weighing less than 45 kg, 2.2 mg/kg of body weight, by mouth, twice-a-day for 60 days. Children weighing 45 kg or more should receive the adult dose.

2.4 Sprinkling the tablet over applesauce

DOXTERIC Tablets may also be administered by carefully breaking up the tablet and sprinkling the tablet contents (delayed-release pellets) on a spoonful of applesauce. The delayed-release pellets must not be crushed or damaged when breaking up the tablet. Any loss of pellets in the transfer would prevent using the dose. The applesauce/DOXTERIC mixture should be swallowed immediately without chewing and may be followed by a glass of water if desired. The applesauce should not be hot, and it should be soft enough to be swallowed without chewing. In the event that a prepared dose of applesauce/DOXTERIC cannot be taken immediately, the mixture should be discarded and not stored for later use.

3 DOSAGE FORMS AND STRENGTHS

DOXTERIC (doxycycline hyclate delayed-release tablets), 50 mg are white, oval scored tablets containing yellow pellets and debossed with "DV" on one face and plain on the other. Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 50 mg of doxycycline.

4 CONTRAINDICATIONS

The drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

5 WARNINGS AND PRECAUTIONS

5.1 Tooth Development

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 it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Doxycycline should not be used in this age group, except for anthrax, including inhalational anthrax (post-exposure), unless other drugs are not likely to be effective or are contraindicated.

5.2 Clostridium difficile associated diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including doxycycline hyclate delayed-release tablets, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.3 Photosensitivity

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.

5.4 Superinfection

As with other antibacterial preparations, use of DOXTERIC may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibacterial should be discontinued and appropriate therapy instituted.

5.5 Intracranial Hypertension

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline including DOXTERIC. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Avoid concomitant use of isotretinoin and DOXTERIC because isotretinoin is also known to cause pseudotumor cerebri.

Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

5.6 Skeletal Development

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

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 also has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the fetus.

5.7 Antianabolic Action

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

5.8 Malaria

Doxycycline offers substantial but not complete suppression of the asexual blood stages of *Plasmodium* strains.

Doxycycline does not suppress *P. falciparum's* sexual blood stage gametocytes. Subjects completing this prophylactic regimen may still transmit the infection to mosquitoes outside endemic areas.

5.9 Development of Drug-Resistant Bacteria

Prescribing DOXTERIC in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.10 Laboratory Monitoring for Long-Term Therapy

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

6 ADVERSE REACTIONS

6.1 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of doxycycline. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline-class. Most of these patients took medications immediately before going to bed [*see Dosage and Administration (2.1)*].

Skin: Maculopapular and erythematous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and erythema multiforme have been reported. Photosensitivity is discussed above [*see Warnings and Precautions (5.3)*].

Renal: Rise in BUN has been reported and is apparently dose-related [*see Warnings and Precautions (5.7)*].

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

Intracranial Hypertension: Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline *[See Warnings and Precautions (5.5)]*

Thyroid Gland Changes: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function are known to occur.

7 DRUG INTERACTIONS

7.1 Anticoagulant Drugs

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

7.2 Penicillin

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin.

7.3 Antacids and Iron Preparations

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate, and iron-containing preparations.

7.4 Oral Contraceptives

Concurrent use of tetracycline may render oral contraceptives less effective.

7.5 Barbiturates and anti-epileptics

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

7.6 Penthrane

The concurrent use of tetracycline and Penthrane® (methoxyflurane) has been reported to result in fatal renal toxicity.

7.7 Drug/Laboratory Test Interactions

False elevations of urinary catecholamines may occur due to interference with the fluorescence test.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects. Pregnancy Category D:

There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for the treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS - the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk.[1]

A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. Sixty-three (0.19%) of the controls and 56 (0.30%) of the cases were treated with doxycycline. This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (i.e., in the second and third months of gestation), with the exception of a marginal relationship with neural tube defect based on only two-exposed cases.[2]

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age.[3]

Nonteratogenic effects: [*see Warnings and Precautions (5.1, 5.6)*].

8.3 Nursing Mothers

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated. The effects of prolonged exposure to doxycycline in breast milk are unknown.[4] Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother [*see Warnings and Precautions (5.1, 5.6)*].

8.4 Pediatric use

Because of the effects of drugs of the tetracycline-class on tooth development and growth, DOXTERIC should not be used in pediatric patients to the age of 8 years, unless the potential benefits are expected to outweigh the risks such as for anthrax, or when other drugs are not likely to be effective or are contraindicated [*see Warnings and Precautions (5.1, 5.6) and Dosage and Administration (2.1, 2.3)*].

8.5 Geriatric use

Clinical studies of DOXTERIC 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.
DOXTERIC 50 mg Tablets contain 3 mg (0.131 mEq) of sodium.

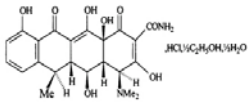
10 OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

11 DESCRIPTION

DOXTERIC (doxycycline hyclate delayed-release tablets), for oral administration, contain specially coated pellets of doxycycline hyclate, a broad-spectrum antibacterial synthetically derived from oxytetracycline, in a delayed-release formulation for oral administration.

The structural formula for doxycycline hyclate is:



with a molecular formula of $C_{22}H_{24}N_2O_8$, HCl, ½ C_2H_6O, ½ H_2O and a molecular weight of 512.9. The chemical designation for doxycycline hyclate is [4S(4aR,5S,5aR,6R,12aS)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-deoxonaphthacene-2-carboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate. Doxycycline hyclate is a yellow crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form. Inactive ingredients in the tablet formulation are: lactose monohydrate; microcrystalline cellulose; sodium lauryl sulfate; sodium chloride; talc, anhydrous lactose; corn starch; crospovidone; magnesium stearate; cellulosic polymer coating.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Doxycycline is an antibacterial drug [*see Microbiology (12.4)*].

