DORYX MPC- doxycycline hyclate tablet, delayed release
Mayne Pharma Commercial LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DORYX MPC safely and effectively. See full prescribing information for DORYX MPC

DORYX MPC (doxycycline hyclate delayed-release tablets), for oral use.
Initial U.S. Approval: 1967

INDICATIONS AND USAGE

DORYX MPC is a tetracycline class drug 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)

Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline hyclate and other antibacterial drugs, DORYX MPC Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.10)

DOSAGE AND ADMINISTRATION

- Important Dosage and Administration Instructions:
  - DORYX MPC is not substitutable on a mg per mg basis with other oral doxycyclines. (2.1)
  - Do not chew or crush tablets. (2.1)
- Dosage in Adult Patients
  - The usual dosage of DORYX MPC is 240 mg on the first day of treatment (administered 120 mg every 12 hours) followed by a maintenance dose of 120 mg daily. (2.3)
  - In the management of more severe infections (particularly chronic infections of the urinary tract), 120 mg every 12 hours is recommended. (2.3)
- Dosage in Pediatric Patients
  - For all pediatric patients weighing less than 45 kg with severe or life threatening infections (e.g., anthrax, Rocky Mountain spotted fever), the recommended dosage of DORYX MPC is 2.6 mg per kg of body weight administered every 12 hours. Pediatric patients weighing 45 kg or more should receive the adult dose. (2.4)
  - For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg), the recommended dosage schedule of DORYX MPC is 5.3 mg per kg of body weight divided into two doses on the first day of treatment, followed by a maintenance dose of 2.6 mg per kg of body weight (given as a single daily dose or divided into twice daily doses). For pediatric patients weighing over 45 kg, the usual adult dose should be used. (2.4)

- See Full Prescribing Information for additional indication specific dosage information and important administration instructions for DORYX MPC. (2.2, 2.5, 2.6)

DOSAGE FORMS AND STRENGTHS

DORYX MPC Delayed-Release Tablets 60 mg (3)

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)
- *Clostridioides 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. If such infections occur, discontinue use and institute appropriate therapy. (5.4)

ADVERSE REACTIONS

Adverse reactions observed in patients receiving tetracyclines include anorexia, nausea, vomiting, diarrhea, rash, photosensitivity, urticaria, 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, including DORYX MPC is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron-containing preparations (7.3)
- Concurrent use of tetracyclines, including DORYX MPC may render oral contraceptives less effective (7.4)
- Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline (7.5)

USE IN SPECIFIC POPULATIONS

- Tetracycline-class drugs can cause fetal harm when administered to a pregnant woman, but data for doxycycline are limited. (5.6, 8.1)
- Tetracyclines are excreted in human milk; however, the extent of absorption of doxycycline in the breastfed infant is not known. DORYX MPC use during nursing should be avoided if possible. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Rickettsial Infections

DORYX MPC is indicated for treatment of Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by *Rickettsiae*.

1.2 Sexually Transmitted Infections

DORYX MPC is indicated for treatment of the following 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

DORYX MPC is indicated for treatment of the following 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

DORYX MPC is indicated for treatment of the following 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.

DORYX MPC 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

DORYX MPC is indicated for treatment of the following 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)

DORYX MPC is indicated for treatment of 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

DORYX MPC is indicated as an alternative treatment for the following selected infections when penicillin is contraindicated:

- Syphilis caused by *Treponema pallidum*.
- Yaws caused by *Treponema pallidum* subspecies *pertenue*.
- Listeriosis due to *Listeria monocytogenes*.
- 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, DORYX MPC may be a useful adjunct to amebicides.

In severe acne, DORYX MPC may be useful adjunctive therapy.

1.9 Prophylaxis of Malaria

DORYX MPC 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)*].

1.10 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORYX MPC and other antibacterial drugs, DORYX MPC 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- DORYX MPC is not substitutable on a mg per mg basis with other oral doxycyclines. To avoid prescribing errors, do not substitute DORYX MPC for other oral doxycyclines on a mg per mg basis because of differing bioavailability.
- Do not chew or crush tablets.
- The recommended dosage, frequency of administration and weight-based dosage recommendations of DORYX MPC differ from that of the other tetracyclines [*see Dosage and Administration (2.2, 2.3, 2.4)*]. Exceeding the recommended dosage may result in an increased incidence of adverse reactions.
- Administer DORYX MPC with an adequate amount of fluid to wash down the drug and reduce the risk of esophageal irritation and ulceration [*see Adverse Reactions (6)*].
- If gastric irritation occurs, DORYX MPC may be given with food or milk *[see Clinical Pharmacology (12.3)]*.

