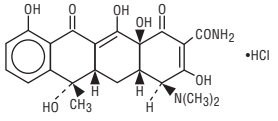
To reduce the development of drug-resistant bacteria and maintain the effectiveness of tetracycline hydrochloride and other antibacterial drugs, tetracycline hydrochloride should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Tetracycline is a yellow, odorless, crystalline powder. Tetracycline is stable in air but exposure to strong sunlight causes it to darken. Its potency is affected in solutions of pH below 2 and is rapidly destroyed by alkali hydroxide solutions. Tetracycline is very slightly soluble in water, freely soluble in dilute acid and in alkali hydroxide solutions, sparingly soluble in alcohol, and practically insoluble in chloroform and in ether. The chemical name for tetracycline hydrochloride is 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,-12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecar-boxamide monohydrochloride. Its structural formula is as follows:



$C_{22}H_{24}N_2O_8$•HCl M.W. 480.9

Each capsule, for oral administration, contains 250 mg or 500 mg tetracycline hydrochloride USP, and has the following inactive ingredients: colloidal silicon dioxide, D&C Yellow #10, gelatin, pregelatinized starch, propylene glycol, shellac glaze (modified), stearic acid, and titanium dioxide. The 250 mg capsules also contain black iron oxide, FD&C Blue #1 Aluminum Lake, FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake, and FD&C Yellow #6. The 500 mg capsules also contain ammonium hydroxide, FD&C Blue #1, FD&C Red #40, and simethicone.

CLINICAL PHARMACOLOGY

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. They are concentrated by the liver in the bile and excreted in the urine and feces at high concentrations in a biologically active form.

Microbiology

Tetracyclines are primarily bacteriostatic and exert their antimicrobial effect by the inhibition of protein synthesis. Tetracycline is active against a wide range of gram-negative and gram-positive organisms. The drugs in the tetracycline class have closely similar antimicrobial spectra, and cross-resistance among them is common.

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

Gram-negative Bacteria

Neisseria gonorrhea
Haemophilus ducreyi
Haemophilus influenzae
Yersinia pestis (formerly Pasteurella pestis)
Francisella tularensis (formerly Pasteurella tularensis)
Vibrio cholera (formerly Vibrio comma)
Bartonella bacilliformis
Brucella species

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

Escherichia coli
Klebsiella species
Enterobacter aerogenes
Shigella species
Acinetobacter species (formerly Mima species and Herellea species)
Bacteroides species

Gram-positive Bacteria

Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracycline, culture and susceptibility testing are recommended. Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organisms have been demonstrated to be susceptible.

Streptococcus pyogenes
Streptococcus pneumoniae
Enterococcus group (Streptococcus faecalis and Streptococcus faecium)
Alpha-hemolytic Streptococci (viridans group)

Other microorganisms

Chlamydia psittaci
Chlamydia trachomatis
Ureaplasma urealyticum
Borrelia recurrentis
Treponema pallidum
Treponema pertenue
Clostridia species
Fusobacterium fusiforme
Actinomyces species
Bacillus anthraxis
Propionibacterium acnes
Entamoeba species
Balantidium coli

Susceptibility Testing

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, Ref4) (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 *Enterobacteriaceae, Acinetobacter* species, *Staphylococcus* spp., *Enterococcus* spp., and *Vibrio cholerae*:

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

For testing *Streptococcus* spp. Beta-hemolytic group:

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

These interpretive standards are applicable to broth microdilution susceptibility testing using cation-adjusted Mueller-Hinton broth with 2.5 to 5% lysed horse blood and agar microdilution susceptibility testing using Mueller-Hinton agar with 5% sheep blood.

For testing *Haemophilus influenzae*:

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

These interpretive standards are applicable only to broth microdilution susceptibility testing using *Haemophilus* Test Medium.

