MINOCIN®

Minocycline For Injection
100 Mg/Vial Intravenous

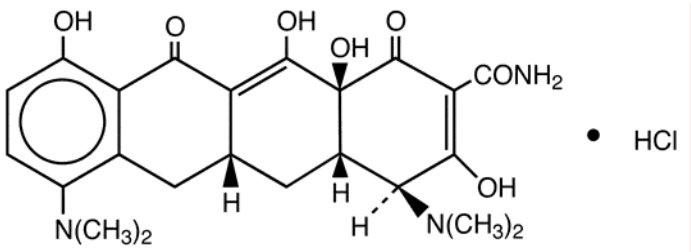
R_x **only**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MINOCIN® (minocycline) Injection and other antibacterial drugs, MINOCIN® (minocycline) injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

MINOCIN, minocycline for injection, a sterile formulation of a semisynthetic derivative of tetracycline, is 4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride.

Its structural formula is:



$C_{23}H_{27}N_3O_7$•HCl M.W. 493.94

Each vial, dried by cryodesiccation, contains minocycline HCl equivalent to 100 mg minocycline. When reconstituted with 5 mL of Sterile Water for Injection USP the pH ranges from 2.0 to 2.8.

CLINICAL PHARMACOLOGY

Following a single dose of 200 mg administered intravenously to 10 healthy male volunteers, serum levels ranged from 2.52 to 6.63 µg/mL (average 4.18), after 12 hours they ranged from 0.82 to 2.64 µg/mL (average 1.38). In a group of 5 healthy male volunteers, levels of 1.4 to 1.8 µg/mL were maintained at 12 and 24 hours with doses of 100 mg every 12 hours for three days. When given 200 mg once daily for three days, the serum levels had fallen to approximately 1 µg/mL at 24 hours. The serum half-life following I.V. doses of 100 mg every 12 hours or 200 mg once daily did not differ significantly and ranged from 15 to 23 hours. The serum half-life following a single 200 mg oral dose in 12 essentially normal volunteers ranged from 11 to 17 hours, in 7 patients with hepatic dysfunction it ranged from 11 to 16 hours, and in 5 patients with renal dysfunction from 18 to 69 hours.

Intravenously administered minocycline appears similar to oral doses in excretion. The urinary and fecal recovery of oral minocycline when administered to 12 normal volunteers was 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 a similar antimicrobial spectrum of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracycline is common.

Minocycline has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section:

AEROBIC GRAM-POSITIVE MICROORGANISMS

Because many strains of the following gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are especially recommended. Tetracycline antibiotics should not be used for streptococcal diseases unless the organism has been demonstrated to be susceptible. Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.

Bacillus anthracis[1]
Listeria monocytogenes[1]
Staphylococcus aureus
Streptococcus pneumoniae

AEROBIC GRAM-NEGATIVE MICROORGANISMS

Bartonella bacilliformis
Brucella species
Calymmatobacterium granulomatis
Campylobacter fetus
Francisella tularensis
Haemophilus ducreyi
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
Enterobacter aerogenes
Escherichia coli
Haemophilus influenzae
Klebsiella species
Neisseria gonorrhoeae[1]
Neisseria meningitidis[1]
Shigella species

“OTHER” MICROORGANISMS
Actinomyces species[1]
Borrelia recurrentis
Chlamydia psittaci
Chlamydia trachomatis
Clostridium species[1]
Entamoeba species
Fusobacterium nucleatum subspecies *fusiforme*[1]
Mycobacterium marinum
Mycoplasma pneumoniae
Propionibacterium acnes
Rickettsiae
Treponema pallidum subspecies *pallidum*[1]
Treponema pallidum subspecies *pertenue*[1]
Ureaplasma urealyticum

[1]When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of infections caused by the cited microorganisms

Susceptibility Tests

Susceptibility testing should be performed with tetracycline since it predicts susceptibility to minocycline. However, certain organisms (eg, some staphylococci, and Acinetobacter species) may be more susceptible to minocycline and doxycycline than to tetracycline.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (Ref1, Ref3) (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of tetracycline powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic gram-negative microorganisms (Enterobacteriaceae), *Acinetobacter* species and *Staphylococcus aureus*:

MIC (µg/mL)	Interpretation
≤4.0	Susceptible (S)
8.0	Intermediate (I)
≥16.0	Resistant (R)

For testing *Haemophilus influenzae*[2] and *Streptococcus pneumonia*[3]:

