

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**63065**

**DRAFT FINAL PRINTED LABELING**

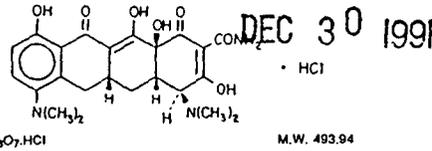
APPROVED

MINOCYCLINE  
HYDROCHLORIDE  
CAPSULES,  
USP

ORIGINAL  
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MINOCYCLINE HYDROCHLORIDE CAPSULES, USP

**DESCRIPTION:** Minocycline hydrochloride, a semisynthetic derivative of tetracycline, is [4S-(4a,4aa,5aa,12aa)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride. The structural formula is represented below:



Each minocycline hydrochloride capsule for oral administration contains the equivalent of 50 mg or 100 mg of minocycline. In addition each capsule contains the following inactive ingredients: D&C Yellow No. 10, D&C Red No. 28, gelatin, magnesium stearate, starch (corn) and titanium dioxide.

Minocycline Hydrochloride Capsules, 100 mg also contain black iron oxide.

**CLINICAL PHARMACOLOGY:** Following oral administration of minocycline hydrochloride capsules, absorption from the gastrointestinal tract is rapid. Maximum serum concentrations following a single dose of minocycline hydrochloride to normal fasting adult volunteers were attained in 1 to 4 hours. The serum half-life in normal volunteers ranges from approximately 11 hours to 22 hours.

In previous studies with other minocycline dosage forms, the minocycline serum half-life ranged from 11 to 16 hours in 7 patients with hepatic dysfunction, and from 18 to 63 hours in 5 patients with renal dysfunction. The urinary and fecal recovery of minocycline when administered to 12 normal volunteers is one-half to one-third that of other tetracyclines.

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

While *in vitro* studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

**Gram-Negative Bacteria**

*Bartonella bacilliformis*  
*Brucella* species  
*Campylobacter fetus*  
*Francisella tularensis*  
*Haemophilus ducreyi*  
*Haemophilus influenzae*  
*Listeria monocytogenes*  
*Neisseria gonorrhoeae*  
*Vibrio cholerae*  
*Yersinia pestis*

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

*Acinetobacter* species  
*Bacteroides* species  
*Enterobacter aerogenes*  
*Escherichia coli*  
*Klebsiella* species  
*Shigella* species

**Gram-Positive Bacteria**

Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are especially recommended. Up to 44 percent of *Streptococcus pyogenes* strains have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

Alpha-hemolytic streptococci (viridans group)

*Streptococcus pneumoniae*  
*Streptococcus pyogenes*

**Other Microorganisms**

*Actinomyces* species  
*Bacillus anthracis*  
*Balanidium coli*  
*Borrelia recurrentis*  
*Chlamydia psittaci*  
*Chlamydia trachomatis*  
*Clostridium* species  
*Entamoeba* species  
*Fusobacterium fusiforme*  
*Propionibacterium acnes*  
*Treponema pallidum*  
*Treponema pertenue*  
*Ureaplasma urealyticum*

**Susceptibility Tests: Diffusion Techniques:** The use of antibiotic disk susceptibility test methods which measure zone diameter give an accurate estimation of susceptibility of microorganisms to minocycline. One such standard procedure<sup>1</sup> has been recommended for use with disks for testing antimicrobials. Either the 30 mcg tetracycline-class disk or the 30 mcg minocycline disk should be used for the determination of the susceptibility of microorganisms to minocycline.

With this type of procedure a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With either the tetracycline-class disk or the minocycline disk, zone sizes of 19 mm or greater indicate susceptibility, zone sizes of 14 mm or less indicate resistance, and zone sizes of 15 to 18 mm indicate intermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mcg tetracycline disk should give zone diameters between 19 and 28 mm for *Staphylococcus aureus* ATCC 25923 and between 18 and 25 mm for *Escherichia coli* ATCC 25922. The 30 mcg minocycline disk should give zone diameters between 25 and 30 mm for *S. aureus* ATCC 25923 and between 19 and 25 mm for *E. coli* ATCC 25922.

