

CTD MODULE 1
ADMINISTRATIVE INFORMATION AND
PRODUCT INFORMATION

Product Name :	TETRAREN CAPSULES (Tetracycline Hydrochloride 250mg)
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1.5 Product Information: TETRAREN CAPSULES

1.5.1 Prescribing information (Summary of products characteristics):

1. Name of the Medicinal Product: TETRAREN CAPSULES

Strength:

Each hard gelatin capsule contains Tetracycline Hydrochloride BP 250mg

Pharmaceutical form: Capsules

2. Qualitative and Quantitative composition:

Qualitative composition:

Sr. No.	Ingredient	Specification	Uses
1	Tetracycline HCl	BP	Active
2	Maize starch	BP	Disintegrant
3	Colloidal silicone Dioxide	BP	Glidant
4	Purified Talc	BP	Smoothing agent
5	Magnesium Stearate	BP	Lubricant
6	EHG Capsules (Tetraren)	IH	Vehicle

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Quantitative composition:

Sr. No.	Ingredient	Specification	Quantity mg per Capsule
1	Tetracycline HCl	BP	250.000
2	Maize starch	BP	77.000
3	Colloidal silicone Dioxide	BP	1.000
4	Purified Talc	BP	10.000
5	Magnesium Stearate	BP	2.000
6	EHG Capsules (Tetraren)	IH	1 Unit

3.Pharmaceutical form: Capsules

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4. Clinical particular's:

4.1 Therapeutic indication:

Tetracycline is a bacteriostatic broad-spectrum antibiotic, active against a wide variety of Gram-positive and Gram-negative organisms.

Infections caused by tetracycline-sensitive organisms include:

- 1) Respiratory tract infections: Pneumonia and other lower respiratory tract infections due to susceptible strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and other organisms. *Mycoplasma pneumoniae pneumoniae*. Treatment of chronic bronchitis (including the prophylaxis of acute exacerbations) and whooping cough.
- 2) Urinary tract infections: Caused by susceptible strains of the *Klebsiella* species. *Enterobacter* species, *Escherichia coli*, *Streptococcus faecalis* and other organisms.
- 3) Sexually transmitted diseases: Infections due to *Chlamydia trachomatis* including uncomplicated urethral, endocervical or rectal infections. Non- gonococcal urethritis caused by *Ureaplasma urealyticum*. Tetracycline is also indicated in chancroid, granuloma inguinale and lymphogranuloma venereum. Tetracycline is an alternative drug in the treatment of penicillin resistant gonorrhoea and syphilis.
- 4) Skin Infections: *Acne vulgaris* when antibiotic therapy is considered necessary and severe rosacea.
- 5) Ophthalmic infections: Trachoma, although the infectious agent, as judged by immunofluorescence, is not always eliminated. Inclusion conjunctivitis may be treated with oral tetracycline alone or in combination with topical agents.
- 6) Rickettsial infections: Rocky Mountain spotted fever, typhus group, Q fever and *Coxiella endocarditis* and tick fevers.
- 7) Other infections: Stagnant loop syndrome. Psittacosis, brucellosis (in combination with streptomycin), cholera, bubonic plague, louse and tick-borne relapsing fever, tularaemia, glanders, melioidosis and acute intestinal amoebiasis (as an adjunct to amoebicides).

Tetracycline is an alternative drug in the treatment of leptospirosis, gas- gangrene and tetanus.

4.2 Posology and method of administration:

Posology

Tetracycline should be given one hour before or two hours after meals, since food and some dairy products interfere with absorption. The tablets should be taken with a good drink of water. Therapy should be continued for up to three days after symptoms have subsided.

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

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Adults (including the elderly) and children over 12 years: The minimum recommended dosage is 250mg every six hours. Therapeutic levels are attained more rapidly by the administration of 500mg initially, followed by 250mg every six hours. For severe infections, the dosage may be increased to 500mg every six hours.

Children under 12 years: Contraindicated in this age group.

Elderly: Usual adult dose. Caution should be observed as subclinical renal insufficiency may lead to drug accumulation.

Renal impairment: In general tetracyclines are contraindicated in renal impairment and the dosing recommendations only apply if use of this class of drug is deemed absolutely essential. Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

Dosage recommendations in specific infections:

Skin infections: 250-500mg daily in single or divided doses should be administered for at least three months in the treatment of acne vulgaris and severe rosacea.

Streptococcal infections: A therapeutic dose of tetracycline should be administered for at least 10 days.

Brucellosis: 500mg tetracycline four times daily accompanied by streptomycin.