12.3 Pharmacokinetics

Doxycycline is virtually completely absorbed after oral administration. Following administration of a single 200 mg dose to adult volunteers, average serum doxycycline levels were 2.6 mcg/mL at 2 hours decreasing to 1.45 mcg/mL at 24 hours. The mean C_{max} and $AUC_{0-\infty}$ of doxycycline are 24% and 13% lower, respectively, following single dose administration of DOXTERIC Tablets, 100 mg with a high fat meal (including milk) compared to fasted conditions. The mean C_{max} of doxycycline is 19% lower and the $AUC_{0-\infty}$ is unchanged following single dose administration of doxycycline hyclate tablets, 150 mg with high fat meal (including milk) compared to fasted conditions. The clinical significance of these differences is unknown.

When DOXTERIC Tablets are sprinkled over applesauce and taken with or without water, the extent of doxycycline absorption is unchanged, but the rate of absorption is increased slightly.

Tetracyclines are concentrated in bile by the liver and excreted in the urine and feces at high concentrations and in a biologically active form. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with a creatinine clearance of about 75 mL/min. This percentage may fall as low as 1-5%/72 hours in individuals with a creatinine clearance below 10 mL/min.

Studies have shown no significant difference in the serum half-life of doxycycline (range 18 to 22 hours) in individuals with normal and severely impaired renal function. Hemodialysis does not alter the serum half-life.

12.4 Microbiology

Mechanism of Action

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria. Cross-resistance between tetracyclines is common.

Doxycycline has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for DOXTERIC Tablets [see *Indications and Usage (1)*].

Gram-Negative Bacteria
Acinetobacter species
Bartonella bacilliformis
Brucella species

Campylobacter fetus
Enterobacter aerogenes
Escherichia coli
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Klebsiella granulomatis
Klebsiella species
Neisseria gonorrhoeae
Shigella species
Vibrio cholerae
Yersinia pestis

Gram-Positive Bacteria
Bacillus anthracis
Streptococcus pneumoniae

Anerobic Bacteria
Clostridium species
Fusobacterium fusiforme
Propionibacterium acnes

Other Bacteria
Norcardiae and other aerobic *Actinomyces* species
Borrelia recurrentis
Chlamydophila psittaci
Chlamydia trachomatis
Mycoplasma pneumoniae
Rickettsiae
Treponema pallidum
Treponema pallidum subspecies *pertenue*
Ureaplasma urealyticum

Parasites *Balantidium*
coli Entamoeba species
*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 Test Methods
When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth and/or agar).[5,6,8] The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion Techniques
Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. Zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standard test method.[5,7,8] This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of bacteria to doxycycline. The disk diffusion interpretive criteria are provided in Table 1.

Anaerobic Techniques
For anaerobic bacteria the susceptibility to doxycycline can be determined by a standardized test method.[9] The MIC values obtained should be interpreted according to the criteria provided in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline

Bacteria[a]	Minimal Inhibitory Concentration (mcg/mL)			Zone Diameter (mm)			Agar Dilution (mcg/mL)		
	S	I	R	S	I	R	S	I	R
Acinetobacter spp,									
Doxycycline	≤4	8	≥16	≥13	10-12	≤9	-	-	-
Tetracycline	≤4	8	≥16	≥15	12-14	≤11	-	-	-
Anaerobes									
Tetracycline	-	-	-	-	-	-	≤4	8	≥16
Bacillus anthracis[ab]									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
Brucella species[ab]									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
Enterobacteriacea									
Doxycycline	≤4	8	≥16	≥14	11-13	≤10	-	-	-
Tetracycline	≤4	8	≥16	≥15	12-14	≤11	-	-	-
FranciscelIa tularensis[ab]									
Doxycycline	≤4	-	-	-	-	-	-	-	-
Tetracycline	≤4	-	-	-	-	-	-	-	-
Haemophilus influenzae									
Tetracycline	≤2	4	≥8	≥29	26-28	≤25	-	-	-
Mycoplasma pneumoniae									
Tetracycline	-	-	-	-	-	-	≤2	-	-
Nocardiae and other aerobic *Actinomyces* species[ab]									
Doxycycline	≤1	2-4	≥8						
Neisseria gonorrhoeae[c]									
Tetracycline	-	-	-	≥38	31-37	≤30	≤0.25	0.5-1	≥2
Streptococcus pneumoniae									
Doxycycline	≤0.25	0.5	≥1	≥28	25-27	≤24	-	-	-
Tetracycline	≤1	2	≥4	≥28	25-27	≤24	-	-	-
Vibrio cholerae									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
Yersinia pestis									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
Ureaplasma urealyticum									
Tetracycline	-	-	-	-	-	-	≤1	-	≥2

[a]Organisms susceptible to tetracycline are also considered susceptible to doxycycline, However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline.

[b]The current absence of resistance isolates þrecludes defining any results other than "Susceptible". If isolates yielding MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

[c]Gonococci with 30 mcg tetracycline disk zone diameters of less than 19 mm usually indicate a plasmid-mediated tetracycline resistant *Neisseria gonorrhoeae* isolate. Resistance in these strains should be confirmed by a dilution test (MIC greater than or equal to 16 mcg/mL).

A report of *Susceptible* (S) indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of *Intermediate* (I) indicates that the result should be considered equivocal, and, if the bacteria is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* (R) indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the

assay, and the techniques of the individuals performing the test.[5,6,7,8,9,10,11] Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 30 mcg doxycycline disk the criteria noted in Table 2 should be achieved.