**Dilution Techniques:** When using the NCCLS agar dilution or broth dilution (including microdilution) method<sup>2</sup> or equivalent, a bacterial isolate may be considered susceptible if the MIC (minimal inhibitory concentration) of minocycline is 4 mcg/mL or less. Organisms are considered resistant if the MIC is 18 mcg/mL or greater. Organisms with an MIC value of less than 16 mcg/mL but greater than 4 mcg/mL are expected to be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard tetracycline or minocycline powder should give MIC values of 0.25 mcg/mL to 1.0 mcg/mL for *S. aureus* ATCC 25923, and 1.0 mcg/mL to 4.0 mcg/mL for *E. coli* ATCC 25922.

**INDICATIONS AND USAGE:** Minocycline Hydrochloride Capsules are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:

Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers caused by Rickettsiae  
Respiratory tract infections caused by *Mycoplasma pneumoniae*  
Lymphogranuloma venereum caused by *Chlamydia trachomatis*  
Psittacosis (Ornithosis) due to *Chlamydia psittaci*  
Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated, as judged by immunofluorescence  
Inclusion conjunctivitis caused by *Chlamydia trachomatis*  
Nongonococcal urethritis in adults caused by *Ureaplasma urealyticum* or *Chlamydia trachomatis*  
Relapsing fever due to *Borrelia recurrentis*  
Chancroid caused by *Haemophilus ducreyi*  
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*  
Granuloma inguinale caused by *Calymmatobacterium granulomatis*

Minocycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

*Escherichia coli*  
*Enterobacter aerogenes*  
*Shigella* species  
*Acinetobacter* species  
Respiratory tract infections caused by *Haemophilus influenzae*  
Respiratory tract and urinary tract infections caused by *Klebsiella* species

Minocycline hydrochloride capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by *Streptococcus pneumoniae*  
Skin and skin structure infections caused by *Staphylococcus aureus*. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections when penicillin is contraindicated.

*Bacteroides* species  
*Enterobacter aerogenes*  
*Escherichia coli*  
*Klebsiella* species  
*Shigella* species

#### Gram-Positive Bacteria

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*Chlamydia trachomatis*  
*Clostridium* species  
*Entamoeba* species  
*Fusobacterium fusiforme*  
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*Treponema pertenue*  
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As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard tetracycline or minocycline powder should give MIC values of 0.25 mcg/mL to 1.0 mcg/mL for *S. aureus* ATCC 25923, and 1.0 mcg/mL to 4.0 mcg/mL for *E. coli* ATCC 25922.

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Psittacosis (Ornithosis) due to *Chlamydia psittaci*  
Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis caused by *Chlamydia trachomatis*  
Nongonococcal urethritis in adults caused by *Ureaplasma urealyticum* or *Chlamydia trachomatis*  
Relapsing fever due to *Borrelia recurrentis*  
Chancroid caused by *Haemophilus ducreyi*  
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*  
Granuloma inguinale caused by *Calymatobacterium granulomatis*

Minocycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

*Escherichia coli*  
*Enterobacter aerogenes*  
*Shigella* species  
*Acinetobacter* species  
Respiratory tract infections caused by *Haemophilus influenzae*  
Respiratory tract and urinary tract infections caused by *Klebsiella* species

Minocycline hydrochloride capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by *Streptococcus pneumoniae*  
Skin and skin structure infections caused by *Staphylococcus aureus*. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)  
Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections when penicillin is contraindicated.