2.2 Switching from DORYX to DORYX MPC

When switching from DORYX to DORYX MPC*:*
- A 60 mg dose of DORYX MPC will replace a 50 mg dose of DORYX
- A 120 mg dose of DORYX MPC will replace a 100 mg dose of DORYX

2.3 Dosage in Adult Patients
- The usual dosage of DORYX MPC is 240 mg on the first day of treatment (administered 120 mg every 12 hours) followed by a maintenance dose of 120 mg daily. The maintenance dose may be administered as a single dose or as 60 mg every 12 hours.
- In the management of more severe infections (particularly chronic infections of the urinary tract), 120 mg every 12 hours is recommended.
- For certain selected specific indications, the recommended duration or dosage and duration of DORYX MPC in adult patients are as follows:
  1. Streptococcal infections, therapy should be continued for 10 days.
  2. Uncomplicated urethral, endocervical, or rectal infection caused by *C. trachomatis*: 120 mg, by mouth, twice-a-day for 7 days.
  3. Uncomplicated gonococcal infections in adults (except anorectal infections in men): 120 mg, by mouth, twice-a-day for 7 days. As an alternate single visit dose, administer 360 mg followed in one hour by a second 360 mg dose.
  4. Nongonococcal urethritis (NGU) caused by *C. trachomatis* and *U. urealyticum*: 120 mg, by mouth, twice-a-day for 7 days.
  5. Syphilis – early: Patients who are allergic to penicillin should be treated with doxycycline 120 mg, by mouth, twice-a-day for 2 weeks.
  6. Syphilis of more than one year's duration: Patients who are allergic to penicillin should be treated with doxycycline 120 mg, by mouth, twice-a-day for 4 weeks.
  7. Acute epididymo-orchitis caused by *N. gonorrhoeae*: 120 mg, by mouth, twice-a-day for at least 10 days.
  8. Acute epididymo-orchitis caused by *C. trachomatis*: 120 mg, by mouth, twice-a-day for at least 10 days

2.4 Dosage in Pediatric Patients
- For all pediatric patients weighing less than 45 kg with severe or life threatening infections (e.g., anthrax, Rocky Mountain spotted fever), the recommended dosage of DORYX MPC is 2.6 mg per kg of body weight administered every 12 hours. Pediatric patients weighing 45 kg or more should receive the adult dose *[see*

Warnings and Precautions (5.1)].

- For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg), the recommended dosage schedule of DORYX MPC is 5.3 mg per kg of body weight divided into two doses on the first day of treatment, followed by a maintenance dose of 2.6 mg per kg of body weight (given as a single daily dose or divided into twice daily doses). For pediatric patients weighing over 45 kg, the usual adult dose should be used.

2.5 Dosage for Prophylaxis of Malaria

For adults, the recommended dose of DORYX MPC is 120 mg daily.

For pediatric patients 8 years of age and older, the recommended dosage of DORYX MPC is 2.4 mg per kg of body weight administered once daily. Pediatric patients weighing 45 kg or more should receive 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.

2.6 Dosage for Inhalational Anthrax (Post-Exposure)

For adults, the recommended dosage is 120 mg, of DORYX MPC, by mouth, twice-a-day for 60 days.

For pediatric patients weighing less than 45 kg, the recommended dosage of DORYX MPC is 2.6 mg per kg of body weight, by mouth, twice-a-day for 60 days. Pediatric patients weighing 45 kg or more should receive the adult dose.

3 DOSAGE FORMS AND STRENGTHS

DORYX MPC (doxycycline hyclate delayed-release tablets), 60 mg are white, oval tablets containing yellow pellets and debossed with "D6" on one face and plain on the other. Each tablet contains doxycycline 60 mg (equivalent to doxycycline hyclate 69.4 mg).