MIC (µg/mL)	Interpretation
≤2.0	Susceptible (S)
4.0	Intermediate (I)
≥8.0	Resistant (R)

[2] These interpretative standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* using Haemophilus Test Medium.Ref1

[3] These interpretative standards are applicable only to broth microdilution susceptibility testing using cation-adjusted Muller-Hinton broth with 2-5% lysed horse blood.[1]

For testing *Neisseria gonorrhoeae*[4]:

MIC (µg/mL)	Interpretation
≤0.25	Susceptible (S)
0.5-1.0	Intermediate (I)
≥2.0	Resistant (R)

[4] These interpretative standards are applicable only to agar dilution susceptibility testing using GC agar base and 1% defined growth supplements.Ref1

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism 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 which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard tetracycline powder should provide the following MIC values:

Microorganism	MIC Range (µg/mL)
Escherichia coli ATCC 25922	0.5-2.0
Enterococcus faecalis ATCC 29212	8.0-32.0
Staphylococcus aureus ATCC 29213	0.25-1.0
Haemophilus influenzae ATCC 49247	4.0-32.0
Streptococcus pneumoniae ATCC 49619	0.12-0.5
Neisseria gonorrhoeae ATCC 49226	0.25-1.0

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure (Ref2, Ref3) requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg tetracycline (class disk) or 30 µg minocycline to test the susceptibility of microorganisms to minocycline.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-µg tetracycline or minocycline disk should be interpreted according to the following criteria:

For testing aerobic gram-negative microorganisms (Enterobacteriaceae), *Acinetobacter* species and *Staphylococcus aureus*:

Zone Diameter (mm)	Interpretation
≥19	Susceptible (S)
15-18	Intermediate (I)
≤14	Resistant (R)

For testing *Haemophilus influenzae*[5]:

Zone Diameter (mm)	Interpretation
≥29	Susceptible (S)
26-28	Intermediate (I)
≤25	Resistant (R)

[5] These zone diameter standards are applicable only to susceptibility testing with *Haemophilus influenzae* using Haemophilus Test Medium and a 30-µg tetracycline disk. Ref2

For testing *Neisseria gonorrhoeae*[6]:

Zone Diameter (mm)	Interpretation
≥38	Susceptible (S)
31-37	Intermediate (I)
≤30	Resistant (R)

[6] These interpretative standards are applicable only to disk diffusion testing using GC agar and 1% growth supplements, and a 30-µg tetracycline disk. Ref2

For testing *Streptococcus pneumoniae*[7]:

Zone Diameter (mm)	Interpretation
≥23	Susceptible (S)
19-22	Intermediate (I)
≤18	Resistant (R)

[7] These interpretative standards are applicable only to disk diffusion testing using Muller-Hinton agar adjusted with 5% sheep blood and a 30-µg tetracycline disk. Ref2

For testing *Vibrio cholerae*[8]:

Zone Diameter (mm)	Interpretation
≥19	Susceptible (S)
15-18	Intermediate (I)
≤14	Resistant (R)

[8] These interpretative standards are applicable only to disk diffusion testing performed with a 30-µg tetracycline disk.(Ref2)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for tetracycline.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-µg tetracycline or minocycline disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter Range (mm)	
	Tetracycline	Minocycline
Escherichia coli ATCC 25922	18-25	19-25
Staphylococcus aureus ATCC 25923	24-30	25-30
Haemophilus influenzae ATCC 49247	14-22	–
Neisseria gonorrhoeae ATCC 49226	30-42	–
Streptococcus pneumoniae ATCC 49619	27-31	–

INDICATIONS AND USAGE

MINOCIN® Intravenous is 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, endocervical, or rectal infections 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 the 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.

MINOCIN® Intravenous is 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.)

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

Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections.
Infections in women caused by *Neisseria gonorrhoeae*.
Meningitis due to *Neisseria meningitidis*.
Syphilis caused by *Treponema pallidum* subspecies *pallidum*.
Yaws caused by *Treponema pallidum* subspecies *pertenue*.
Listeriosis due to *Listeria monocytogenes*.
Anthrax due to *Bacillus anthracis*.
Vincent'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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MINOCIN® (minocycline) Injection and other antibacterial drugs, MINOCIN® (minocycline) Injection 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.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or to any of the components of the product formulation.

