
DECLOMYCIN[®] TABLETS

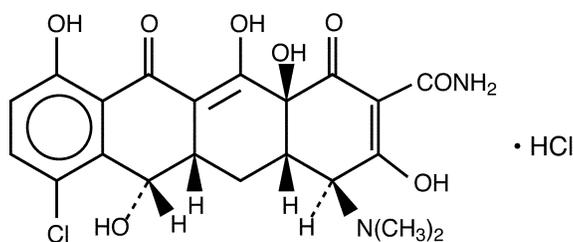
Demeclocycline Hydrochloride Tablets, U.S.P.

R_x only

DESCRIPTION

DECLOMYCIN demeclocycline hydrochloride is an antibiotic isolated from a mutant strain of *Streptomyces aureofaciens*. Chemically it is 7-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxo-2-naphthacencarboxamide monohydrochloride.

Its structural formula is:



DECLOMYCIN Tablets for oral administration contain 150 mg or 300 mg of demeclocycline hydrochloride and the following inactive ingredients: alginic acid, corn starch, ethylcellulose, hydroxypropyl methylcellulose, magnesium stearate, D&C Red 7, sorbitol, titanium dioxide, FD&C Yellow 10 and other ingredients. May also contain sodium lauryl sulfate.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The absorption of demeclocycline is slower than that of tetracycline. The time to reach the peak concentration is about 4 hours. After a 150 mg oral dose of demeclocycline tablet, the mean concentrations at 1 hour and 3 hours are 0.46 and 1.22 $\mu\text{g/mL}$ ($n = 6$), respectively. The serum half-life ranges between 10 and 16 hours.

When demeclocycline hydrochloride is given concomitantly with some dairy products, or antacids containing aluminum, calcium, or magnesium, the extent of absorption is reduced by more than 50%.

Demeclocycline hydrochloride penetrates well into various body fluids and tissues. The percent of demeclocycline hydrochloride bound to plasma protein is about 40% using a dialysis equilibrium method and 90% using an ultra-filtration method. Demeclocycline hydrochloride, like other tetracyclines, is concentrated in the liver and excreted into the bile where it is found in much higher concentrations than in the blood. The rate of demeclocycline hydrochloride renal clearance ($35 \text{ mL/min}/1.73 \text{ m}^2$) is less than half that of tetracycline. Following a single 150 mg dose of demeclocycline hydrochloride in normal volunteers, 44% ($n = 8$) was excreted in urine

and 13% and 46%, respectively, were excreted in feces in two patients within 96 hours as active drug.

Microbiology

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

Demeclocycline 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:

Bacillus anthracis
Listeria monocytogenes
Staphylococcus aureus
Streptococcus pneumoniae

AEROBIC GRAM-NEGATIVE MICROORGANISMS:

Bartonella bacilliformis
Brucella species
Calymmatobacterium granulomatis
Campylobacter fetus
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
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 testing are especially recommended:

Acinetobacter species
Enterobacter aerogenes
Escherichia coli
Klebsiella species
Shigella species

OTHER MICROORGANISMS:

Actinomyces israelii
Borrelia recurrentis
Chlamydia psittaci
Chlamydia trachomatis
Clostridium species

Entamoeba species
Fusobacterium fusiforme
Mycoplasma pneumoniae
Propionibacterium acnes
Rickettsiae
Treponema pallidum subspecies *pallidum*
Treponema pallidum subspecies *pertenue*
Ureaplasma urealyticum

Susceptibility Tests

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of demeclocycline hydrochloride or tetracycline powder.¹ The MIC values should be interpreted according to the following criteria:

For organisms other than *Haemophilus* species, *Neisseria gonorrhoeae* and *Streptococcus* species:²

MIC (µg/mL)	Interpretation
≤ 4	Susceptible (S)
8	Intermediate (I)
≥ 16	Resistant (R)

For *Haemophilus* and *Streptococcus* species:²

MIC (µg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

For *Neisseria gonorrhoeae*:²

MIC (µg/mL)	Interpretation
≤ 0.25	Susceptible (S)
0.5 to 1	Intermediate (I)
≥ 2	Resistant (R)

A report of “Susceptible” indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. 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 usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that 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 demeclocycline or tetracycline powder should provide the following MIC values:²

Microorganism	MIC (µg/mL)
<i>E. coli</i> , ATCC 25922	1 to 4
<i>E. faecalis</i> , ATCC 29212	8 to 32
<i>H. influenzae</i> , ATCC 49247	4 to 32
<i>N. gonorrhoeae</i> , ATCC 49226	0.25 to 1
<i>S. aureus</i> , ATCC 29213	0.25 to 1
<i>S. pneumoniae</i> , ATCC 49619	0.12 to 0.5

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 requires the use of standardized inoculum concentrations.² This procedure uses paper disks impregnated with 30-µg tetracycline (as a class disk) or a 30-µg demeclocycline hydrochloride disk to test the susceptibility of microorganisms to demeclocycline.