For testing *Streptococcus pneumoniae*:

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

These interpretive standards are applicable only to broth microdilution susceptibility testing using cation-adjusted Mueller-Hinton broth with 2.5 to 5% lysed horse blood. -

For testing *Neisseria gonorrhoeae*:

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

These interpretative standards are applicable only to agar dilution susceptibility testing using GC agar base and 1% defined growth supplement.

For testing *Bacillus anthracis* and *Brucella* spp.:

MIC (mcg/mL)	Interpretation
≤ 1	Susceptible (S)
-	Intermediate (I)
-	Resistant (R)

For testing *Burkholderia malleii, Burkholderia pseudomallei,* and *Yersinia pestis*:

MIC (mcg/mL)	Interpretation
< 4	Susceptible (S)
8	Intermediate (I)
> 8	Resistant (R)

For testing *Franciscella tularensis*:

MIC (mcg/mL)	Interpretation
≤ 4	Susceptible (S)
-	Intermediate (I)
-	Resistant (R)

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 (mcg/mL)
Escherichia coli ATCC 25922	0.5 to 2
Enterococcus faecalis ATCC 29212	8 to 32
Staphylococcus aureus ATCC 29213	0.12 to 1
Pseudomonas aeruginosa ATCC 27853	8 to 32
Haemophilus influenzae ATCC 49247	4 to 32
Streptococcus pneumoniae ATCC 49619	0.06 to 0.5
Neisseria gonorrhoeae ATCC 49226	0.25 to 1

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, Ref4), uses paper disks impregnated with 30 mcg tetracycline to test the susceptibility of microorganisms to tetracycline.

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

For testing *Enterobacteriaceae, Acinetobacter* spp. and *Vibrio cholera*:

Zone Diameter (mm)	Interpretation	MIC (mcg/mL)
≥ 15	Susceptible (S)	≤ 4
12 to 14	Intermediate (I)	-
≤ 11	Resistant (R)	≥ 16

For testing *Staphylococcus* spp. and *Enterococcus* spp.

Zone Diameter (mm)	Interpretation	MIC (mcg/mL)
≥ 19	Susceptible (S)	≤ 4
15 to 18	Intermediate (I)	-
≤ 14	Resistant (R)	≥ 16

For testing *Haemophilus influenzae*:

Zone Diameter (mm)	Interpretation	MIC (mcg/mL)
≥ 29	Susceptible (S)	≤ 2
26 to 28	Intermediate (I)	-
≤ 25	Resistant (R)	≥ 8

These zone diameter standards are applicable only to susceptibility testing with *Haemophilus* species using *Haemophilus* Test Medium and a 30 mcg tetracycline disk.

For testing *Neisseria gonorrhoeae*:

Zone Diameter (mm)	Interpretation	MIC (mcg/mL)
≥ 38	Susceptible (S)	≤ 0.25
31 to 37	Intermediate (I)	-
≤ 30	Resistant (R)	≥ 2

These interpretative standards are applicable only to disk diffusion testing using GC agar and 1% growth supplement, and a 30 mcg tetracycline disk.

For testing *Streptococcus pneumoniae*:

Zone Diameter (mm)	Interpretation	MIC (mcg/mL)
≥ 23	Susceptible (S)	≤ 2
19 to 22	Intermediate (I)	-
≤ 18	Resistant (R)	≥ 8

These interpretative standards are applicable only to disk diffusion testing using Mueller-Hinton agar adjusted with 5% sheep blood and a 30 mcg tetracycline disk.

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 mcg tetracycline disk should provide the following zone diameters in these laboratory test quality control strains:

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

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of tetracycline hydrochloride capsules USP and other antibacterial drugs, tetracycline hydrochloride capsules USP 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.

