MODULE 1 – ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed.

MODULE 1 – ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1. Name of drug product

Tetracycline Capsule B.P 250 mg

1.1 (Trade) name of product

Auscel Tetracycline Capsule

1.2 Strength

Tetracycline HCL B.P 250 mg

Composition:

Each capsule contains

Tetracycline Hydrochloride B.P 250 mg

1.3 Pharmaceutical Dosage Form

Capsules

2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Composition:

Each capsule contains

Tetracycline Hydrochloride B.P 250 mg

2.2 Quantitative Declaration

Batch Formula:

Batch Size: 100000 Capsules

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Approved Name	Specification	Label Claim	Quantity / capsule in mg	Quantity/Batch Kg
Tetracycline HCl BP	BP	250.00 mg	250 mg	25.20 kg
Lactose B.P	BP	-	20 mg	2.00 kg
Cornstarch powder B.P	BP	-	20 mg	2.00 kg
Cornstarch paste B.P	BP	-	27 mg	2.70 kg
Gelatin B.P	BP	-	10 mg	1.00 kg
Magnesium stearate B.P	IHS	-	1 mg	0.10 kg
Aerosil BP	BP	-	0.5 mg	0.05 kg
Methyl paraben B.P	BP	-	0.24 mg	0.024kg
Propyl paraben B.P	BP	-	0.12 mg	0.012kg
Deionized water	BP	-	-	qs

* Extra starch added to compensate LOD .

3. PHARMACEUTICAL DOSAGE FORM

Capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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* pneumonia. 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

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

4.3 Contraindications

- Hypersensitivity to the active substance, any of the tetracyclines or to any of the excipients listed in section 6.1.
- Chronic renal/hepatic dysfunction;
- Renal impairment, particularly if severe;
- Systemic lupus erythematosus;
- Children under 12 years (see sections 4.4, 4.6 and 4.8);
- Pregnancy and breastfeeding women.
- 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 Warnings and Precautions for Use

• 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 non susceptible 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 long term 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.

• The use of tetracycline in general is contraindicated in renal impairment due to excessive systemic accumulation and 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.

4.5 Interaction with other medicinal products and other forms of interaction

• 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.

• 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.

• Tetracycline may increase the hypoglycaemic effects of insulin and sulfonylureas 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.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

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, (see sections 4.3, 4.4 and 4.8).

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.

<u>Breast-feeding</u>

Tetracyclines are also excreted in breast milk and are therefore contraindicated in nursing mothers.

<u>Use in newborns, infants and children:</u>

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

The following convention has been utilised for the classification of frequency. Very common (≥ 1/10); common(≥ 1/100 and < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10,000 and < 1/1000); very rare (< 1/10,000); Frequency not known (cannot be estimated from the available data).

Infections and infestations:

Frequency not known: overgrowth of resistant organisms (Candida albicans, in particular); this may cause glossitis, stomatitis, pseudomembranous colitis (Clostridium difficile overgrowth), enterocolitis (caused by resistant staphylococci), rectal and vaginal irritation, inflammatory lesions (with candidial overgrowth) in the anogenital regions (see section 4.4)

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 (see sections 4.3 and 4.8), 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 (see section 4.3). Presenting features were headache, dizziness, tinnitus and visual disturbances including blurring of vision, scotomata and diplopia. 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)

Frequency not known: gastrointestinal irritations, nausea, abdominal discomfort, vomiting, diarrhoea, anorexia, pancreatitis, permanent tooth discolouration and enamel hypoplasia in children (see sections 4.3, 4.4 and 4.6). 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 (see section 4.4).

Renal & urinary disorders:

Rare: acute renal failure, nephritis.

4.9 Overdose

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 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

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5.1 Pharmacodynemic property

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tetracycline hydrochloride is a broad-spectrum bacteriostatic antibiotic.

ATC code: D06AA04

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

<u>Absorption</u>

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

<u>Distribution</u>

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.

<u>Elimination</u>

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 Pre-clinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:

Lactose

Corn starch powder

Gelatin

Magnesium Stearate

Aerosil

Methyl Paraben

Propyl Paraben

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

3 years

6.3 Special Precautions for Storage

Do not store above 25°C.

6.4 Nature and Contents of Container

Blister strips formed from 25μm aluminium foil and 250μm thick opaque PVC/PVdC foil

Blister packs of 10 and 1000 capsules.

Not all pack sizes may be marketed.

7. Marketing authorisation holder

Auscel Laboratories Ltd.

Plot.40799, Shinco Road,

Mai-Adiko Jos, Plateau State.

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8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation

10. Date of revision of the text