Sexually transmitted diseases: 500mg four times daily for seven days is recommended in the following infections: Uncomplicated gonococcal infections (except anorectal infections in man); uncomplicated urethral, endocervical or rectal infection caused by Chlamydia trachomatis; non- gonococcal urethritis caused by Ureaplasma urealyticum. Acute epididymo- orchitis caused by Chlamydia trachomatis, or Neisseria gonorrhoea, 500mg four times daily for 10 days. Primary and secondary syphilis: 500mg four times daily for 15 days. Syphilis of more than one year's duration, (latent syphilis of uncertain or more than one year's duration, cardiovascular or late benign syphilis) except neurosyphilis, should be treated with 500mg, four times daily for 30 days. Patient compliance with this regimen may be difficult so care should be taken to encourage optimal compliance. Close follow-up including laboratory tests, is recommended.

Method of Administration: Oral route.

4.3 Contraindication:

Known hypersensitivity to any of the tetracyclines or any of the other constituents in the formulation; chronic renal/hepatic dysfunction; renal impairment, particularly if severe; in systemic lupus erythematosus; children under 12 years, pregnancy and breastfeeding women.

Tetracycline 250 mg Coated Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactase malabsorption should not take this medicine.

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Tetracycline 250 mg Coated Tablets contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Benign intracranial hypertension has been reported following the concomitant use of tetracyclines and Vitamin A or retinoids and therefore concurrent use should be contraindicated.

4.4 Special warning and precaution for use:

Tetracyclines depress plasma prothrombin activity; therefore reduced dosages of concurrent anticoagulants may be required.

- Tetracycline drugs may cause permanent tooth discolouration (yellow-grey- brown), if administered during tooth development, in the last half of pregnancy and in infancy up to twelve years of age (see sections 4.3, 4.6 and 4.8). Enamel hypoplasia has also been reported. This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses.
- The anti-anabolic action of 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 azotaemia, hyperphosphataemia and acidosis.
- When treating venereal disease, where co-existent syphilis is suspected, proper diagnostic procedures should be utilised. In all such cases, monthly serological tests should be made for at least four months.
- The use of antibiotics may occasionally result in the overgrowth of nonsusceptible organisms including *Candida* (see section 4.8). Constant observation of the patients is essential. If a resistant organism appears, the antibiotic should be discontinued and appropriate therapy instituted.
- Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment (including several weeks after treatment) with Tetracycline tablets, may be symptomatic of *Clostridium difficile*- associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis (see section 4.8). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with Tetracycline tablets. If CDAD is suspected or confirmed Tetracycline tablets should be stopped immediately and appropriate therapy initiated without delay. Anti-peristaltic drugs are contraindicated in this clinical situation.
- In longterm therapy, periodic laboratory evaluation of organ systems, including haematopoietic, renal and hepatic studies should be performed.
- High doses of tetracyclines have been associated with a syndrome involving fatty liver degeneration and pancreatitis.

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- The use of tetracycline in general is contraindicated in renal impairment due to excessive systemic accumulation. They should not be used with penicillins and they should not be discontinued if supra-infection occurs.
- Tetracyclines should also be used with caution in patients with hepatic impairment or those receiving drugs which may have hepatotoxic effects; high doses should be avoided.
- Photosensitivity reactions may occur in hypersensitive persons and such patients should be warned to avoid direct exposure to natural or artificial sunlight and to discontinue therapy at the first sign of skin discomfort.
 - SLE (systemic lupus erythematosus) can be exacerbated by the use of tetracyclines.
 - Care is advised when administered to patients with myasthenia gravis.
 - Tetracycline 250mg Coated Tablets contains Sunset yellow FCF (E110) which may cause allergic reactions.