Table 2: Acceptable Quality Control Ranges for Susceptibility Testing for Doxycycline and Tetracycline

QC Strain	Minimal Inhibitory Concentration (mcg/mL)	Zone Diameter (mm)	Agar Dilution (mcg/mL)
Enterococcus faecalis ATCC 29212			
Doxycycline	2-8	-	-
Tetracycline	8-32	-	-
Escherichia coli ATCC 25922			
Doxycycline	0.5-2	18-24	-
Tetracycline	0.5-2	18-25	-
Eubacterium lentum ATCC 43055			
Doxycycline	2 - 16	-	-
Haemophilus influenzae ATCC 49247			
Tetracycline	4-32	14-22	-
Neisseria gonorrhoeae ATCC 49226			
Tetracycline	-	30-42	0.25-1
Staphylococcus aureus ATCC 25923			
Doxycycline	-	23-29	-
Tetracycline	-	24-30	-
Staphylococcus aureus ATCC 29213			
Doxycycline	0.12-0.5		-
Tetracycline	0.12-1		-
Staphylococcus pneumoniae ATCC 49619			
Doxycycline	0.015-0.12	25-34	-
Tetracycline	0.06-0.5	27-31	-
Bacteroides fragilis ATCC 25285			
Tetracycline	-	-	0.125-0.5
Bacteroides thetaiotaomicron ATCC 29741			
Doxycycline	2 - 8	-	-
Tetracycline	-	-	8-32
Mycoplasma pneumoniae ATCC 29342			
Tetracycline	0.06-0.5	-	0.06-0.5
Ureaplasma urealyticum ATCC 33175			
Tetracycline	-	-	≥8

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted However, there has been evidence of oncogenic activity in rats in studies with the related antibiotics, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors) Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibacterials (tetracycline, oxytetracycline).

Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats Effect on male fertility has not been studied.

13.2 Animal Toxicology and/or Pharmacology

Hyperpigmentation of the thyroid has been produced by members of the tetracycline-class in the following species: in rats by oxytetracycline, doxycycline, tetracycline PO_4, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO_4, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO_4, methacycline, doxycycline, tetracycline base, oxytetracycline HCl, and tetracycline HCl, were goitrogenic in rats fed a low iodine diet This goitrogenic effect was accompanied by high radioactive iodine uptake Administration of minocycline also produced a large goiter with high radioiodine uptake in rats fed a relatively high iodine diet.

Treatment of various animal species with this class of drugs has also resulted in the induction of thyroid hyperplasia in the following: in rats and dogs (minocycline); in chickens (chlortetracycline); and in rats and mice (oxytetracycline) Adrenal gland hyperplasia has been observed in goats and rats treated with oxytetracycline.

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

15 REFERENCES

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2. Cziezel AE and Rockenbauer M Teratogenic study of doxycycline *Obstet Gynecol* 1997; 89: 524-528.
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5. Clinical and Laboratory Standards Institute (CLSI) *Performance Standards for Antimicrobial Susceptibility Testing; Twenty- fourth Informational Supplement.* CLSI document M100-S24 Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2014.
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7. Clinical and Laboratory Standards Institute (CLSI) *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard - Eleventh Edition.* CLSI document M02-A11, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2012.
8. Clinical and Laboratory Standards Institute (CLSI) *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline – Second Edition.* CLSI document M45-A2, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2010.
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10. Clinical and Laboratory Standards Institute (CLSI) *Methods for Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard – Second Edition* CLSI document M24-A2, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2011.
11. Clinical and Laboratory Standards Institute (CLSI) *Methods for Antimicrobial Susceptibility Testing for Human Mycoplasmas; Approved Guideline* CLSI document M43-A, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2011.

16 HOW SUPPLIED/STORAGE AND HANDLING

DOXTERIC (doxycycline hyclate delayed-release tablets), 50 mg are white, oval scored tablets containing yellow pellets and debossed with "DV" on one face and plain on the other Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 50 mg of doxycycline.

Bottles of 120 tablets
N 68308-555-12

Store at 25° C (77° F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature] Dispense in a tight, light-resistant container (USP).

17 PATIENT COUNSELING INFORMATION

Patients taking doxycycline for malaria prophylaxis should be advised:

- that no present-day antimalarial agent, including doxycycline, guarantees protection against malaria.
- to avoid being bitten by mosquitoes by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to dawn (for example, staying in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellent).
- that doxycycline prophylaxis:
  - should begin 1 to 2 days before travel to the malarious area,
  - should be continued daily while in the malarious area and after leaving the malarious area,
  - should be continued for 4 further weeks to avoid development of malaria after returning from an endemic area,
  - should not exceed 4 months.

All patients taking doxycycline should be advised:

- to avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (for example, skin eruptions, etc.) occurs Sunscreen or sunblock should be considered [*see Warnings and Precautions (5.3)*]
- to drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration [*see Adverse Reactions (6.1)*]
- that the absorption of tetracyclines is reduced when taken with foods, especially those that contain calcium However, the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk [*see Drug Interactions (7.3)*]
- that the absorption of tetracyclines is reduced when taken with antacids containing aluminum, calcium or magnesium, bismuth subsalicylate, and iron-containing preparations [*see Drug Interactions (7.3)*].
- that the use of doxycycline might increase the incidence of vaginal candidiasis.

Diarrhea is a common problem caused by antibacterials which usually ends when the antibacterial is discontinued Sometimes after starting treatment with antibacterials, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of antibacterial If this occurs, patients should contact their physician as soon as possible.

Patients should be counseled that antibacterial drugs including DOXTERIC should only be used to treat bacterial infections They do not treat viral infections (for example, the common cold) When DOXTERIC is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by DOXTERIC or other antibacterial drugs in the future.

Rx only

Manufactured by:
Mayne Pharma International Pty Ltd
1538 Main North Road
Salisbury South, SA 5106 Australia

Distributed by: Mayne
Pharma USA
Greenville, NC 27834
1-844-825-8500

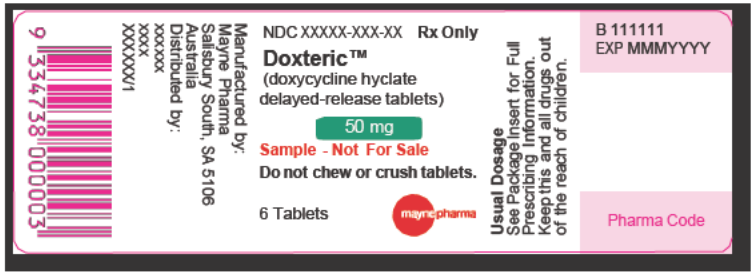
(b) (4)