4 CONTRAINDICATIONS

DORYX MPC 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. Use DORYX MPC in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain

spotted fever), particularly when there are no alternative therapies.

5.2 *Clostridioides* difficile Associated Diarrhea

Clostridioides difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including DORYX MPC 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 Potential for Microbial Overgrowth

DORYX MPC may result in overgrowth of non-susceptible organisms, including fungi. If such infections occur, discontinue use and institute appropriate therapy.

5.5 Severe Skin Reactions

Severe skin reactions, such as exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients receiving doxycycline [See Adverse Reactions (6)]. If severe skin reactions occur, doxycycline should be discontinued immediately and appropriate therapy should be instituted.

5.6 Intracranial Hypertension

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline including DORYX MPC. 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 DORYX MPC 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.

5.7 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. [*See Use in Specific Populations (8.1)*].

5.8 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.

5.9 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.

5.10 Development of Drug-Resistant Bacteria

Prescribing DORYX MPC 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.

5.11 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

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, inflammatory lesions (with monilial overgrowth) in the anogenital region, and pancreatitis. 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 (5.8)*].

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 (5.6)*]

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, including DORYX MPC in conjunction with penicillin.

7.3 Antacids and Iron Preparations

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

7.4 Oral Contraceptives

Concurrent use of tetracyclines, including DORYX MPC 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

Risk Summary

There are no adequate 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] In the U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively [*see Data*].

Clinical Considerations

Embryo/Fetal Risk

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

Data

Human Data

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]

8.2 Lactation

Risk Summary

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 contraindicated. The effects of prolonged exposure to doxycycline on breast milk production and breast fed neonates, infants and children are unknown.[4] The developmental and health benefits of breast feeding should be considered along with the mother's clinical need for DORYX MPC and any potential adverse effects on the breast fed child from DORYX MPC or from the underlying maternal condition [*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, use DORYX MPC in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies [*see Warnings and Precautions (5.1, 5.6) and Dosage and Administration (2.1, 2.4)*].

8.5 Geriatric Use

Clinical studies of DORYX MPC 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. DORYX MPC Tablets each contain less than 10 mg of sodium.

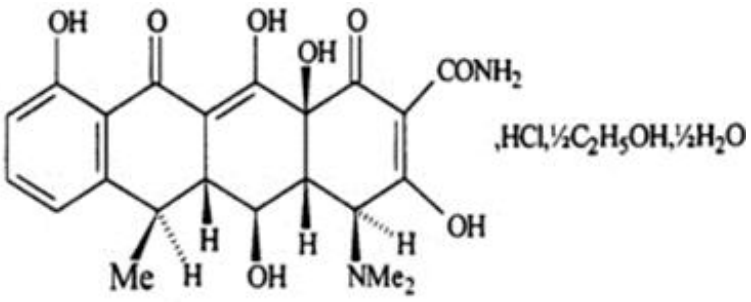
10 OVERDOSAGE

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

Doryx MPC (doxycycline hyclate delayed-release tablets) for oral use, contain doxycycline hyclate, a tetracycline class drug synthetically derived from oxytetracycline, in a delayed-release formulation consisting of pellets with a modified polymer enteric coat that has increased acid resistance.

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 name 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.

Each tablet contains doxycycline 60 mg (equivalent to doxycycline hyclate 69.4 mg) or doxycycline 120 mg (equivalent to doxycycline hyclate 138.8 mg). 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.

Each DORYX MPC 60 mg Tablet contains 3.6 mg (0.157 mEq) of sodium.

Each DORYX MPC 120 mg Tablet contains 7.2 mg (0.313 mEq) of sodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Doxycycline is a tetracycline-class antimicrobial drug [*see Microbiology (12.4)*].

12.3 Pharmacokinetics

Effect of Food

Following administration of a single dose of DORYX MPC under fasting conditions, the AUC_{inf} and C_{max} were 26.7 mcg-h/mL and 1.6 mcg/mL, respectively. The Tmax was 2.8 hours. In a single-dose study to evaluate the relative bioavailability in healthy adult subjects under fasted conditions, DORYX MPC 120 mg Tablets were found to be bioequivalent to Doryx 100 mg Tablets. When a single dose of DORYX MPC 120 mg Tablet was administered with a standardized high-fat high-calorie meal, (937kcal consisting of approximately 55% fat, 30% carbohydrate and 15% protein), the C_{max} was approximately 30% lower, but there was no significant difference in the AUC_{inf} compared to administration under fasting conditions *[see Dosage and Administration (2.1)]*.