Tetracycline hydrochloride USP is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

- Upper respiratory tract infections caused by *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Hemophilus influenzae*. Note: Tetracycline should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.
- Lower respiratory tract infections caused by *Streptococcus pyogenes*, *Streptococcus pneumoniae, Mycoplasma pneumoniae* (Eaton agent, and *Klebsiella* sp.)
- Skin and soft tissue infections caused by *Streptococcus pyogenes*, *Staphylococcus aureaus*. (Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infections.)
- Infections caused by rickettsia including Rocky Mountain spotted fever, typhus group infections, Q fever, rickettsialpox.
- Psittacosis or ornithosis caused by *Chlamydia Psittaci*.
- Infections caused by *Chlamydia trachomatis* such as uncomplicated urethral, endocervical or rectal infections, inclusion conjunctivitis, trachoma, and lymphogranuloma venereum.
- Granuloma inquinale caused by *Calymmatobacterium granulomatis*.
- Relapsing fever caused by *Borrelia* sp.
- Bartonellosis caused by Bartonella *bacilliformis*.
- Chancroid caused by *Hemophilus ducreyi*.
- Tularemia caused by *Francisella tularensis*.
- Plaque caused by *Yersinia pestis*.
- Cholera caused by *Vibrio cholerae*.
- Brucellosis caused by *Brucella* species (tetracycline may be used in conjunction with an aminoglycoside).
- Infections due to *Campylobacter fetus*.
- As adjunctive therapy in intestinal amebiasis caused by *Entamoeba histolytica*.
- Urinary tract infections caused by susceptible strains of *Escherichia coli*, *Klebsiella*, etc.
- Other infections caused by susceptible gram-negative organisms such as *E. coli, Enterobacter* aerogenes, Shigella sp., Acinetobacter sp., *Klebsiella* sp., and *Bacteroides* sp.
- In severe acne, adjunctive therapy with tetracycline may be useful.

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

- Syphilis and yaws caused by *Treponema pallidum* and *pertenue*, respectively,
- Vincent's infection caused by *Fusobacterium fusiforme*,
- Infections caused by *Neisseria gonorrhoeae*,
- Anthrax caused by *Bacillus anthracis*,
- Infections due to *Listeria monocytogenes*,
- Actinomycosis caused by *Actinomyces* species,
- Infections due to *Clostridium* species.

CONTRAINDICATIONS

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

WARNINGS

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 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 fibula growth rate has been observed in premature 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. If this drug 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. Tetracycline drugs should not be used during pregnancy unless absolutely necessary.

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. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs. Treatment should be discontinued at the first evidence of skin erythema.

Rev. D 4/2013

TETRACYCLINE HYDROCHLORIDE CAPSULES USP
For Oral Use
℞ only

2416
2407

The antianabolic 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 renal function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia and acidosis.

PRECAUTIONS

General

As with other antibiotics, 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.

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

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

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

Prescribing tetracycline in the absence of 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

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

Laboratory Tests

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

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

Drug Interactions

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

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

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

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

Concurrent use of tetracycline may render oral contraceptives less effective.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies are currently being conducted to determine whether tetracycline hydrochloride has carcinogenic potential.

Some related antibiotics (oxytetracycline, minocycline) have shown evidence of oncogenic activity in rats. In two *in vitro* mammalian cell assay systems (L 51784y mouse lymphoma and Chinese hamster lung cells), there was evidence of mutagenicity at tetracycline hydrochloride concentrations of 60 and 10 mcg/mL, respectively.

Tetracycline hydrochloride had no effect on fertility when administered in the diet to male and female rats at a daily intake of 25 times the human dose.

Pregnancy

Teratogenic Effects

Pregnancy Category D

(See **WARNINGS**.)

Nonteratogenic Effects

(See **WARNINGS**.)

Pregnant women with renal disease may be more prone to develop tetracycline-associated liver failure.

Labor and Delivery

The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers

Because of the potential for serious adverse reaction in nursing infants from tetracyclines, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother (see **WARNINGS**).

Pediatric Use

See **WARNINGS** and **DOSAGE AND ADMINISTRATION**.

ADVERSE REACTIONS

Gastrointestinal: anorexia, nausea, epigastric distress, vomiting, diarrhea, glossitis, black hairy tongue, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region.