WARNINGS

MINOCIN, 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 drugs 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 the fibula growth rate has been observed in premature human infants 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, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis. Under such conditions, monitoring of creatinine and BUN is recommended, and the total daily dosage should not exceed 200 mg in 24 hours. (See **DOSAGE AND ADMINISTRATION**.) If renal impairment exists, even usual oral or parenteral doses may lead to systemic accumulation of the drug and possible liver toxicity.

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

Central nervous system side effects including light-headedness, dizziness or vertigo have been reported. 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.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including MINOCIN®, 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 antibiotic 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 antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

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 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 soon after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

Hepatotoxicity has been reported with minocycline; therefore, minocycline should be used with caution in patients with hepatic dysfunction and in conjunction with other hepatotoxic drugs.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy when indicated.

Prescribing MINOCIN® Injection 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.

Information For Patients

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, 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 the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Patients should be counseled that antibacterial drugs including MINOCIN® (minocycline) Injection should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). When MINOCIN® (minocycline) Injection 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 MINOCIN® (minocycline) Injection or other antibacterial drugs in the future.

Laboratory Tests
Periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed.

All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with minocycline should have a follow-up serologic test for syphilis after 3 months.

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.

The concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracyclines with oral contraceptives may render oral contraceptives less effective.

Administration of isotretinoin should be avoided shortly before, during, and shortly after minocycline therapy. Each drug alone has been associated with pseudotumor cerebri. (See **PRECAUTIONS**.)

Increased risk of ergotism when ergot alkaloids or their derivatives are given with tetracyclines.

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 (ie, adrenal and pituitary tumors). Likewise, although mutagenicity studies of minocycline have not been conducted, positive results in in vitro mammalian cell assays (ie, 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.

Pregnancy
Teratogenic Effects: Pregnancy Category D. (See **WARNINGS**.)
All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. There are no adequate and well-controlled studies on the use of minocycline in pregnant women. Minocycline, like other tetracycline-class antibiotics, crosses the placenta and may cause fetal harm when administered to a pregnant woman. Rare spontaneous reports of congenital anomalies including limb reduction have been reported in post-marketing experience. Only limited information is available regarding these reports; therefore, no conclusion on causal association can be established. If minocycline is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nonteratogenic Effects: (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 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
Minocycline is not recommended for use in children below 8 years of age unless the expected benefits of therapy outweigh the risks. (See **WARNINGS**.)

Geriatric Use
Clinical studies of intravenous minocycline did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. (See **WARNINGS**, **DOSAGE AND ADMINISTRATION.**)

MINOCIN® IV (sterile minocycline hydrochloride, USP) does not contain sodium.

ADVERSE REACTIONS
The following adverse reactions have been observed in patients receiving tetracyclines.

Body as a whole: Fever, and discoloration of secretions.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, dyspepsia, stomatitis, glossitis, dysphagia, enamel hypoplasia, enterocolitis, pseudomembranous colitis, pancreatitis, inflammatory lesions (with monilial overgrowth) in the oral and anogenital regions. These reactions have been caused by both the oral and parenteral administration of tetracyclines.

Genitourinary: Vulvovaginitis.

Hepatic toxicity: Hyperbilirubinemia, hepatic cholestasis, increases in liver enzymes, fatal hepatic failure, jaundice. Hepatitis, including autoimmune hepatitis, and liver failure have been reported. (See **PRECAUTIONS**.)

Skin: Alopecia, erythema nodosum, hyperpigmentation of nails, pruritus, toxic epidermal necrolysis, and vasculitis. Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported. Fixed drug eruptions have been reported. Lesions occurring on the glans penis have caused balanitis. Erythema multiforme and Stevens-Johnson syndrome have been reported. Photosensitivity is discussed above. (See **WARNINGS**.) Pigmentation of the skin and mucous membranes has been reported.

Local Reactions: Injection site erythema and injection site pain.

Respiratory: Cough, dyspnea, bronchospasm, exacerbation of asthma, and pneumonitis.

Renal toxicity: Interstitial nephritis. Elevations in BUN have been reported and are apparently dose related. (See **WARNINGS**.) Acute renal failure has been reported.

Musculoskeletal: Arthralgia, arthritis, bone discoloration, myalgia, joint stiffness, and joint swelling.

Hypersensitivity reactions: Urticaria, angioneurotic edema, polyarthralgia, anaphylaxis/anaphylactoid reaction (including shock and fatalities), anaphylactoid purpura, myocarditis, pericarditis, exacerbation of systemic lupus erythematosus, and pulmonary infiltrates with eosinophilia have been reported. A lupus-like syndrome and serum sickness-like reactions also have been reported.