Absorption

Doxycycline is virtually completely absorbed after oral administration.

Elimination

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.

Specific Populations

Patients with Renal Impairment

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.

Pediatric Patients

Population pharmacokinetic analysis of sparse concentration-time data of doxycycline. following standard of care intravenous and oral dosing in 44 children (2-18 years of age) showed that allometrically-scaled clearance of doxycycline in children ≥2 to ≤8 years of age (median [range] 3.58 [2.27-10.82] L/h/70 kg, N=11) did not differ significantly from children >8 to 18 years of age (3.27 [1.11-8.12] L/h/70 kg, N=33). For pediatric patients weighing ≤45 kg, body weight normalized doxycycline CL in those ≥2 to ≤8 years of age (median [range] 0.071 [0.041-0.202] L/kg/h, N=l0) did not differ significantly from those >8 to 18 years of age (0.081 [0.035-0.126] L/kg/h, N=8). In pediatric patients weighing >45 kg no clinically significant differences in body weight normalized doxycycline CL were observed between those ≥2 to ≤8 years (0.050 L/kg/h, N=l) and those >8 years of age (0.044 [0.014-0. 121] L/kg/h, N=25). No clinically significant difference in CL differences between oral and IV were observed in the small cohort of pediatric patients who received the oral (N=l9) or IV (N=21) formulation alone.

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.

Resistance

Cross-resistance between tetracyclines is common.

Antimicrobial Activity

Doxycycline has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections [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
Listeria monocytogenes
Streptococcus pneumoniae

Anaerobic Bacteria

Clostridium species
Fusobacterium fusiforme
Propionibacterium acnes

Other Bacteria

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

Parasites

Balantidium coli
Entamoeba species
Plasmodium falciparum[1]

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1 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 Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

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

1. Friedman JM, Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS)*. Baltimore, MD: The Johns Hopkins University Press: 2000: 149-195. The TERIS (Teratogen Information System) is available at: http://www.micromedexsolutions.com/ (cited: 2016 Jan).
2. Cziezel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997; 89: 524-528.
3. Horne HW Jr. and Kundsin RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25: 315-317.
4. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); [Last Revision Date 2015 March 10; cited 2016 Jan]. Doxycycline; LactMed Record Number: 100; [about 3 screens]. Available from: http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

16 HOW SUPPLIED/STORAGE AND HANDLING

DORYX MPC (doxycycline hyclate delayed-release tablets), 60 mg are white, oval tablets containing yellow pellets and debossed with "D6" on one face and plain on the other. Each tablet contains doxycycline 60 mg (equivalent to doxycycline hyclate 69.4 mg).

The 60 mg tablet is supplied in bottles of 60 tablets (NDC 51862-560-60) and 120 tablets (NDC 51862-560-12).

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

17 PATIENT COUNSELING INFORMATION

Advise patients taking DORYX MPC for malaria prophylaxis:

- 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.

Advise all patients taking DORYX MPC:

- 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 DORYX MPC to reduce the risk of esophageal irritation and ulceration [*see Adverse Reactions (6)*]
- that the absorption of tetracyclines is reduced when taken with foods, especially those that contain calcium. [*see Drug Interactions (7.3)*]
- that if gastric irritation occurs, DORYX MPC may be given with food or milk [*see Clinical Pharmacology (12.3)*]
- 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.

Advise patients that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterial drugs, 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 DORYX MPC should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When DORYX MPC 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 DORYX MPC or other antibacterial drugs in the future.

