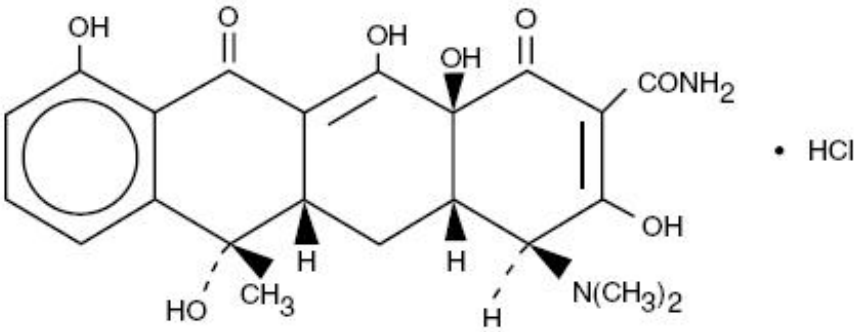
TETRACYCLINE HYDROCHLORIDE- tetracycline hydrochloride capsule
Bryant Ranch Prepack

TETRACYCLINE HYDROCHLORIDE CAPSULES USP

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-naphthacenecarboxamide monohydrochloride. Its structural formula is as follows:



$C_{22}H_{24}N_2O_8$•HCl M.W. 480.90

Each capsule, for oral administration, contains 250 mg or 500 mg tetracycline hydrochloride. In addition, each capsule contains the following inactive ingredients: colloidal silicon dioxide, pregelatinized starch and stearic acid. The inactive ingredients for the gelatin capsules include: (250 mg) FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide; (500 mg): FD&C Blue No. 1, FD&C Red No. 40, D&C Yellow No. 10, and titanium dioxide.

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

A tetracycline disk may be used to determine microbial susceptibility to drugs in the tetracycline class. If the Kirby-Bauer method of disk susceptibility testing is used, a 30 mcg tetracycline disk should give a zone of at least 19 mm when tested against a tetracycline susceptible bacterial strain. Microorganisms may be considered susceptible if the MIC (minimum inhibitory concentration) is not more than 4 mcg/mL and intermediate if the MIC is 4 to 12.5 mcg/mL.

INDICATIONS AND USAGE

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 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 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.

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 Iymphoma 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 Carcinogenicity, Mutagenicity, 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**).

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 HCI and tetracycline HCI 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.

TEVA PHARMACEUTICALS USA

Sellersville, PA 18960

Rev. A 6/2009

Tetracycline HCL 250mg Capsule

TETRACYCLINE HYDROCHLORIDE

tetracycline hydrochloride capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:63629-1501(NDC:0172-2416)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TETRACYCLINE HYDROCHLORIDE (TETRACYCLINE)	TETRACYCLINE HYDROCHLORIDE	250 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE	
STARCH, CORN	

STEARIC ACID	
FD&C YELLOW NO. 6	
D&C YELLOW NO. 10	
TITANIUM DIOXIDE	

Product Characteristics

Color	ORANGE (orange opaque)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	2416
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-1501-1	20 in 1 BOTTLE		
2	NDC:63629-1501-2	40 in 1 BOTTLE		
3	NDC:63629-1501-3	60 in 1 BOTTLE		
4	NDC:63629-1501-4	30 in 1 BOTTLE		
5	NDC:63629-1501-5	28 in 1 BOTTLE		
6	NDC:63629-1501-6	112 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA060704	03/23/2010	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-1501), RELABEL(63629-1501)