Blood: Agranulocytosis, hemolytic anemia, thrombocytopenia, leukopenia, neutropenia, pancytopenia, and eosinophilia have been reported.

Central Nervous System: Convulsions, dizziness, hypesthesia, paresthesia, sedation, and vertigo. Pseudotumor cerebri (benign intracranial hypertension) in adults and bulging fontanels in infants. (See **PRECAUTIONS** - **General**.) Headache has also been reported.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid gland. Cases of abnormal thyroid function have been reported.

Tooth discoloration in pediatric patients less than 8 years of age (see **WARNINGS**) and in adults has been reported.

Oral cavity discoloration (including tongue, lip, and gum) have been reported.

Tinnitus and decreased hearing have been reported in patients on MINOCIN® (minocycline for injection).

The following syndromes have been reported. In some cases involving these syndromes, death has been reported. As with other serious adverse reactions, if any of these syndromes are recognized, the drug should be discontinued immediately:

Hypersensitivity syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present.

Lupus-like syndrome consisting of positive antinuclear antibody; arthralgia, arthritis, joint stiffness, or joint swelling; and one or more of the following: fever, myalgia, hepatitis, rash, and vasculitis.

Serum sickness-like syndrome consisting of fever; urticaria or rash; and arthralgia, arthritis, joint stiffness, or joint swelling. Eosinophilia may be present.

OVERDOSAGE

The adverse events more commonly seen in overdose are dizziness, nausea, and vomiting.

No specific antidote for minocycline is known.

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures. Minocycline is not removed in significant quantities by hemodialysis or peritoneal dialysis.

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.

Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not adequate or tolerated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

For Pediatric Patients Above 8 years of Age

Usual pediatric dose: 4 mg/kg initially followed by 2 mg/kg every 12 hours, not to exceed the usual adult dose.

Adults

Usual adult dose: 200 mg followed by 100 mg every 12 hours and should not exceed 400 mg in 24 hours. The cryodesiccated powder should be reconstituted with 5 mL Sterile Water for Injection USP and immediately further diluted to 500 mL to 1,000 mL with Sodium Chloride Injection USP, Dextrose Injection USP, Dextrose and Sodium Chloride Injection USP, Ringer's Injection USP, or Lactated Ringer's Injection USP, but not with other solutions containing calcium because a precipitate may form especially in neutral and alkaline solutions. When further diluted in 500 mL to 1,000 mL of compatible solutions (except Lactated Ringer's), the pH usually ranges from 2.5 to 4.0. The pH of MINOCIN® IV 100 mg in Lactated Ringer's 500 mL to 1,000 mL usually ranges from 4.5 to 6.0.

Final dilutions (500 mL to 1,000 mL) should be administered immediately but product and diluents are compatible at room temperature for 24 hours without a significant loss of potency. Any unused portions must be discarded after that period.

The pharmacokinetics of minocycline in patients with renal impairment (CL_{CR} <80 mL/min) have not been fully characterized. Current data are insufficient to determine if a dosage adjustment is warranted. The total daily dosage should not exceed 200 mg in 24 hours. However, due to the anti-anabolic effect of tetracyclines, BUN and creatinine should be monitored. (See **WARNINGS**.)

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Incompatibilities

MINOCIN® IV should not be mixed before or during administration with any solutions containing: adrenocorticotropic hormone (ACTH), aminophylline, amobarbital sodium, amphotericin B, bicarbonate infusion mixtures, calcium gluconate or chloride, carbenicillin, cephalothin sodium, cefazolin sodium, chloramphenicol succinate, colistin sulfate, heparin sodium, hydrocortisone sodium succinate, iodine sodium, methicillin sodium, novobiocin, penicillin, pentobarbital, phenytoin sodium, polymyxin, prochlorperazine, sodium ascorbate, sulfadiazine, sulfisoxazole, thiopental sodium, vitamin K (sodium bisulfate or sodium salt), whole blood.

HOW SUPPLIED

MINOCIN® (minocycline for injection) Intravenous is supplied as 100 mg vials of sterile cryodesiccated powder.

Product No. NDC 14290-525-62

Store at Controlled Room Temperature 20° to 25°C (68° to 77°F).

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.

REFERENCES

Ref1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically – Fourth Edition; Approved Standard. NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA, January 1997.

Ref2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disks Susceptibility Tests – Sixth Edition; Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA, January 1997.