(b) (4)


Rx only
Doxteric™
(doxycycline hyclate
delayed-release tablets)
50
Sample - Not For Sale
6 Tablets
Manufactured by:
Mayne Pharma
Salisbury South, SA 5106
Australia
Distributed by:
xxxx
xxx
1-800-xxx
XXXXXX/1
9 334738 000003
B 111111
EXP MMMYYYY
Rx Only
Usual Dosage:
See Package Insert for Full Prescribing Information.
Keep this and all drugs out of the reach of children.
50 mg
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].
6 Tablets
NDC XXXXX-XXX-XX
Rx Only
Doxteric™
(doxycycline hyclate
delayed-release tablets)
50 mg
Sample - Not For Sale
Do not chew or crush tablets.
Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 50 mg of doxycycline.
6 Tablets
Rx Only
Doxteric™
(doxycycline hyclate
delayed-release tablets)
50 mg
Sample - Not For Sale
6 Tablets

(b) (4)

(b) (4)


9 334738 000003
Manufactured by:
Mayne Pharma
Salisbury South, SA 5106
Australia
Distributed by:
xxxxxx
xxxx
XXXXXX1
NDC XXXXX-XXX-XX Rx Only
Doxteric™
(doxycycline hyclate
delayed-release tablets)
50 mg
Sample - Not For Sale
Do not chew or crush tablets.
6 Tablets
maynepharma
Usual Dosage
See Package Insert for Full
Prescribing Information.
Keep this and all drugs out
of the reach of children.
B 111111
EXP MMMYYYY
Pharma Code

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S19

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1	1. ORGANIZATION	2. NDA NUMBER	Original ☒
	ONDQA	N 050795	RESUBMISSION ☐

3. NAME AND ADDRESS OF APPLICANT

Company Name: Mayne Pharma International Pty Ltd
Street Address: 1538 Main North Road
City: Salisbury South
State: South Australia
Country: Australia
Zip Code: 5106

4. SUPPLEMENT(S)

NUMBER(S)	TYPE
S-019	PAS

5. DATE(S)

Submit Date	August 25, 2014
FDA Receipt Date	August 28, 2014
Goal Date	December 28, 2014
Chemist Receipt Date	September 5, 2014
Amendments	October 14, 2014 November 5, 2014 November 14, 2014
Date Completed	December 11, 2014

6. PROPRIETARY NAME	7. NAME OF THE DRUG
Doxteric	Doxycycline Hyclate Delayed-Release Tablets

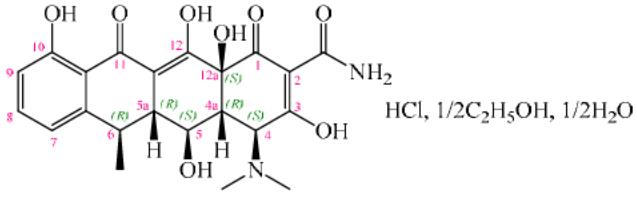
8. SUPPLEMENT PROVIDES FOR:

Add an additional drug product strength - 50 mg

9. INDICATION	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
for Rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, Anthrax, including inhalational anthrax (post-exposure), alternative treatment for selected infections when penicillin is contraindicated, adjunctive therapy in acute intestinal amebiasis and severe acne, and prophylaxis of malaria.	RX ☒ OTC ☐	
12. DOSAGE FORM	**13. POTENCY**	
Tablet	75mg, 80mg, 100mg, 150mg, 200 mg	

14. CHEMICAL NAME AND STRUCTURE

[4S(4aR,5S,5aR,6R,12aS)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6methyl-1,11-deoxonapthtacene-2-carboxamide monohydrochloride



Chemical Formula: $C_{22}H_{24}N_2O_8$, HCl. $1/2C_2H_5OH$, $1/2H_2O$
Molecular Weight: 512.9

15. RECORDS AND REPORTS

16. COMMENTS

In this submission, the applicant did not propose any changes to the drug substance or the drug product manufacturers. The applicant provided comparative batch formula for the proposed and currently approved tablets. The formulation for the proposed strength is the same as the currently approved strengths. No changes were made to the manufacturing process, controls, and excipirnts. The drug product specifications remain the same except for the description and release specifications. The analytical methods remain the same. The applicant provided batch analysis data for (b) (4) batches. No OOS results are reported. However (b) (4) . Upon request, the applicant provided additional samples (currently approved and proposed 50 mg strength) as well as (b) (4) . The applciant indicated that (b) (4) (b) (4) . Additional (b) (4) were conducted by Dr. Ziyaur Rahman (FDA/CDER/OPS/OTR). The data generated by Dr. Rahman were consistent with the applicant's results, indicating that the proposed (b) (4) have adequate (b) (4) and there are no major (b) (4) concerns. The 3 months stability data provided by the applicant shows no major trends or OOS data.

The biowaiver request, and proposed dissolution specifications and data were evaluated by Dr. Kelly Kitchens on December 02, 2014, and were found to be acceptable.

The applicant provided new PI and carton and container labels. The carton and container labels are acceptable from the CMC point of view. The DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections of the PI was evaluated. The applicant was asked to include (b) (4) in the DESCRIPTION section. The revised PI, container and carton labeling were also reviewed and found acceptable by the DMEPA reviewer Ms. Jacqueline Sheppard on December 05, 2014.

EES Status: The OC has provided an overall acceptable recommendation based on DO on September 24, 2014.

17. CONCLUSION AND RECOMMENDATION

This submission is recommended for approval from the stand point of chemistry, manufacturing and controls pending applicant's acceptance of the recommended change to the DESCRIPTION section of the PI (include (b) (4) in formulation).