Reports from the laboratory providing results of the standard single-disk susceptibility test with either a 30- μ g tetracycline-class disk or a 30- μ g demeclocycline disk should be interpreted according to the following criteria:

For organisms other than *Haemophilus* species, *Neisseria gonorrhoeae* and *Streptococcus* species:²

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

For *Haemophilus* species:²

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

For *N. gonorrhoeae*:²

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

For *Streptococcus* species:²

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

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 demeclocycline hydrochloride or tetracycline.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30- μ g demeclocycline hydrochloride disk or the 30- μ g tetracycline-class disk should provide the following zone diameters in these laboratory test quality control strains:²

Microorganism	Zone Diameter (mm)
<i>E. coli</i> , ATCC 25922	18 to 25
<i>H. influenzae</i> , ATCC 49247	14 to 22
<i>N. gonorrhoeae</i> , ATCC 49226	30 to 42
<i>S. aureus</i> , ATCC 25923	24 to 30
<i>S. pneumoniae</i> , ATCC 49619	27 to 31

INDICATIONS AND USAGE

DECLOMYCIN is indicated in the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions below:

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 due to *Chlamydia trachomatis*;

Psittacosis (Ornithosis) due to *Chlamydia psittaci*;

Trachoma due to *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*;

Demeclocycline hydrochloride 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.

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

Upper respiratory infections caused by *Streptococcus pneumoniae*;

Skin and skin structure infections caused by *Staphylococcus aureus*. (Note: Tetracyclines, including demeclocycline, are not the drugs of choice in the treatment of any type of staphylococcal infection.)

When penicillin is contraindicated, tetracyclines, including demeclocycline hydrochloride, are alternative drugs in the treatment of the following infections:

Uncomplicated urethritis in men due to *Neisseria gonorrhoeae*, and for the treatment of other uncomplicated 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*;

Clostridial diseases caused by *Clostridium* species.

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

In severe acne, demeclocycline hydrochloride may be a useful adjunctive therapy.

CONTRAINDICATIONS

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

WARNINGS

DEMECLOCYCLINE HYDROCHLORIDE, 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 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 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.

If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation 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. Phototoxic reactions can occur in individuals taking demeclocycline, and are characterized by severe burns of exposed surfaces resulting from direct exposure of patients to sunlight during therapy with moderate or large doses of demeclocycline. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur, and treatment should be discontinued at the first evidence of erythema of the skin.

Administration of DECLOMYCIN has resulted in appearance of the diabetes insipidus syndrome (polyuria, polydipsia and weakness) in some patients on long-term therapy. The syndrome has been shown to be nephrogenic, dose-dependent and reversible on discontinuance of therapy.

Patients who are experiencing central nervous system symptoms associated with demeclocycline therapy, should be cautioned about driving vehicles or using hazardous machinery while on demeclocycline therapy.

PRECAUTIONS

General

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.

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.

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.

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

Patients should be informed that demeclocycline hydrochloride tablets should be taken at least 1 hour before meals or 2 hours after meals. (See **DOSAGE AND ADMINISTRATION**.)

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

Patients who are experiencing headache, dizziness, light-headedness, vertigo, or blurred vision while on demeclocycline therapy, should be cautioned about driving vehicles or using hazardous machinery while receiving demeclocycline therapy. (See **WARNINGS**.)

Laboratory Tests

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 4 months.

In long-term therapy, 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 demeclocycline hydrochloride 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 penicillins, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of demeclocycline hydrochloride have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibiotics oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors).

Although mutagenicity studies of demeclocycline hydrochloride 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). (See **WARNINGS** and **ANIMAL PHARMACOLOGY AND ANIMAL TOXICOLOGY**.)

Demeclocycline hydrochloride had no effect on fertility when administered in the diet to male and female rats at a daily intake of 45 times the human dose.