4.5 Interactions with other medicinal products and other forms of interactions:

- The absorption of tetracycline from the gastrointestinal tract is impaired by the concomitant administration of di and trivalent cations such as iron, calcium, aluminium, magnesium, bismuth and zinc salts. Administration of medicinal products containing these cations and tetracycline should be maximally separated by at least two to three hours. The following should be avoided when taking tetracycline: antacids, bismuth containing ulcer-healing drugs, drugs such as quinapril tablets which contain magnesium carbonate and didanosine which contains calcium and magnesium excipients.
- Absorption of tetracycline is impaired by food, milk, and milk products.
- Since tetracycline has been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require a downward adjustment of their anticoagulant dosage. Tetracycline may prolong the action of coumarin anticoagulants.
- Plasma-atovaquone concentration is reduced by tetracycline.
- There is a possible increased risk of benign intracranial hypertension with tetracyclines and retinoids (acitretin, isotretinoin, tretinoin). Concomitant use should be avoided.
- Antidiarrhoeal preparations such as kaolin-pectin and bismuth subsalicylate hinder absorption of tetracyclines.
- Combination of tetracyclines with diuretics may be detrimental to renal function and may aggravate nephrotoxicity by volume depletion.
- Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.
- A few cases of pregnancy or breakthrough bleeding have been attributed to the concurrent use of tetracycline with oral contraceptives and alternative contraceptive advice should be sought where necessary.
- There have been reports of nephrotoxicity (increased blood urea nitrogen and serum creatinine) and death in some cases when tetracycline therapy has been combined with methoxyflurane.

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- Tetracycline may increase the hypoglycaemic effects of insulin and sulphonylureas in patients with diabetes mellitus.
- The absorption of tetracycline may be reduced by the concomitant administration of sucralfate. Separating administration should be considered.
- Tetracycline may cause an increase in serum lithium levels.
- Tetracycline may cause an increase in serum digoxin levels.
- Tetracycline may cause an increase the risk of methotrexate toxicity. Regular monitoring of toxicity is necessary when taken concurrently.
- Absorption of tetracycline is impaired by strontium ranelate (manufacturer of strontium ranelate advises avoid concomitant use).
- Absorption of tetracycline is possibly reduced by colestipol and colestyramine.
- Increased risk of ergotism when tetracycline given with ergotamine and methysergide.

Additional information on special populations:

Not Applicable

4.6 Fertility, pregnancy and lactation:

Tetracycline may be deposited in deciduous and permanent teeth giving permanent discolouration. It should not be used during pregnancy or lactation. Not to be used in pregnancy unless essential to the patient's welfare. Tetracyclines cross the placenta and may have toxic effects on foetal tissues, particularly on skeletal development. The use of tetracycline compounds during pregnancy has been associated with reports of maternal liver toxicity. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the foetus. Tetracyclines are also excreted in breast milk and are therefore contraindicated in nursing mothers.

Use in newborns, infants and children: 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 25mg/kg every 6 hours. This reaction was reversed when drug was discontinued.

4.7 Effects on ability to drive and use machines:

None known.

4.8 Undesirable effects:

Infections and infestations:

Frequency not known: overgrowth of resistant organisms (Candida albicans, in particular); this may cause glossitis, stomatitis, pseudomembranous colitis (Clostridium

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difficile overgrowth), enterocolitis (caused by resistant staphylococci), rectal and vaginal irritation, inflammatory lesions (with candidial overgrowth) in the anogenital regions.

Blood and lymphatic system disorders:

Rare: haemolytic anaemia, thrombocytopenia, neutropenia, eosinophilia, agranulocytosis, aplastic anaemia.

Immune system disorders:

Frequency not known: hypersensitivity reactions including Stevens-Johnson syndrome, angioedema, toxic epidermal necrolysis, urticaria, anaphylaxis, anaphylactoid purpura, pericarditis, and exacerbation of systemic lupus erythematosus, fixed drug eruptions, exfoliative dermatitis.

Endocrine disorders:

Frequency not known: brown-black microscopic discolouration of thyroid tissue. No abnormalities of thyroid function are known to occur.

Nervous system disorders:

Frequency not known: headache.

Eye disorders:

Frequency not known: visual disturbances, permanent visual loss.

Vascular disorders:

Frequency not known: bulging fontanelles in infants; benign intracranial hypertension in juveniles and adults. Presenting features were headache, dizziness, tinnitus and visual disturbances including blurring of vision, scotomata and diplopia. Permanent visual loss has been reported. Treatment should cease if evidence of raised intracranial pressure develops.

Gastrointestinal disorders:

Rare: dysphagia, oesophagitis and oesophageal ulceration (most of these patients took medication immediately before going to bed or with inadequate fluids).

Frequency not known: gastrointestinal irritations, nausea, abdominal discomfort, vomiting, diarrhoea, anorexia, pancreatitis, permanent tooth discolouration and enamel hypoplasia in children. Tooth discolouration has also been seen in adults. If gastric irritation occurs, tablets should be taken with food.

Hepatobiliary disorders:

Rare: transient increases in liver function tests, hepatitis, jaundice, hepatic failure.

Frequency not known: hepatotoxicity associated with fatty liver.