18. REVIEWERS SIGNATURE	**REVIEWER**	**BRANCH CHIEF**
See appended electronic signature sheet	Anamitro Banerjee, Ph.D.	Thomas Oliver, Ph.D.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S19

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 50-795	Submission Date(s): 8/28/14
Drug	Doxycycline
Trade Name	DOXTERIC (proposed)
OCP Reviewers	Ryan P. Owen, Ph.D.
OCP Team Leader	Kimberly L. Bergman, Pharm.D.
OCP Division	DCP4
OND division	DAIP
Sponsor	Mayne Pharma International
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	50 mg doxycycline hyclate tablets
Indication	All approved doxycycline indications
Dosage and Administration	Adult dose: Usual dose: 200 mg of the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. In the management of severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended. [redacted] (b) (4)

1. EXECUTIVE SUMMARY

The Sponsor (Mayne Pharma) is seeking approval for an additional product strength (50 mg doxycycline hyclate delayed release tablet) via a CMC supplement. They refer to the Doryx NDA which includes doxycycline hyclate delayed-release tablet strengths of 75 mg, 80 mg, 100 mg, 150 mg, and 200 mg. The submission included a label with the new strength but did not include any human studies (see attached final label).

Some changes were made to the numbers describing the pharmacokinetics of doxycycline in Section 12.3 of the label. Although the purpose of this was original unclear, further investigation revealed that the numbers in the proposed label represented a reversion to a prior version of the label. The Sponsor likely made this change because [redacted] (b) (4) that is currently in the DORYX label which was generated with different strengths. From a clinical pharmacology perspective, this change is acceptable and no further labeling revisions were necessary.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology components of this NDA and is recommending that this application by approved.

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/s/

RYAN P OWEN
01/09/2015

KIMBERLY L BERGMAN
01/09/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S19

OTHER REVIEW(S)

Review of Label Revision
Division of Anti-Infective Products

NDA / Supplement #:	50,795 / S-19
Applicant:	Mayne Pharma
Drug:	Doxteric (Doxycycline Hyclate)
Dose and Form:	50 mg Delayed Release Oral Tablets
Indications:	Various
Materials Reviewed:	1. Cover Letter, Labeling History 2. Proposed labeling received 8/28/2014, 9/18/2014, 10/14/2014, 11/6/2014, 11/14/2014
Date Completed:	12/16/2014
Clinical Reviewers:	Edward Weinstein, MD, PhD
Team Leader:	John Alexander, MD, MPH

Doxycycline is a semisynthetic tetracycline. Supplement 19 is a Prior Approval Manufacturing Supplement submitted on August 25, 2014. The product marketed by the Applicant includes the 75 mg, 80 mg, 100 mg, 150 mg and 200 mg doxycycline hyclate delayed release tablets. Each of these strengths is supplied under the tradename DORYX® which is owned by the Applicant's distributor, Warner Chilcott (now owned by Actavis). The Applicant is seeking to add a 50 mg dose strength tablet to its NDA. The Applicant intends to supply this 50 mg tablet independently of Warner Chilcott and therefore it will not be marketed under the DORYX® tradename. The Applicant intends to market the 50 mg tablet under the DOXTERIC tradename.

There have been a number of changes to the reference listed drug (RLD), Vibramycin® Hyclate 100 mg capsule (NDA 50-007), including the WARNINGS and ADVERSE REACTIONS sections of the full prescribing information, specifically the language describing intracranial hypertension.

The following edits were recommended to the Applicant for the following sections of the labeling:

5 WARNINGS AND PRECAUTIONS

5.5 Intracranial Hypertension

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline including DOXTERIC. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Avoid concomitant use of isotretinoin and DOXTERIC because isotretinoin is also known to cause pseudotumor cerebri.

Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

6 ADVERSE REACTIONS

Intracranial Hypertension: Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline [See Warnings and Precuations (5.5)]

Additional minor changes were communicated. The Application is approvable form the clinical perspective, pending submission of an updated version of the labeling. The FDA proposed changes were accepted by the Applicant in a message dated 12/16/2014.

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/s/

JOHN J ALEXANDER
12/19/2014
Entered for primary reviewer, Dr. Weinstein

Division of Anti-Infective Products
Office of Antimicrobial Products (OND/CDER)
Clinical Microbiology Labeling Review

Date	12/12/2014
Clinical Microbiology Reviewer:	**Simone M. Shurland**
NDA/ ANDA # (Supplement #):	**NDA 50-795 (S19: SDN 275, 276, 277, 282, 283)**
Date Company Submitted:	8/25/2014, 9/17/2014, 10/13/2014, 11/5/2014, 11/13/2014
Date Received by CDER:	8/28/2014, 9/18/2014, 10/14/2014, 11/6/2014, 11/14/2014
Date Assigned:	10/7/2014
Applicant Name:	Mayne Pharma International Pty Ltd. 1538 Main North Road Salisbury South, Australia 5106 Contact Person: Phone: +61 8 8614 7704 Fax: + 31 8 8281 6998
Proprietary Name:	DOXTERIC™
Established Name:	Doxycycline
Dosage Forms (Route of Administration):	Delayed Release Tablets (Oral)
Dosage Strength:	50 mg
Recommended Action:	*Approvable, pending accepted version of the labeling.*

EXECUTIVE SUMMARY

Doxycycline is a semisynthetic tetracycline. Supplement#019 is a Prior Approval Supplement submitted on August 25, 2014. The product marketed by the Applicant includes the 75 mg, 80 mg, 100 mg, 150 mg and 200 mg doxycycline hyclate delayed-release tablets. Each of these strengths is supplied under the tradename DORYX® which is owned by the Applicant's distributor, Warner Chilcott (now owned by Actavis). The Applicant is seeking to add a 50 mg dose strength tablet to its NDA. The Applicant intends to supply this 50 mg tablet independently of Warner Chilcott and therefore it will not be marketed under the DORYX® tradename. The Applicant intention is to only supply the 50 mg tablet under the DOXTERIC™ tradename.