When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:

Infections in women caused by *Neisseria gonorrhoeae*  
Syphilis caused by *Treponema pallidum*  
Yaws caused by *Treponema pertenue*  
Listeriosis due to *Listeria monocytogenes*  
Anthrax due to *Bacillus anthracis*  
Vincet's infection caused by *Fusobacterium fusiforme*  
Actinomycosis caused by *Actinomyces israelii*  
Infections caused by *Clostridium* species

In acute intestinal amebiasis, minocycline may be a useful adjunct to amebicides.

In severe acne, minocycline may be useful adjunctive therapy.

Oral minocycline is indicated in the treatment of asymptomatic carrier of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carrier, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcal meningitis is high.

Oral minocycline is not indicated for the treatment of meningococcal infection.

Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used successfully in the treatment of infections caused by *Mycobacterium marinum*.

**CONTRAINDICATIONS:** This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

MINOCYCLINE  
HYDROCHLORIDE  
CAPSULES,  
USP

**WARNINGS:** MINOCYCLINE, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. 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. 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 drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED DURING TOOTH DEVELOPMENT UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED. All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in young animals (rats and rabbits) 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 has been noted in animals treated early in pregnancy.

The anti-anabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, high serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported rarely with minocycline.

Central nervous system side effects including light-headedness, dizziness, or vertigo have been reported with minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

**PRECAUTIONS: General:** As with other antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted. Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve after discontinuation of tetracycline, the possibility for permanent sequelae exists.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy when indicated. Information for Patients: 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. This reaction has been reported rarely with use of minocycline.

Patients who experience central nervous system symptoms (see WARNINGS) should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy.

Concurrent use of tetracycline may render oral contraceptives less effective (see Drug Interactions).

Laboratory Tests: In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least four months.

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

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

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

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium, and iron-containing preparations. The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracyclines may render oral contraceptives less effective. Breakthrough bleeding has been reported.

**Drug/Laboratory Test Interactions:** False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Dietary administration of minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasia in rats and dogs. In addition, there has been evidence of oncogenic activity in rats in studies with a related antibiotic, oxytetracycline (i.e., adrenal and pituitary tumors). Likewise, although mutagenicity studies of minocycline have not been conducted, positive results in *in vitro* mammalian cell assays (i.e., mouse lymphoma and Chinese hamster lung cells) have been reported for related antibiotics (tetracycline hydrochloride and oxytetracycline). Segment I (fertility and general reproduction) studies have provided evidence that minocycline impairs fertility in male rats.

**Teratogenic Effects: Pregnancy: Pregnancy Category D** (See WARNINGS).

**Labor and Delivery:** The effect of tetracyclines on labor and delivery is unknown.

**Nursing Mothers:** Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see WARNINGS).

**Pediatric Use:** (See WARNINGS).

**ADVERSE REACTIONS:** Due to oral minocycline'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 esophageal region, increases in liver enzymes, and rarely hepatitis have been reported. Rare instances of esophagitis and esophageal ulcerations have been reported in patients taking the tetracycline-class antibiotics in capsule and tablet form. Most of these patients took the medication immediately before going to bed (see DOSAGE AND ADMINISTRATION).

**Skin:** Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Erythema multiforme and rarely Stevens-Johnson syndrome have been reported. Photosensitivity is discussed above (see WARNINGS). Pigmentation of the skin and mucous membranes has been reported.

**Renal toxicity:** Elevations in BUN have been reported and are apparently dose related (See WARNINGS).

**Hypersensitivity reactions:** Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus and rarely pulmonary infiltrates with eosinophilia have been reported.

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

**Central nervous system:** Bulging fontanels in infants and benign intracranial hypertension (Pseudotumor cerebri) in adults (see PRECAUTIONS-General) have been reported.

**Other:** When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid glands. No abnormalities of thyroid function are known to occur in man.

Tooth discoloration in children less than 8 years of age (see WARNINGS) and also, rarely, in adults have been reported.

**OVERDOSAGE:** In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures.

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

Minocycline hydrochloride capsules may be taken with or without food.

**Adults:** The usual dosage of minocycline hydrochloride is 200 mg initially followed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily.