Distributed by:
Mayne Pharma
Raleigh, NC 27609

61596

PRINCIPAL DISPLAY PANEL - 60 mg Tablet Bottle Label

NDC 51862-560-12

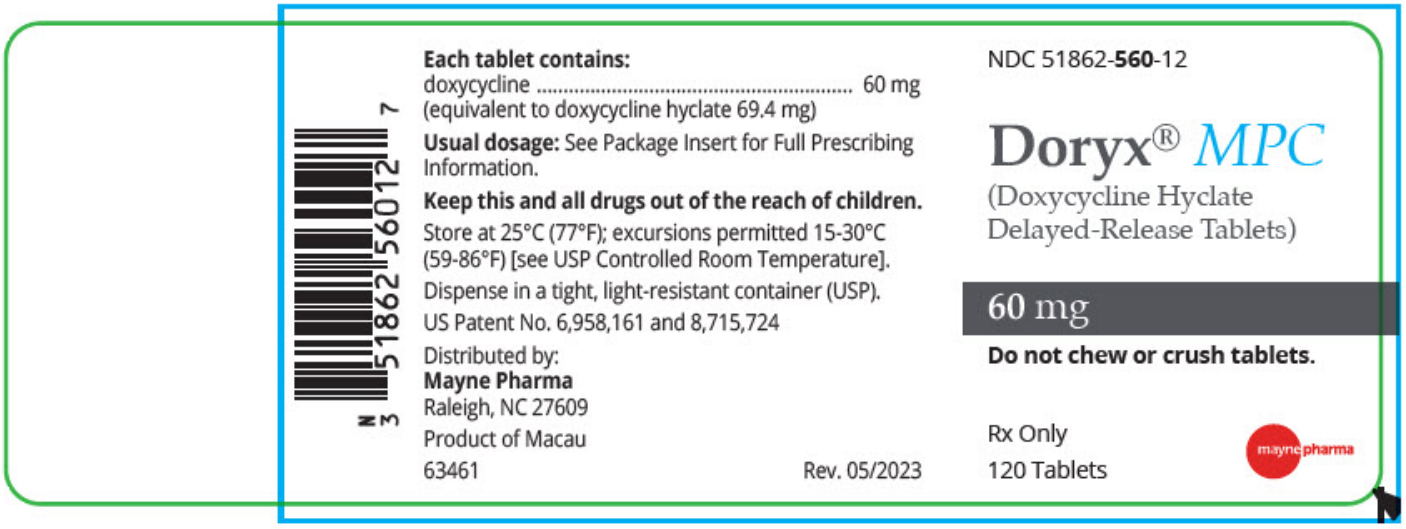
Doryx® MPC
(Doxycycline Hyclate
Delayed-Release Tablets)

60 mg

Do not chew or crush tablets.

Rx Only
120 Tablets

mayne pharma



PRINCIPAL DISPLAY PANEL - 120 mg Tablet Bottle Label

NDC 51862-559-30

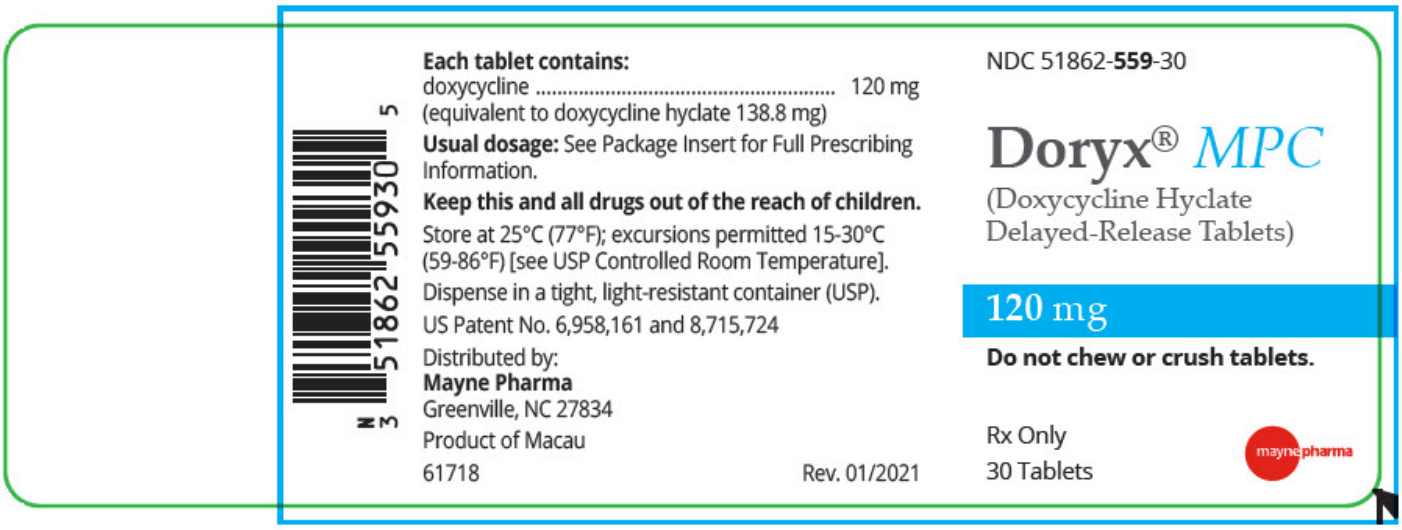
Doryx® MPC
(Doxycycline Hyclate
Delayed-Release Tablets)