This review focuses on the proposed labeling for DOXTERIC™, more specifically the microbiology section of the full prescribing information provided by the applicant on November 13, 2014. Since filing there has been a number of changes to the reference listed drug (RLD), Vibramycin® Hyclate 100 mg capsule (NDA 50-007). It is recommended that similar changes be made for this NDA Supplement. These changes include updates to *in vitro* susceptibility testing and quality control parameters as follows:

- For *Streptococcus pneumoniae*, the MIC and zone diameter interpretive criteria have been lowered.
- The quality control parameters in the RLD (Vibramycin®) FDA package insert have included new quality control parameters for doxycycline against *Eubacterium lentum* ATCC 43055 and *Bacteroides thetaiotaomicron* ATCC 29741 using the broth dilution method as published by CLSI M100-S24.

The following edits were recommended to the Applicant for the microbiology section of the labeling.

- **INDICATIONS AND USAGE**
  - Change *Calymmatobacterium granulomatis* to *Klebsiella granulomatis*
  - Change *Treponema pertunue* to *Treponema pallidum* subspecies *pertenue*

- **LIST OF MICROORGANISMS**
  - Similar to the Indications and Usage section change to *Calymmatobacterium granulomatis* to *Klebsiella granulomatis* as well as *Treponema pertunue* to *Treponema pallidum* subspecies *pertenue*

- **SUSCEPTIBILITY TEST METHODS AND INTERPRETIVE CRITERIA**
  - *Streptococcus pneumoniae:* The MIC interpretive criteria for the susceptible, intermediate and resistant for doxycycline should be changed to ≤0.25, 0.5 and ≥1 μg/mL, respectively and for tetracycline should be changed to ≤1, 2 and ≥4 μg/mL, respectively. The disk diffusion interpretive criteria for both doxycycline and tetracycline for the susceptible, intermediate and resistant zone diameters should be changed to ≥28, 25 – 27 and ≤24 mm, respectively.
  - *Eubacteria lentum ATCC 43055:* It is recommended that the quality control parameters for the doxycycline MICs be provided based on CLSI M100-S24 guidelines.
  - *Bacteroides thetaiotaomicron ATCC 29741:* It is recommended that the quality control parameters for the doxycycline MICs be provided based on CLSI M100-S24 guidelines.

- **REFERENCES**
  - Update the existing Clinical Laboratory Standards Institute (CLSI) references in the package insert to the most recent versions of the documents.

SUMMARY AND RECOMMENDATIONS

The Application is approvable with respect to clinical microbiology, pending an updated version of the labeling.

Simone M. Shurland, Ph.D.
Clinical Microbiology Reviewer
DAIP
December 10, 2014

Kerry Snow, MS, MT(ASCP)
Microbiology Team Leader
DAIP
December 12, 2014

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/s/

SIMONE SHURLAND
12/12/2014

KERRY SNOW
12/12/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 5, 2014
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 050795/S-019
Product Name and Strength:	Doxteric (Doxycycline Hyclate) tablets, 50 mg
Submission Date:	November 5, 2014
Applicant/Sponsor Name:	Mayne Pharmaceuticals
OSE RCM #:	2014-1903-1
DMEPA Primary Reviewer:	Jacqueline Sheppard, PharmD
DMEPA Acting Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

Division of Anti-Infective Products requested that we review the revised container labels and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

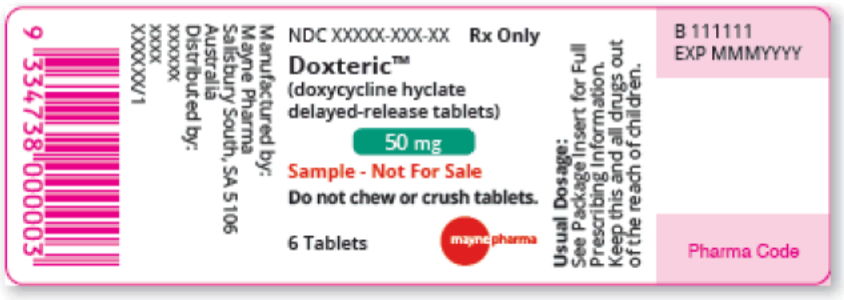
2 CONCLUSIONS

The revised container labels and carton labeling are acceptable from a medication error perspective.

[1] Sheppard J. Label and Labeling Review for Doxycycline Hyclate (NDA 050795). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Oct 24. 12 p. OSE RCM No.: 2014-1903

