PT. PFIZER INDONESIA
Local Product Document

Generic Name: Oxytetracycline
Trade Name: Terramycin
CDS Effective Date: September 07, 2011
Supersedes: January 14, 2010

DESCRIPTION

Oxytetracycline is a product of the metabolism of *Streptomyces rimosus* and is one of the family of tetracycline antibiotics. A 1% solution in water is acidic (pH about 2 .5). Its potency is affected in solutions more acid than pH 2 and it is rapidly destroyed by alkali hydroxides.

Oxytetracycline is chemically designated as 4-(Dimethylamino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 5, 6, 10, 12, 12a-hexahydroxy-6-methyl-1, 11-dioxo-2-naphthacenecarboxamide and has a molecular formula of $C_{22}H_{24}N_2O_9$.

Terramycin available form, Terramycin IM solution 10 ml as (50 mg/ml).

ACTIONS

Oxytetracycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Oxytetracycline 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;

Oxytetracycline and its salts are readily absorbed orally and are 10-40% bound to plasma proteins. Between 40 and 70% is excreted unchanged in the urine via glomerular filtration. A serum half-life of 6-10 hours has been reported for oxytetracycline in patients with normal renal function.

Oxytetracycline diffuses readily through the placenta into the fetal circulation, into the pleural fluid and, under some circumstances, into the cerebrospinal fluid. It appears to be concentrated in the hepatic system and excreted in the bile, so that it appears in the feces, as well as in the urine, in a biologically active form.

INDICATIONS

Oxytetracycline is indicated in infections caused by the following microorganisms:
Rickettsiae (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers).

Mycoplasma pneumoniae (PPLO, Eaton Agent),
Chlamydia psittaci (formerly agents of psittacosis and ornithosis),
Chlamydia trachomatis (formerly agents of lymphogranuloma venereum),
Calymmatobacterium (Donovania) *granulomatis* (formerly agents of granuloma inguinale),
The spirochetal agent of relapsing fever (*Borrelia recurrentis*).

The following gram-negative microorganisms:
Neisseria gonorrhoeae,
Haemophilus ducreyi (chancroid),
Yersinia pestis (formerly *Pasteurella pestis*),
Francisella tularensis (formerly *Pasteurella tularensis*),
Bartonella bacilliformis,
Bacteroides species,
Vibrio cholerae (formerly *Vibrio comma*),
Campylobacter fetus (formerly *Vibrio fetus*),
Brucella species (in conjunction with streptomycin).

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

Oxytetracycline 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 (formerly *Aerobacter aerogenes*),
Shigella species,
Acinetobacter species (formerly *Mima* species and *Herellea* species),
Haemophilus influenzae (respiratory infections),
Klebsiella species (respiratory and urinary tract infections).

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

Streptococcus pneumoniae (formerly *Diplococcus pneumoniae*),
Staphylococcus aureus (skin and soft tissue infections).

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

Treponema pallidum and *Treponema pertenue* (syphilis and yaws),
Listeria monocytogenes,
Clostridium species,
Bacillus anthracis,

Leptotrichia buccalis (formerly *Fusobacterium fusiforme*) (Vincent's infection), *Actinomyces* species.

In acne vulgaris and rosacea, oxytetracycline capsule is useful in long term treatment.

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

Tetracyclines are indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis may be treated with oral tetracyclines or with a combination of oral and topical agents.

CONTRAINDICATIONS

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

Oxytetracycline is contraindicated 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.

WARNINGS

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 circumstances, 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. Persons apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs.

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

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.

When the treating physician considers the need for intensive treatment outweighs its potential dangers (mostly during pregnancy or in individuals, with known or suspected renal or liver impairment), it is advisable to perform renal and liver function tests before and during therapy. Also, tetracycline serum concentration should be followed.

Depending on the formulation, TERRAMYCIN preconstituted intramuscular solution contains sodium formaldehyde sulfoxylate that upon oxidation can form a sulfite, which may possibly result in or aggravate anaphylactoid reactions, or TERRAMYCIN preconstituted intramuscular contains sodium metabisulfite, a sulfite which may possibly result in or aggravate anaphylactoid reactions.

Usage in Newborns, Infants and Children

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 the fibula growth rate has been observed in prematures given oral tetracyclines in dosages of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

PRECAUTIONS

As with other antibiotic preparations, TERRAMYCIN may result in overgrowth of nonsusceptible organisms, including fungi. If super infection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including oxytetracycline, 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.

In venereal diseases when coexistent syphilis is suspected, a dark field examination should be performed 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 studies should be performed.

All infections due to Group A beta-hemolytic streptococci should be treated for at least 10 days.

Fertility, pregnancy and lactation

Use in Pregnancy

Oxytetracycline has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgement of the physician, the potential benefit outweights the risk.