Rare instances of esophagitis and esophageal ulceration have been reported in patients receiving particularly the capsule and also the tablet forms of tetracyclines.

Most of the patients were reported to have taken medication immediately before going to bed (see **DOSAGE AND ADMINISTRATION**).

Teeth: permanent discoloration of teeth may be caused during tooth development. Enamel hypoplasia has also been reported (see **WARNINGS**).

Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Onycholysis and discoloration of the nails have been reported rarely. Photosensitivity is discussed in **WARNINGS**.

Renal toxicity: rise in BUN has been reported and is apparently dose related.

Liver: hepatotoxicity and liver failure have been observed in patients receiving large doses of tetracycline and in tetracycline-treated patients with renal impairment.

Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, and serum sickness-like reactions, as fever, rash, and arthralgia.

Blood: hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, neutropenia and eosinophilia have been reported.

Other: bulging fontanels in infants and intracranial pressure in adults (see **PRECAUTIONS, General**).

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.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Tetracycline is not dialyzable.

DOSAGE AND ADMINISTRATION

Adults

Usual daily dose, 1 gram as 500 mg b.i.d. or 250 mg q.i.d. Higher doses such as 500 mg q.i.d. may be required for severe infections or for those infections which do not respond to the smaller doses.

Children above eight years of age

Usual daily dose, 10 to 20 mg/lb (25 to 50 mg/kg) body weight divided in four equal doses.

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

For treatment of brucellosis, 500 mg tetracycline q.i.d. for three weeks should be accompanied by streptomycin, 1 gram intramuscularly twice daily the first week and once daily the second week.

For the treatment of syphilis in patients allergic to penicillin, the following dosage of tetracycline is recommended: early syphilis (less than one year's duration), 500 mg q.i.d. for 15 days. Syphilis of more than one year's duration (except neurosyphilis), 500 mg q.i.d. for 30 days.

For treatment of gonorrhea, the recommended dose is 500 mg by mouth four times a day for seven days.

In cases of moderate to severe acne which, in the judgement of the clinician, require long-term treatment, the recommended initial dosage is 1 gram daily in divided doses. When improvement is noted, dosage should be gradually reduced to maintenance levels ranging from 125 mg to 500 mg daily. In some patients it may be possible to maintain adequate remission of lesions with alternate-day or intermittent therapy. Tetracycline therapy of acne should augment the other standard measures known to be of value. Duration of long-term treatment which can safely be recommended has not been established (see **WARNINGS** and **Carcinogenesis**, **Mutagenesis, Impairment of Fertility**).

Concomitant therapy

Absorption of tetracycline is impaired by antacids containing aluminum, calcium or magnesium and preparations containing iron, zinc, or sodium bicarbonate.

Food and some dairy products also interfere with absorption.

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

In patients with renal impairment (see **WARNINGS**): total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

Uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis:* 500 mg, by mouth, four times a day for at least seven days.

Administration of adequate amounts of fluid with the capsule formulation of tetracycline is recommended to wash down the drug and reduce the risk of esophageal irritation and ulceration (see **ADVERSE REACTIONS**).

HOW SUPPLIED

Tetracycline Hydrochloride Capsules USP, 250 mg are available as orange opaque and yellow opaque capsules, imprinted with "Z" and "2416" in black ink, containing 250 mg of tetracycline hydrochloride, packaged in bottles of 100 and 1000 capsules, and unit-dose boxes of 100 capsules.

Tetracycline Hydrochloride Capsules USP, 500 mg are available as black and yellow capsules, imprinted with "Z" and "2407" in white ink, containing 500 mg of tetracycline hydrochloride, packaged in bottles of 100 and 1000 capsules, and unit-dose boxes of 100 capsules.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

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

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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, minocycline, 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 accomplished 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

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Ninth Edition.* CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition.* CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

3. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline – Second Edition.* CLSI document M45-A, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2010.

4. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard - Eight Edition.* CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087 USA, 2012.

5. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-third Informational Supplement.* CLSI document M100-S23. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. D 4/2013