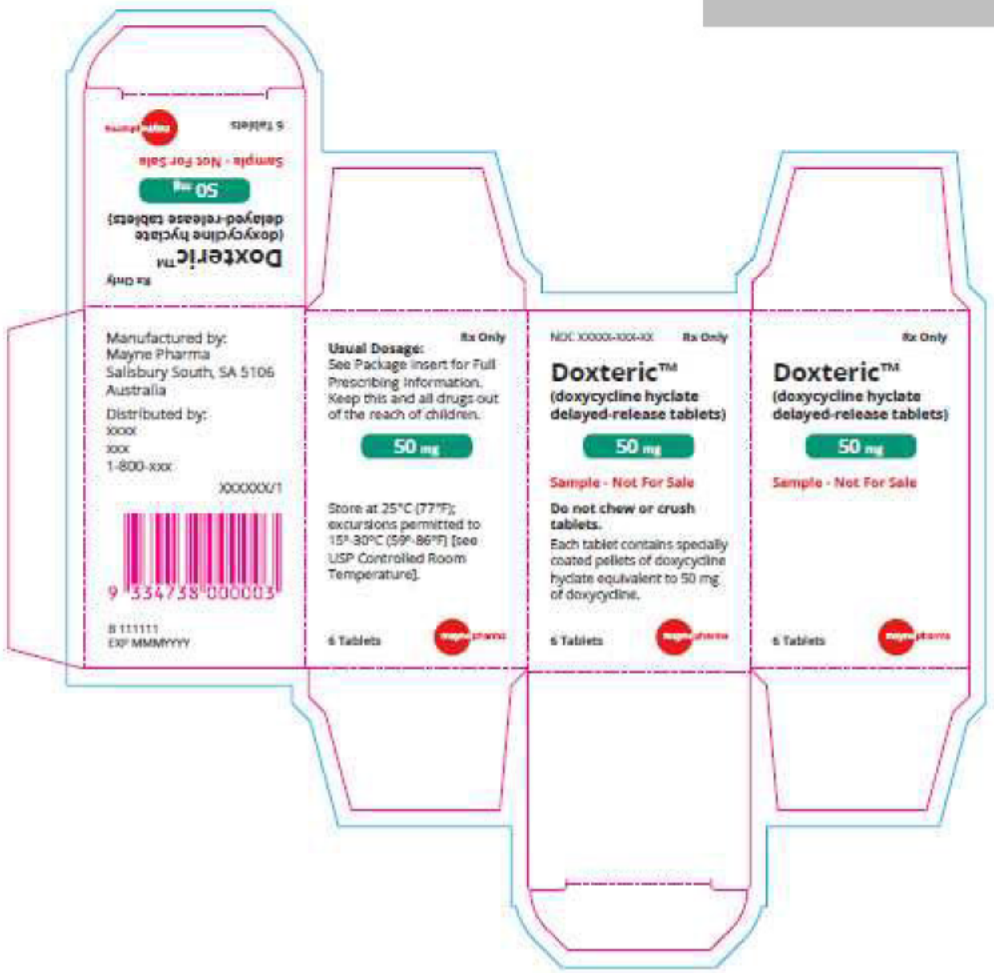
APPENDIX A. LABEL AND LABELING SUBMITTED ON NOVEMBER 5, 2014

Physician Sample Label



Physician Sample Carton

(b) (4)



Trade Bottle Label

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/s/

JACQUELINE E SHEPPARD
12/05/2014

BRENDA V BORDERS-HEMPHILL
12/05/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-795/S19

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 050795/S-019

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Mayne Pharma International Pty Ltd
c/o Metrics, Inc
1240 Sugg Parkway
Greenville, NC 27834

ATTENTION: Susan Canady
Regulatory Affairs Specialist

Dear Ms. Canady:

Please refer to your Supplemental New Drug Application (sNDA) dated, August 25,2014, received August 28,2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doxycycline Hyclate Tablets, 50 mg.

We also refer to your November 4, 2014, correspondence, received November 5, 2014, requesting review of your proposed proprietary name, Doxteric.

We have completed our review of the proposed proprietary name, Doxteric, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your November 5, 2014, submission are altered prior to approval of the marketing application, the proprietary name must be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact Naseya Minor, Regulatory Project Manager in the Office of New Drugs, at (301)796-0756.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
12/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50795/S-019

INFORMATION REQUEST

Mayne Pharma International Pty Ltd
c/o Metrics, Inc.
Attention: Nicole M. Wilkerson
Regulatory Affairs Specialist
1240 Sugg Parkway
Greenville, NC 27834

Dear Ms. Wilkerson:

Please refer to your Supplemental New Drug Application (sNDA) dated August 25, 2014, received August 28, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for doxycycline hyclate delayed-released tablets 50 mg.

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. The highlights (HL) must be in a minimum of 8 point font and should be in two-column format, with ½ inch margins on all sides and between columns.
2. A horizontal line must separate the Table of Contents (TOC) and the Full Prescribing Information (FPI).
3. The TOC should be in a two-column format.
4. In the TOC, all subsection headings must be indented.
5. The bolded section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56 (d)(1) (section and subsection headings should be in UPPER CASE and title case, respectively) If a section/subsection required by regulation is omitted, the number must not change. Additional subsection headings (i.e., those not named by regulation) must also be bolded and numbered.
6. The following heading must be bolded and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION**". This heading should be in UPPER CASE.
7. When postmarketing adverse reaction data are included, the following verbatim statement of appropriate medication should precede the presentation of adverse reactions:

   > "The following adverse reactions have been identified during post-approval use of (drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

8. See the attached for a sample tool illustrating the format for the HL.

We request that you resubmit labeling that addresses these issues by November 14, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

If you have any questions, call Naseya Minor, Regulatory Project Manager, at (301) 796-0756.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center of Drug Evaluation and Research

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR **and Medication Guide].**

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

FRANCES V LESANE
11/04/2014

From:Minor, Naseya
Sent:Tuesday, October 28, 2014 3:54 PM
To:'nicole.wilkerson@maynepharma.com'
Subject:NDA 050795 Carton and Container Information IR

Hi Nicole,
The Division of Medication Error Prevention and Analysis (DMEPA) has completed their review of the carton and container labeling for NDA 50795/S-19 and concluded that the container label and carton labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

1.Container Label
a.Remove all references to the previous proposed proprietary name.
b.Decrease the font size and remove the circle around the bottle quantity as it makes the quantity overly prominent and may cause confusion with product strength.
c.Replace the “Usual Adult Dosage” statement with a “Usual Dosage” statement in order to minimize the risk of confusion.
d.In order to reduce the amount of visual clutter on the Principal Display Panel, we recommend minimizing the prominence of the ‘Rx only’ statement by relocating the statement to the top right corner of the PDP and changing the font color from red to black.
e.Remove or relocate the MM/Year statement above the barcode to a different area or decrease the prominence of this statement in order to avoid confusion with the actual expiration date.

2.Carton Labeling
a. See Section 1a – 1e.
b.Debold the storage requirements on the container label in order to increase readability and decrease prominence.

Please submit the revised carton and container labeling for review as soon as you can.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
10/28/2014

Townsend, Karen

From: Mudge, Stuart <Stuart.Mudge@maynepharma.com>
Sent: Thursday, September 11, 2014 8:51 PM
To: Townsend, Karen
Cc: Nicole Wilkerson; audrey zaweski; Carmichael, Heike; DeBellas, Carmen
Subject: RE: FDA question on Stone 50 Project

Dear Karen, this is just a quick note to confirm we satisfactorily addressed your questions below?

Should Mayne expect to receive written confirmation that the proprietary name submission for (b) (4) and NDA 50-795 is complete and also confirmation of the target PDUFA date for the review?