Skin and subcutaneous tissue disorders:

Frequency not known: erythematous and maculo-papular rashes, photosensitivity (Patients exposed to direct sunlight or ultraviolet light should be advised to discontinue treatment if any skin reaction occurs), pruritis, bullous dermatoses, skin discolouration.

Musculoskeletal, connective tissue and bone disorders:

Frequency not known: increased muscle weakness in patients with myasthenia gravis.

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Renal & urinary disorders:

Rare: acute renal failure, nephritis.

Frequency not known: raised serum urea, renal dysfunction, especially in patients with pre-existing renal impairment.

4.9 Overdose and Treatment:

Symptoms

- There may be nausea and vomiting.
- Crystalluria and haematuria may occur following very large doses.
- Hypersensitivity reactions may occur.

Treatment

There is no specific antidote.

- Gastric decontamination is not normally necessary.
- Give oral fluids for severe vomiting and diarrhoea if required.
- Manage anaphylaxis reactions conventionally.
- Single brief convulsions do not require treatment. If frequent or prolonged control with intravenous diazepam or lorazepam.
- General symptomatic therapy as indicated by the patient's clinical condition.

5. Pharmacological Properties:

5.1 Pharmacodynamic properties:-

Tetracycline hydrochloride is a broad-spectrum bacteriostatic antibiotic.

Tetracyclines are taken up into sensitive bacterial cells by an active transport process. Once within the cell they bind reversibly to the 30S subunit of the ribosome, preventing the binding of aminoacyl transfer RNA and inhibiting protein synthesis and hence cell growth. Although tetracyclines also inhibit protein synthesis in mammalian cells they are not actively taken up, permitting selective effects on the infecting organism.

5.2 Pharmacokinetic properties:

Most tetracyclines are incompletely absorbed from the gastrointestinal tract, about 60-80% of a dose of tetracycline usually being available. The degree of absorption is diminished by the presence of divalent and trivalent metal ions with which tetracyclines form stable insoluble complexes and to a variable degree by milk or food. Formulation with phosphate may enhance the absorption of tetracycline.

Plasma concentrations will depend upon the degree of absorption. Administration of tetracycline 500mg every 6 hours generally produces steady-state concentrations of 4-5µg/ml. Peak plasma concentrations occur about 1-3 hours after ingestion. Higher

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concentrations can be achieved after intravenous administration; concentrations may be higher in women than in men.

In the circulation 20-65% of tetracycline is bound to plasma proteins.

They are widely distributed throughout the body tissues and fluids. Concentrations in cerebrospinal fluid are relatively low, but may be raised if the meninges are inflamed.

Small amounts appear in saliva, and the fluids of the eye and lung. Tetracyclines appear in the milk of nursing mothers where concentrations may be 60% or more of those in the plasma. They diffuse across the placenta and appear in the foetal circulation in concentrations of about 25 to 75% of those in the maternal blood. Tetracyclines are retained at sites of new bone formation and recent calcification and in developing teeth. The tetracyclines have been classified in terms of their duration of action in the body, although the divisions appear to overlap somewhat.

The tetracyclines are excreted in the urine and in the faeces. Renal clearance is by glomerular filtration. Up to 55% of a dose is eliminated unchanged in the urine; concentrations in the urine of up to 300µg/ml of tetracycline may be reached two hours after a usual dose is taken and be maintained for up to 12 hours. Urinary excretion is increased if urine is alkalinised. The tetracyclines are excreted in the bile where concentrations 5-25 times those in plasma can occur. Since there is some enterohepatic reabsorption complete elimination is slow. Considerable quantities occur in the faeces after administration.

5.3 Preclinical safety data:

Not applicable.

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6. Pharmaceutical Particulars:

6.1 List of excipients

Tetraren Capsules contains the following excipients:

Colloidal silicon dioxide, Maize starch, Purified talc and Magnesium stearate.

6.2 Incompatibilities

None known

6.3 Shelf life

24 months

6.4 Special precaution for storage

Store in cool & dry place. Below 25°C.

6.5 Nature and contents of container

10 Capsules are packed in Aluminium/PVC blister; such ten blisters are packed in a unit carton along with literature insert.

6.6 Special precautions for disposal

No special precaution.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES:

Marketing Authorization Holder:

Rene Industries Ltd

Address : PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

Manufactured by:

Rene Industries Ltd

Address : PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

8. MARKETING AUTHORISATION NUMBER:

Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION:

Not Applicable

10. DATE OF REVISION OF THE TEXT:

Not Applicable

11. DOSIMETRY (IF APPLICABLE):

Not Applicable

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12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
(IF APPLICABLE):

Not Applicable