Pregnancy

Teratogenic effects. Pregnancy Category D. (See WARNINGS.)

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.

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 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

Not for use in patients younger than eight years of age. See **WARNINGS, PRECAUTIONS (General subsection)** and **DOSAGE AND ADMINISTRATION**.

ADVERSE REACTIONS

The following reactions have been reported in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, pancreatitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region, increases in liver enzymes, and hepatic toxicity has been reported rarely.

Rarely, hepatitis and liver failure have been reported. These reactions have been caused by both the oral and parenteral administration of tetracyclines.

Instances of esophageal ulcerations have been reported in patients receiving oral tetracyclines. Most of the patients were reported to have taken the medication immediately before lying down. (See **DOSAGE AND ADMINISTRATION**.)

Skin: Maculopapular and erythematous rashes, erythema multiforme. Exfoliative dermatitis has been reported but is uncommon. Fixed drug eruptions and Stevens-Johnson syndrome have been reported rarely. Lesions occurring on the glans penis have caused balanitis. Pigmentation of the skin and mucous membranes has also been reported. Photosensitivity is discussed above. (See **WARNINGS**.)

Renal toxicity: Acute renal failure. Rise in BUN has been reported and is apparently dose related. Nephrogenic diabetes insipidus. (See **WARNINGS**.)

Hypersensitivity reactions: Urticaria, angioneurotic edema, polyarthralgia, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, lupus-like syndrome, pulmonary infiltrates with eosinophilia.

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

CNS: Pseudotumor cerebri (benign intracranial hypertension) in adults and bulging fontanel in infants (see **PRECAUTIONS—General**). Dizziness, headache, tinnitus, and visual disturbances have been reported. Myasthenic syndrome has been reported rarely.

Other: 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. Very rare cases of abnormal thyroid function have been reported.

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

Concomitant therapy: Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, and by iron-containing preparations. Foods and some dairy products also interfere with absorption. Oral forms of tetracycline should be given at least 1 hour before or 2 hours after meals.

In patients with renal impairment: (See **WARNINGS**.) Tetracyclines should be used cautiously in patients with impaired renal function. Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

In patients with liver impairment: Tetracyclines should be used cautiously in patients with impaired liver function. Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

Administration of adequate amounts of fluid with the oral formulations of tetracyclines is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. (See **ADVERSE REACTIONS**.)

Adults: Usual daily dose - Four divided doses of 150 mg each or two divided doses of 300 mg each.

For pediatric patients above eight years of age: Usual daily dose, 7 to 13 mg per kg body weight per day, depending upon the severity of the disease, divided into two to four doses not to exceed adult dosage of 600 mg per day.

Gonorrhea patients sensitive to penicillin may be treated with demeclocycline administered as an initial oral dose of 600 mg followed by 300 mg every 12 hours for four days to a total of 3 grams.

HOW SUPPLIED

DECLOMYCIN[®] demeclocycline hydrochloride Tablets, 150 mg, are round, convex, red, film coated tablets, engraved with LL on one side and D11 on the other, and are supplied as follows:

NDC 0005-9218-23 – Bottle of 100

DECLOMYCIN[®] demeclocycline hydrochloride Tablets, 300 mg, are round, convex, red, film coated tablets, engraved with LL on one side and D12 on the other, and are supplied as follows:

NDC 0005-9270-29 – Bottle of 48

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

ANIMAL PHARMACOLOGY AND ANIMAL TOXICOLOGY

Hyperpigmentation of the thyroid has been produced by members of the tetracycline class in the following species: in rats by oxytetracycline, doxycycline, tetracycline PO₄ and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO₄, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO₄, methacycline, doxycycline, tetracycline base, oxytetracycline HCl, and tetracycline HCl were goitrogenic in rats fed a low iodine diet. This goitrogenic effect was accompanied by high radioactive iodine uptake. Administration of minocycline also produced a large goiter with high radioiodine uptake in rats fed a relatively high iodine diet.

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

REFERENCES

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2. National Committee for Clinical Laboratory Standards. (2000). "Performance standards for antimicrobial disk susceptibility tests. Approved Standard M2-A7." National Committee for Clinical Laboratory Standards, Wayne, PA.
3. National Committee for Clinical Laboratory Standards. (2002). "Performance standards for antimicrobial susceptibility testing. Twelfth informational supplement. M100-S12." National Committee for Clinical Laboratory Standards, Wayne, PA.



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