Kind regards,

Stuart Mudge PhD
Vice President, Research & Development
T: +61 3 8614 7704 **M:** +61 424 588 904

From: Townsend, Karen [mailto:Karen.Townsend@fda.hhs.gov]
Sent: Monday, 18 August 2014 23:38
To: Mudge, Stuart
Cc: Nicole Wilkerson; audrey zaweski; Carmichael, Heike; DeBellas, Carmen
Subject: RE: FDA question on Stone 50 Project

Thank you !

From: Mudge, Stuart [mailto:Stuart.Mudge@maynepharma.com]
Sent: Monday, August 18, 2014 9:07 AM
To: Townsend, Karen
Cc: Nicole Wilkerson; audrey zaweski; Carmichael, Heike; DeBellas, Carmen
Subject: Re: FDA question on Stone 50 Project
Importance: High

Dear Karen,

Bill Tilghman, who recently left Mayne Pharma USA, forwarded your email below concerning our proposed proprietary name submission for (b) (4) and NDA 50-795.

Please find below Mayne's responses to your questions.

Please do not hesitate to contact me if you have any further questions. You may also contact Nicole Wilkerson at Mayne Pharma USA in Greenville, NC on 252 317 3943 if more convenient.

1. Since you plan to market doxycycline 50 mg under the proposed name (b) (4), please clarify whether the 75 mg, 80 mg, 100 mg, 150 mg, and 200 mg tablets will be continued to marketed under the proprietary name, Doryx?
Currently, NDA 50-795, held by Mayne Pharma International Pty Ltd (MPI), lists 75 mg, 80 mg, 100 mg, 150 mg, and 200 mg doxycycline hyclate delayed release tablets. Each of these strengths is supplied under the name DORYX, which is a (b) (4)

Later this month, MPI intends to file a Prior Approval Supplement (PAS) seeking to add a 50 mg dose strength tablet to NDA 50-795. MPI intends to supply this 50 mg tablet independently of Warner Chilcott and therefore it will **not** be marketed under the DORYX tradename. MPI's intention is to only supply the 50 mg tablet under the (b) (4) trade name.

With regards to the existing dose strengths (75 mg, 80 mg, 100 mg, 150 mg, and 200 mg tablets), MPI does not (b) (4) intend to supply them under the (b) (4) trade name. (b) (4)

Therefore we respectfully ask the Agency to assess the (b) (4) trade name under the follow situations:

1. The (b) (4) trade name is exclusively used for the new 50mg strength tablet, added to NDA 50-795 via a PAS planned for submission later this month
2. The (b) (4) trade name (b) (4), that is for 75mg, 80mg, 100mg, 150mg and 200mg tablets
3. (b) (4)

In considering the above situations, please note that (b) (4) only the (b) (4) 50 mg tablet would be marketed and therefore Mayne's expectation is that the Orange book would reflect this; that is, the (b) (4) listings for the 75, 80, 100, 150 and 200 mg tablets would be in the inactive or discontinued section of the Orange book until otherwise advised by Mayne.

2. Please clarify whether (b) (4) 50 mg tablet, is interchangeable with splitting a tablet 100 mg Doryx?
As mentioned above, the PAS for the 50 mg tablet strength will be submitted later this month and will address the issue of bioequivalence. Mayne agrees with the concept that taking 50 mg of (b) (4) would be bioequivalent to taking half of a Doryx 100 mg tablet, however, consistent with our answer to #1 above, (b) (4) and Doryx will be marketed as distinct products and therefore would be interchangeable/substitutable at the pharmacy level only at the discretion of the prescribing physician.

Kind regards,

Stuart J Mudge, PhD
Vice President, Research & Development
T: +61 3 8614 7704 **M:** +61 424 588 904

Mayne Pharma
Level 14, 474 Flinders Street
Melbourne VIC 3000 Australia
maynepharma.com

Good morning Mr. Tilghman,

The Division of Medication Error Prevention and Analysis (DMEPA) has the following information request :

During our review of the proposed proprietary name, (b) (4), it is noted that the Mayne pharmaceuticals owns the NDA for Doryx (NDA 50795) but does (b) (4).

1. Since you plan to market doxycycline 50 mg under the proposed name (b) (4), please clarify whether the 75 mg, 80 mg, 100 mg, 150 mg, and 200 mg tablets will be continued to marketed under the proprietary name, Doryx?

2. Please clarify whether (b) (4) 50 mg tablet, is interchangeable with splitting a tablet 100 mg Doryx?

We request a response at your earliest convenience, but no later than COB Monday August 18, 2014. Thank you.

Regards,
Karen

Karen Townsend

Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

KAREN F TOWNSEND
10/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADM NISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: **Mail: OSE**			FROM: Navi Bhandari, Pharm.D, ONDQA RPM DAIP	
DATE September 11, 2014	IND NO.	NDA NO. 50795/S-019	TYPE OF DOCUMENT PAS	DATE OF DOCUMENT 8/28/2014
NAME OF DRUG Doryx (docycycline hyclate)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG Antiobiotic	DESIRED COMPLETION DATE November 28, 2014

NAME OF FIRM: MAYNE PHARMA INTERNATIONAL PTY LTD

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

It is an electronic submission accessible through DARRTS.

This supplemental application, submitted as a “Prior Approval” supplement, provides for the addition of an additional drug product strength of 50mg.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ☐ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

NAVDEEP BHANDARI
09/11/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 50795/S-019

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Mayne Pharma International Pty Ltd
Attention: Nicole Wilkerson
Regulatory Affairs Specialist
1240 Sugg Parkway
Greenville, NC 27834

Dear Ms. Wilkerson:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 50795

SUPPLEMENT NUMBER: S-019

PRODUCT NAME: Doryx® (doxycycline hyclate) Tablet

DATE OF SUBMISSION: August 25, 2014

DATE OF RECEIPT: August 28, 2014

This "Prior Approval" supplemental application provides for the addition of an additional drug product strength of 50 mg.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 27, 2014, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 28, 2014.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me, at 240-402-3815.

Sincerely,

{See appended electronic signature page}

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

NAVDEEP BHANDARI
09/11/2014