**For children above 8 years of age:** The usual dosage of minocycline hydrochloride is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Uncomplicated gonococcal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days, with post-therapy cultures within 2 to 3 days.

In the treatment of uncomplicated gonococcal urethritis in men: 100 mg every 12 hours for five days is recommended.

For the treatment of syphilis, the usual dosage of minocycline should be administered over a period of 10 to 15 days. Close follow-up, including laboratory tests, is recommended.

In the treatment of meningococcal carrier state, the recommended dosage is 100 mg every 12 hours for five days.

*Mycobacterium marinum* infections: Although optimal doses have not been established, 100 mg every 12 hours for 6 to 8 weeks have been used successfully in a limited number of cases.

Uncomplicated nongonococcal urethral infection in adults caused by *Chlamydia trachomatis* or *Ureaplasma urealyticum*: 100 mg orally, every 12 hours for at least seven days.

Ingestion of adequate amounts of fluids along with capsule forms of drugs in the tetracycline-class is recommended to reduce the risk of esophageal irritation and ulceration.

In patients with renal impairment (see WARNINGS), the total dosage should be decreased by either reducing the recommended individual doses and/or by extending the time intervals between doses.

**HOW SUPPLIED:** Minocycline Hydrochloride Capsules, USP, equivalent to 50 mg minocycline are opaque yellow/opaque yellow capsules supplied in bottles of 50, 100 and 500.

Minocycline Hydrochloride Capsules, USP, equivalent to 100 mg minocycline are opaque dark gray/opaque yellow capsules supplied in bottles of 50, 100 and 500.

Dispense in light, light-resistant container with child-resistant closure.

Store at controlled room temperature, 15° - 30°C (59° - 86°F).

Protect from light, moisture and excessive heat.

**CAUTION:** Federal law prohibits dispensing without prescription.

**ANIMAL PHARMACOLOGY AND TOXICOLOGY:** Minocycline hydrochloride has been observed to cause a dark discoloration of the thyroid in experimental animals (rats, minipigs, dogs and monkeys). In the rat, chronic treatment with minocycline hydrochloride has resulted in goiter accompanied by elevated radioactive iodine uptake, and evidence of thyroid tumor production. Minocycline hydrochloride has also been found to produce thyroid hyperplasia in rats and dogs.

should be performed.

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For the treatment of syphilis, the usual dosage of minocycline should be administered over a period of 10 to 15 days. Close follow-up, including laboratory tests, is recommended.

In the treatment of meningococcal carrier state, the recommended dosage is 100 mg every 12 hours for five days.

*Mycobacterium marinum* infections: Although optimal doses have not been established, 100 mg every 12 hours for 6 to 8 weeks have been used successfully in a limited number of cases.

Uncomplicated nongonococcal urethral infection in adults caused by *Chlamydia trachomatis* or *Ureaplasma urealyticum*; 100 mg orally, every 12 hours for at least seven days.

Ingestion of adequate amounts of fluids along with capsule forms of drugs in the tetracycline-class is recommended to reduce the risk of esophageal irritation and ulceration.

In patients with renal impairment (see WARNINGS), the total dosage should be decreased by either reducing the recommended individual doses and/or by extending the time intervals between doses.

**HOW SUPPLIED:** Minocycline Hydrochloride Capsules, USP, equivalent to 50 mg minocycline are opaque yellow/opaque yellow capsules supplied in bottles of 50, 100 and 500.

Minocycline Hydrochloride Capsules, USP, equivalent to 100 mg minocycline are opaque dark gray/opaque yellow capsules supplied in bottles of 50, 100 and 500.

Dispense in light, light-resistant container with child-resistant closure.

Store at controlled room temperature, 15° - 30°C (59° - 86°F).

Protect from light, moisture and excessive heat.