Ref3. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Susceptibility Testing – Eighth Edition; Approved Standard NCCLS Document M100-S8, Vol. 18, No. 1, NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA, January 1998.

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Manufactured for Triax Pharmaceuticals, LLC
20 Commerce Drive, Cranford, NJ 07016
By Wyeth Pharmaceuticals Inc., Philadelphia, PA 19101

152F501
Rev 10/06

MINOCIN®

Minocycline Hydrochloride
Oral Suspension

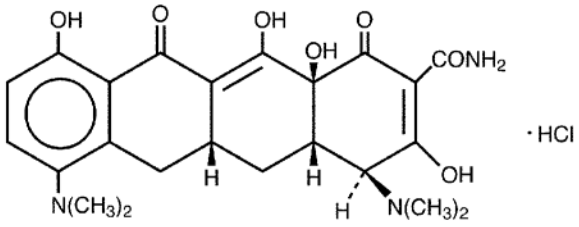
R_x only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MINOCIN® Oral Suspension and other antibacterial drugs, MINOCIN® Oral Suspension should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

MINOCIN® minocycline hydrochloride, is a semisynthetic derivative of tetracycline, 4,7 Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride.

Its structural formula is:



$C_{23}H_{27}N_3O_7 \cdot HCl$ M.W. 493.94

MINOCIN® Oral Suspension contains minocycline HCl equivalent to 50 mg of minocycline per 5 mL (10 mg/mL) and the following inactive ingredients: Alcohol, Butylparaben, Calcium Hydroxide, Cellulose, Decaglyceryl Tetraoleate, Edetate Calcium Disodium, Guar Gum, Polysorbate 80, Propylparaben, Propylene Glycol, Sodium Saccharin, Sodium Sulfite (see **WARNINGS**) and Sorbitol.

CLINICAL PHARMACOLOGY

Following a single dose of two 100 mg minocycline HCl powder-filled capsules administered to ten normal adult volunteers, serum levels ranged from 0.74 to 4.45 µg/mL in one hour (average 2.24); after 12 hours they ranged from 0.34 to 2.36 µg/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 seven patients with hepatic dysfunction it ranged from 11 to 16 hours, and in 5 patients with renal dysfunction it ranged from 18 to 69 hours. The urinary and fecal recovery of minocycline when administered to 12 normal volunteers was 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 a similar antimicrobial spectrum of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracycline is common.

Minocycline has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section:

AEROBIC GRAM-POSITIVE MICROORGANISMS

Because many strains of the following gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are especially recommended. Tetracycline antibiotics should not be used for streptococcal diseases unless the organism has been demonstrated to be susceptible. Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.

Bacillus anthracis[1]
Listeria monocytogenes[1]
Staphylococcus aureus
Streptococcus pneumoniae

AEROBIC GRAM-NEGATIVE MICROORGANISMS

Bartonella bacilliformis
Brucella species
Calymmatobacterium granulomatis
Campylobacter fetus
Francisella tularensis
Haemophilus ducreyi
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
Enterobacter aerogenes
Escherichia coli
Haemophilus influenzae
Klebsiella species
Neisseria gonorrhoeae[1]
Neisseria meningitidis[1]
Shigella species

“OTHER” MICROORGANISMS
Actinomyces species[1]
Borrelia recurrentis
Chlamydia psittaci
Chlamydia trachomatis
Clostridium species[1]
Entamoeba species
Fusobacterium nucleatum subspecies *fusiforme*[1]
Mycobacterium marinum
Mycoplasma pneumoniae
Propionibacterium acnes
Rickettsiae
Treponema pallidum subspecies *pallidum*[1]
Treponema pallidum subspecies *pertenue*[1]
Ureaplasma urealyticum

[1]When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of infections caused by the cited microorganisms.

Susceptibility Tests

Susceptibility testing should be performed with tetracycline since it predicts susceptibility to minocycline. However, certain organisms (eg, some staphylococci, and *Acinetobacter* species) may be more susceptible to minocycline and doxycycline than to tetracycline.