120 mg

Do not chew or crush tablets.

Rx Only
30 Tablets

mayne pharma



DORYX MPC

doxycycline hyclate tablet, delayed release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51862-560
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Doxycycline Hyclate (UNII: 19XTS3T51U) (Doxycycline Anhydrous - UNII:334895S862)	Doxycycline Anhydrous	60 mg

Inactive Ingredients	
Ingredient Name	**Strength**
Lactose Monohydrate (UNII: EWQ57Q8I5X)	
Microcrystalline Cellulose (UNII: OP1R32D61U)	
Sodium Lauryl Sulfate (UNII: 368GB5141J)	
Sodium Chloride (UNII: 451W47IQ8X)	
Talc (UNII: 7SEV7J4R1U)	
Anhydrous Lactose (UNII: 3SY5LH9PMK)	
Starch, Corn (UNII: O8232NY3SJ)	
CROSPOVIDONE (120 .MU.M) (UNII: 68401960MK)	
Magnesium Stearate (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE (containing yellow pellets)	**Score**	no score
Shape	OVAL	**Size**	12mm
Flavor		**Imprint Code**	D;6

Contains	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-560-12	120 in 1 BOTTLE; Type 0: Not a Combination Product	01/02/2023	
2	NDC:51862-560-00	1 in 1 CARTON	01/02/2023	
2		6 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA050795	01/02/2023	

DORYX MPC

doxycycline hyclate tablet, delayed release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51862-559
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Doxycycline Hyclate (UNII: 19XTS3T51U) (Doxycycline Anhydrous - UNII:334895S862)	Doxycycline Anhydrous	120 mg

Inactive Ingredients

Ingredient Name	Strength
Lactose Monohydrate (UNII: EWQ57Q8I5X)	
Microcrystalline Cellulose (UNII: OP1R32D61U)	
Sodium Lauryl Sulfate (UNII: 368GB5141J)	
Sodium Chloride (UNII: 451W47IQ8X)	
Talc (UNII: 7SEV7J4R1U)	
Anhydrous Lactose (UNII: 3SY5LH9PMK)	
Starch, Corn (UNII: O8232NY3SJ)	
CROSPOVIDONE (120 .MU.M) (UNII: 68401960MK)	
Magnesium Stearate (UNII: 70097M6I30)	

Product Characteristics

Color	WHITE (containing yellow pellets)	**Score**	no score
Shape	OVAL	**Size**	15mm
Flavor		**Imprint Code**	D;C
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-559-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/29/2017	06/30/2024

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA050795	07/01/2016	06/30/2024

Labeler - Mayne Pharma Commercial LLC (867220261)

Establishment

Name	Address	ID/FEI	Business Operations
Mayne Pharma International Pty Ltd		756003745	MANUFACTURE(51862-560, 51862-559) , ANALYSIS(51862-560, 51862-559) , PACK(51862-560, 51862-559) , LABEL(51862-560, 51862-559)

Establishment

Name	Address	ID/FEI	Business Operations
Catalent Greenville, Inc.		118812386	PACK(51862-560, 51862-559) , LABEL(51862-560, 51862-559) , ANALYSIS(51862-560, 51862-559)

Revised: 6/2023 Mayne Pharma Commercial LLC