Result of animal studies with the tetracycline families of antimicrobials 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.

In the presence of renal dysfunction, particularly in pregnancy, intravenous tetracycline therapy in daily dosages exceeding the maximum recommended adult dose of two grams has been associated with deaths through liver failure.

A possible association between oral tetracycline exposure during pregnancy and the following events have been reported in population-based case studies and retrospective reviews: neural tube defects and cardiovascular defects (second months of gestation); posterior cleft palate (third and fourth months of gestation).

Lactation

Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in breastfeeding infants, oxytetracycline should be used only when in the opinion of the physician, potential benefit outweighs potential risk.

All tetracyclines including oxytetracycline forms 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 dosages of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

DRUG INTERACTION

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.

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

The concurrent use of tetracycline may render oral contraceptives less effective.

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

ADVERSE REACTIONS

The most frequently reported adverse reactions to TERRAMYCIN Intramuscular therapy are pain on injection, which is reported to occur in less than 7% of patient and erythema which is reported to occur in less than 3% of patients. The intramuscular injection should be deep, with care not to injure the sciatic nerve nor inject intravascularly.

Blood and Lymphatic System Disorders: Haemolytic anaemia, Thrombocytopenia, Neutropenia, Eosinophilia.
Immune System Disorders: Hypersensitivity, Anaphylactic reaction.
Metabolism and Nutrition Disorders: Decreased appetite.
Nervous System Disorders: Fontanelle bulging, Benign intracranial hypertension.
Cardiac Disorders: Pericarditis.
Vascular Disorders: Thrombophlebitis.
Gastrointestinal Disorders: Anorexia, Nausea, Vomiting, Diarrhoea, Glossitis, Enamel hypoplasia (see Warning), Dysphagia, Enterocolitis, Tooth discolouration, Anal inflammation, inflammatory lesions (with monilial overgrowth) in the anogenital region.
These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule forms of drugs in the tetracycline class. Most of these patients took medications immediately before going to bed.

Skin and Subcutaneous Tissue Disorders: Erythema, Urticaria, Angioedema, Anaphylaxis Henoch-Schonlein purpura, Rash maculopapular , Rash erythematous , Dermatitis exfoliative, Photosensitivity reactionMusculoskeletal and connective tissue disorders: Systemic lupus erythematosus.
Congenital, Familial/Genetic Disorders: Tooth hypoplasia.
General Disorders and Administration Site Conditions: Injection site pain, Injection site irritation.
Investigations: Blood urea increased.

DOSAGE AND ADMINISTRATION

TERRAMYCIN Intramuscular:

TERRAMYCIN Intramuscular may be used to initiate therapy when assurance of sustained therapeutic levels is required or in patients in whom oral administration of the antibiotic is not

feasible because of dysphagia, nausea, gastrointestinal intolerance, unconsciousness, lack of cooperation, traumatic or surgical wounds of the gastrointestinal tract or intestinal obstruction.

The intramuscular administration of oxytetracycline produces lower blood levels than oral administration in the recommended dosages. Patients placed on intramuscular oxytetracycline should be changed to the oral dosage form as soon as possible. If rapid, high blood levels are needed, oxytetracycline should be administered intravenously.

Adults: For mild or moderately severe infections, 200 or 300 mg daily given single 100 mg doses every 8 to 12 hours, or as a single daily dose of 250mg. In severe infections, 300 to 500 mg daily, injected in single 100 mg doses every 6 to 8 hours or single 250mg doses every 12 hours.

Children above eight years of age: 15-25 mg/kg body weight, not to exceed the maximum adult dose. Dosage may be divided and given every 8 to 12 hours intervals.

As with all intramuscular preparations, TERRAMYCIN Intramuscular should be injected well within the body of a relative large muscle such as in the upper quadrant of the buttock or the lateral thigh Care should always be taken in selecting the site of administration to avoid injecting into a major nerve To avoid the possibility of radial nerve injury, injections should not be made into the lower or middle thirds of the upper arm. A clean needle free from material deposited on the outside should be attempted before injection to avoid inadvertent administration into a blood vessel. Injections sites should be alternated for each succeeding treatment.

OVERDOSE

There have been no cases of overdosage reported with the use of intramuscular oxytetracycline. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of oxytetracycline on the ability to drive or operate heavy machinery has not been studied. There is no evidence to suggest that oxytetracycline may affect these abilities.

SUPPLY

TERRAMYCIN available form as 50mg/ml
Terramycin IM Solution 10 ml, box of 10 multidose vials, Reg. No. DKL7219809043A1

Store in dry place at temperature below 30^{o}C.

HARUS DENGAN RESEP DOKTER

Manufactured by PT. Pfizer Indonesia, Jakarta