**CAUTION:** Federal law prohibits dispensing without prescription.

**ANIMAL PHARMACOLOGY AND TOXICOLOGY:** Minocycline hydrochloride has been observed to cause a dark discoloration of the thyroid in experimental animals (rats, minkpigs, dogs and monkeys). In the rat, chronic treatment with minocycline hydrochloride has resulted in goiter accompanied by elevated radioactive iodine uptake, and evidence of thyroid tumor production. Minocycline hydrochloride has also been found to produce thyroid hyperplasia in rats and dogs.

#### REFERENCES

1. National Committee for Clinical Laboratory Standards, Approved Standard: *Performance Standards for Antimicrobial Disk Susceptibility Tests*, 3rd Edition, Vol. 4(16):M2-A3, Villanova, PA, December 1984.
2. National Committee for Clinical Laboratory Standards, Approved Standard: *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 2nd Edition, Vol. 5(22):M7-A, Villanova, PA, December 1985.

Manufactured by:  
DANBURY PHARMACAL, INC.  
Danbury, CT 06810

Revised: October 1991  
5694\_5695

MG #6432

**DANBURY**  
PHARMACAL, INC.  
DANBURY, CT 06810

NDC 0591-5695-03  
**MINOCYCLINE  
HYDROCHLORIDE  
CAPSULES, USP**  
equivalent to 100 mg  
Minocycline

**100 mg**

**CAUTION:** Federal law  
prohibits dispensing  
without prescription.  
**500 CAPSULES**

Each capsule contains  
Minocycline hydrochloride  
equivalent to 100 mg minocycline.  
Store at controlled room  
temperature, 15° - 30°C  
(59° - 86°F).

Control N~~o~~ and Exp. Date

**SAMPLE**

**DOSAGE:** See package insert  
for dosage and full prescribing  
information.

Dispense in light, light-resistant  
container with child-resistant  
closure.

**DANBURY**  
 PHARMACAL, INC.  
 DANBURY, CT 06810

NDC 0591-5695-01  
**MINOCYCLINE  
 HYDROCHLORIDE  
 CAPSULES, USP**  
 equivalent to 100 mg  
 Minocycline

**100 mg**

**CAUTION:** Federal law  
 prohibits dispensing  
 without prescription.

**100 CAPSULES**

Each capsule contains Minocycline hydrochloride equivalent to 100 mg minocycline.  
 Store at controlled room temperature, 15° - 30°C (59° - 86°F).

Control No. and Exp. Date  
**LABEL**  
**SAMPLE**

**DOSAGE:** See package insert for dosage and full prescribing information.

Dispense in tight, light-resistant container with child-resistant closure.

1961

**LABEL  
SAMPLE**

Each capsule contains Minocycline hydrochloride equivalent to 100 mg minocycline.  
Store at controlled room temperature, 15° - 30°C (59° - 86°F).  
Control No. and Exp. Date

**DANBURY**  
PHARMACAL, INC.  
DANBURY, CT 06810

NDC 0591-5695-00  
**MINOCYCLINE  
HYDROCHLORIDE  
CAPSULES, USP**  
equivalent to 100 mg  
Minocycline

100 mg

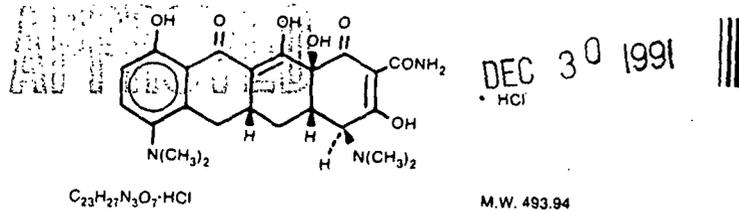
**CAUTION:** Federal law prohibits dispensing without prescription.  
50 CAPSULES

EC  
DOSAGE: See package insert for dosage and full prescribing information.