Dilution techniques:
Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (Ref1, Ref3) (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of tetracycline powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic gram-negative microorganisms (Enterobacteriaceae), *Acinetobacter* species and *Staphylococcus aureus*:

MIC (µg/mL)	Interpretation
≤4.0	Susceptible (S)
8.0	Intermediate (I)
≥16.0	Resistant (R)

For testing *Haemophilus influenzae*[2] and *Streptococcus pneumonia*[3]:

MIC (µg/mL)	Interpretation
≤2.0	Susceptible (S)
4.0	Intermediate (I)
≥8.0	Resistant (R)

[2] These interpretative standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* using Haemophilus Test Medium.Ref1

[3] These interpretative standards are applicable only to broth microdilution susceptibility testing using cation-adjusted Muller-Hinton broth with 2-5% lysed horse blood.[1]

For testing *Neisseria gonorrhoeae*[4]:

MIC (µg/mL)	Interpretation
≤0.25	Susceptible (S)
0.5-1.0	Intermediate (I)
≥2.0	Resistant (R)

[4] These interpretative standards are applicable only to agar dilution susceptibility testing using GC agar base and 1% defined growth supplements.Ref1

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism 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 which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard tetracycline powder should provide the following MIC values:

Microorganism	MIC Range (µg/mL)
Escherichia coli ATCC 25922	0.5-2.0
Enterococcus faecalis ATCC 29212	8.0-32.0
Staphylococcus aureus ATCC 29213	0.25-1.0
Haemophilus influenzae ATCC 49247	4.0-32.0
Streptococcus pneumoniae ATCC 49619	0.12-0.5
Neisseria gonorrhoeae ATCC 49226	0.25-1.0

Diffusion techniques:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure (Ref2, Ref3) requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg tetracycline (class disk) or 30 µg minocycline to test the susceptibility of microorganisms to minocycline.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-µg tetracycline or minocycline disk should be interpreted according to the following criteria:

For testing aerobic gram-negative microorganisms (Enterobacteriaceae), *Acinetobacter* species and *Staphylococcus aureus*:

Zone Diameter (mm)	Interpretation
≥19	Susceptible (S)
15-18	Intermediate (I)
≤14	Resistant (R)

For testing *Haemophilus influenzae*[5]:

Zone Diameter (mm)	Interpretation
≥29	Susceptible (S)
26-28	Intermediate (I)
≤25	Resistant (R)

[5] These zone diameter standards are applicable only to susceptibility testing with *Haemophilus influenzae* using Haemophilus Test Medium and a 30-µg tetracycline disk. Ref2

For testing *Neisseria gonorrhoeae*[6]:

Zone Diameter (mm)	Interpretation
≥38	Susceptible (S)
31-37	Intermediate (I)
≤30	Resistant (R)

[6] These interpretative standards are applicable only to disk diffusion testing using GC agar and 1% growth supplements, and a 30-µg tetracycline disk. Ref2

For testing *Streptococcus pneumoniae*[7]:

Zone Diameter (mm)	Interpretation
≥23	Susceptible (S)
19-22	Intermediate (I)
≤18	Resistant (R)

[7] These interpretative standards are applicable only to disk diffusion testing using Muller-Hinton agar adjusted with 5% sheep blood and a 30-µg tetracycline disk. Ref2

For testing *Vibrio cholerae*[8]:

Zone Diameter (mm)	Interpretation
≥19	Susceptible (S)
15-18	Intermediate (I)
≤14	Resistant (R)

[8] These interpretative standards are applicable only to disk diffusion testing performed with a 30-µg tetracycline disk.(Ref2)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for tetracycline.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-µg tetracycline or minocycline disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter Range (mm)	
	Tetracycline	Minocycline
Escherichia coli ATCC 25922	18-25	19-25
Staphylococcus aureus ATCC 25923	24-30	25-30
Haemophilus influenzae ATCC 49247	14-22	–
Neisseria gonorrhoeae ATCC 49226	30-42	–
Streptococcus pneumoniae ATCC 49619	27-31	–

INDICATIONS AND USAGE

MINOCIN® Oral Suspension is 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, rickettsial pox 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, endocervical, or rectal infections 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 the 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.

MINOCIN® Oral Suspension is 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.)

When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:
Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections.
Infections in women caused by *Neisseria gonorrhoeae*.
Syphilis caused by *Treponema pallidum* subspecies *pallidum*.
Yaws caused by *Treponema pallidum* subspecies *pertenue*.
Listeriosis due to *Listeria monocytogenes*.
Anthrax due to *Bacillus anthracis*.
Vincent'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 carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carriers, 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*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MINOCIN® Oral Suspension and other antibacterial drugs, MINOCIN® Oral Suspension 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.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or to any of the components of the product formulation.