991  
Dispense in light-resistant container with child-resistant closure.

# MINOCYCLINE HYDROCHLORIDE CAPSULES, USP

**DESCRIPTION:** Minocycline hydrochloride, a semisynthetic derivative of tetracycline, is named [4S-(4a, 4aa, 5aa, 12aa)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride. The structural formula is represented below:



Minocycline Hydrochloride 50 mg and 100 mg Capsules contain the following inactive ingredients: D&C yellow #10, D&C red #28, gelatin, magnesium stearate, starch (corn) and titanium dioxide.

Minocycline Hydrochloride Capsules 100 mg also contain black iron oxide.

**ACTIONS: Microbiology:** The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. Minocycline HCl is a tetracycline with antibacterial activity comparable to other tetracyclines with activity against a wide range of gram-negative and gram-positive organisms.

**Tube dilution testing:** Microorganisms may be considered susceptible (likely to respond to minocycline therapy) if the minimum inhibitory concentration (MIC) is not more than 4.0 mcg/mL. Microorganisms may be considered intermediate (harboring partial resistance) if the MIC is 4.0 to 12.5 mcg/mL and resistant (not likely to respond to minocycline therapy) if the MIC is greater than 12.5 mcg/mL.

**Susceptibility plate testing:** If the Kirby-Bauer method of susceptibility testing (using a 30 mcg tetracycline disc) gives a zone of 18 mm or greater, the bacterial strain is considered to be susceptible to any tetracycline. Minocycline shows moderate *in vitro* activity against certain strains of staphylococci which have been found resistant to other tetracyclines. For such strains minocycline susceptibility powder may be used for additional susceptibility testing.

**Human Pharmacology:** Following a single dose of two 100 mg minocycline HCl capsules administered to ten normal adult volunteers, serum levels ranged from 0.74 to 4.45 mcg/mL in one hour (average 2.24); after 12 hours, they ranged from 0.34 to 2.36 mcg/mL (average 1.25). The serum half-life following a single 200 mg dose in 12 essentially normal volunteers ranged from 11 to 17 hours; in 7 patients with hepatic dysfunction, ranged from 11 to 16 hours; and in 5 patients with renal dysfunction, from 18 to 69 hours. The urinary and fecal recovery of minocycline when administered to 12 normal volunteers is one half to one third of other tetracyclines.

**INDICATIONS:** Minocycline is indicated in infections caused by the following microorganisms:

Rickettsiae: (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, tick fevers).

given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

**PRECAUTIONS:** As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy should be instituted.

In venereal diseases when coexistent syphilis is suspected, darkfield examination should be done before treatment is started and the blood serology repeated monthly for at least four months.

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

All infections due to Group A beta-hemolytic streptococci should be treated for at least ten days.

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

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

Reduced efficacy and increased incidence of breakthrough bleeding has been suggested with concomitant use of tetracyclines and oral contraceptive preparations.

**ADVERSE REACTIONS: Gastrointestinal:** Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, and increases in liver enzymes; rarely, hepatitis.

These reactions have been caused by both the oral and parenteral administration of tetracyclines.

**Skin:** Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Erythema multiforme and, rarely, Stevens-Johnson Syndrome have been reported. Photosensitivity is discussed above. (See **WARNINGS**).

Pigmentation of the skin and mucous membranes has been reported.

Tooth discoloration has been reported rarely in adults.

**Renal toxicity:** Rise in BUN has been reported and is apparently dose-related (See **WARNINGS**).

**Hypersensitivity reactions:** Urticaria, angioneurotic edema, polyarthralgia, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus and, rarely, pulmonary infiltrates with eosinophilia.

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

**CNS:** (See **WARNINGS**). When given over prolonged periods, tetracyclines have been reported to produce brown black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

Bulging fontanels have been reported in young infants following full therapeutic dosage. Pseudotumor Cerebri has been reported in adults. Headache has rarely been reported.

**DOSAGE AND ADMINISTRATION:** Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided.

**Concomitant therapy:** Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given to patients taking oral tetracycline.

Studies to date have indicated that the absorption of minocycline is not notably influenced by foods and dairy products.

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