WARNINGS

MINOCIN ORAL SUSPENSION, 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 IN THIS AGE GROUP 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 the fibula growth rate has been observed in premature human infants 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 also been noted in animals treated early in pregnancy.

The safety of MINOCIN® for use during pregnancy has not been established.

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, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis. Under such conditions, monitoring of creatinine and BUN is recommended, and the total daily dosage should not exceed 200 mg in 24 hours. (See **DOSAGE AND ADMINISTRATION**.) If renal impairment exists, even usual oral or parenteral doses may lead to systemic accumulation of the drug and possible liver toxicity.

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

Central nervous system side effects including light-headedness, dizziness, or vertigo have been reported. 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.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including MINOCIN®, 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 antibiotic 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 antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

MINOCIN® Oral Suspension contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

General

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 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 soon after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

Hepatotoxicity has been reported with minocycline; therefore, minocycline should be used in caution in patients with hepatic dysfunction and in conjunction with other hepatotoxic drugs.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy when indicated.

Prescribing MINOCIN® Oral Suspension 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.

Information for Patients

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, 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 the antibiotic. If this occurs, patients should contact their physician as soon as possible.

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 with use of minocycline.

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

Concurrent use of tetracyclines with oral contraceptives may render oral contraceptives less effective. (See **Drug Interactions**.)

Patients should be counseled that antibacterial drugs including MINOCIN® Oral Suspension should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When MINOCIN® Oral Suspension 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 MINOCIN® Oral Suspension or other antibacterial drugs in the future.

Unused supplies of tetracycline antibiotics should be discarded by the expiration date.

Laboratory Tests

Periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic, should be performed.

All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with minocycline should have a follow-up serologic test for syphilis after 3 months.

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.

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 with oral contraceptives may render oral contraceptives less effective.

Administration of isotretinoin should be avoided shortly before, during, and shortly after minocycline therapy. Each drug alone has been associated with pseudotumor cerebri. (See **PRECAUTIONS**.)

Increased risk of ergotism when ergot alkaloids or their derivatives are given with tetracyclines.

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 (ie, adrenal and pituitary tumors). Likewise, although mutagenicity studies of minocycline have not been conducted, positive results in in vitro mammalian cell assays (ie, 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.

Pregnancy
Teratogenic Effects: Pregnancy Category D. (See **WARNINGS**.)
All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. There are no adequate and well-controlled studies on the use of minocycline in pregnant women. Minocycline, like other tetracycline-class antibiotics, crosses the placenta and may cause fetal harm when administered to a pregnant woman. Rare spontaneous reports of congenital anomalies including limb reduction have been reported in post-marketing experience. Only limited information is available regarding these reports; therefore, no conclusion on causal association can be established. If minocycline is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nonteratogenic Effects: (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 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
Minocycline is not recommended for use in children below 8 years of age unless the expected benefits of therapy outweigh the risks. (See **WARNINGS**.)

Geriatric Use

Clinical studies of oral minocycline did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. (See **WARNINGS**, **DOSAGE AND ADMINISTRATION**.)

MINOCIN® Oral Suspension contains 4.3 mg (0.18 mEq) of sodium per 5 mL.

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.

Body as a whole: Fever, and discoloration of secretions.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, dyspepsia, stomatitis, glossitis, dysphagia, enamel hypoplasia, enterocolitis, pseudomembranous colitis, pancreatitis, inflammatory lesions (with monilial overgrowth) in the oral and anogenital regions. These reactions have been caused by both the oral and parenteral administration of tetracyclines.

Genitourinary: Vulvovaginitis.

Hepatic toxicity: Hyperbilirubinemia, hepatic cholestasis, increases in liver enzymes, fatal hepatic failure, jaundice. Hepatitis, including autoimmune hepatitis, and liver failure have been reported. (See **PRECAUTIONS**.)

Skin: Alopecia, erythema nodosum, hyperpigmentation of nails, pruritus, toxic epidermal necrolysis, and vasculitis. Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported. Fixed drug eruptions, including balanitis, have been reported. Erythema multiforme and Stevens-Johnson syndrome have been reported. Photosensitivity is discussed above. (See **WARNINGS**.) Pigmentation of the skin and mucous membranes has been reported.

Respiratory: Cough, dyspnea, bronchospasm, and exacerbation of asthma, and pneumonitis.

Renal toxicity: Interstitial nephritis. Elevations in BUN have been reported and are apparently dose related. (See **WARNINGS**.) Acute renal failure has been reported.

Musculoskeletal: Arthralgia, arthritis, bone discoloration, myalgia, joint stiffness, and joint swelling.

Hypersensitivity reactions: Urticaria, angioneurotic edema, polyarthralgia, anaphylaxis/anaphylactoid reaction (including shock and fatalities), anaphylactoid purpura, myocarditis, pericarditis, exacerbation of systemic lupus erythematosus and pulmonary infiltrates with eosinophilia have been reported. A transient lupus-like syndrome and serum sickness-like reactions also have been reported.

Blood: Agranulocytosis, hemolytic anemia, thrombocytopenia, leukopenia, neutropenia, pancytopenia, and eosinophilia have been reported.

Central Nervous System: Convulsions, dizziness, hypesthesia, paresthesia, sedation, and vertigo. Pseudotumor cerebri (benign intracranial hypertension) in adults and bulging fontanels in infants. (See **PRECAUTIONS – General**.) Headache has also been reported.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid gland. Cases of abnormal thyroid function have been reported.

Tooth discoloration in pediatric patients less than 8 years of age (see **WARNINGS**) and also, in adults has been reported.

Oral cavity discoloration (including tongue, lip, and gum) have been reported.

Tinnitus and decreased hearing have been reported in patients on MINOCIN® (minocycline hydrochloride).

The following syndromes have been reported. In some cases involving these syndromes, death has been reported. As with other serious adverse reactions, if any of these syndromes are recognized, the drug should be discontinued immediately:

Hypersensitivity syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present.

Lupus-like syndrome consisting of positive antinuclear antibody; arthralgia, arthritis, joint stiffness, or joint swelling; and one or more of the following: fever, myalgia, hepatitis, rash, and vasculitis.

Serum sickness-like syndrome consisting of fever; urticaria or rash; and arthralgia, arthritis, joint stiffness, or joint swelling. Eosinophilia may be present.

OVERDOSAGE

The adverse events more commonly seen in overdose are dizziness, nausea, and vomiting.

No specific antidote for minocycline is known.

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures. Minocycline is not removed in significant quantities by hemodialysis or peritoneal dialysis.

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.

Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided.

Studies to date have indicated that the absorption of MINOCIN® Oral Suspension is not notably influenced by foods and dairy products.

The pharmacokinetics of minocycline in patients with renal impairment (CL_{CR} <80 mL/min) have not been fully characterized. Current data are insufficient to determine if a dosage adjustment is warranted. The total daily dosage should not exceed 200 mg in 24 hours. However, due to the anti-anabolic effect of tetracyclines, BUN and creatinine should be monitored. (See **WARNINGS**.**)**

In the treatment of streptococcal infections, a therapeutic dose of tetracycline should be administered for at least ten days.

For Pediatric Patients Above 8 Years Of Age

The usual dosage of MINOCIN® is 4 mg/kg initially followed by 2 mg/kg every 12 hours, not to exceed the usual adult dose.

Adults

The usual dosage of MINOCIN® is 200 mg initially followed by 100 mg every 12 hours.

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

Gonorrhea patients sensitive to penicillin may be treated with MINOCIN®, administered as 200 mg initially, followed by 100 mg every 12 hours for a minimum of 4 days, with post-therapy cultures within 2 to 3 days.

In the treatment of meningococcal carrier state, recommended dosage is 100 mg every 12 hours for 5 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 urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis* or *Ureaplasma urealyticum*: 100 mg, orally, every 12 hours for at least 7 days.[1]

In the treatment of uncomplicated gonococcal urethritis in men, 100 mg twice a day orally for 5 days is recommended.

HOW SUPPLIED

MINOCIN® (minocycline hydrochloride) Oral Suspension contains minocycline hydrochloride equivalent to 50 mg minocycline per teaspoonful (5 mL). Preserved with propylparaben 0.10% and butylparaben 0.06% with Alcohol USP 5% v/v. Custard-flavored.

NDC 14290-545-61 Bottle 2 fl. oz. (60 mL)

Store at controlled room temperature 20° to 25°C (68° to 77°F).

DO NOT FREEZE.

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.

REFERENCES

Ref1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically – Fourth Edition; Approved Standard. NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA, January 1997.

Ref2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disks Susceptibility Tests – Sixth Edition; Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA, January 1997.

Ref3. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Susceptibility Testing – Eighth Edition; Approved Standard NCCLS Document M100-S8, Vol. 18, No. 1, NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA, January 1998.

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