SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tetracycline Tablets BP 250mg

2 Qualitative and Quantitative Composition

Each tablet contains 250mg Tetracycline Hydrochloride PhEur.

Excipients with known effect:
Sunset yellow FCF aluminium lake (E110)
Croscarmellose sodium (1.28mg sodium content from croscarmellose sodium per tablet)Sodium lauryl sulfate (0.08mg sodium content from sodium lauryl sulfate per tablet)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Orange film-coated tablets
Orange, circular, biconvex film-coated tablets, impressed “C” on one face and the identifying letters “TE” on the reverse.

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
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.
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.

B*rucellosis:* 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
For oral administration.

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 (see section 4.5 and 4.8).

4.4 Special warnings and precautions 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.
- 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.

Excipients

Sunset yellow
Tetracycline tablets contain sunset yellow (E110), which can cause allergic - type reactions.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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.
- 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.
- 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

Pregnancy
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, (see sections 4.3, 4.4 and 4.8).
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.

Breast-feeding
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

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

Infections and infestations:
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:

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

Nervous system disorders:
Not known: headache.

Eye disorders:
Not known: visual disturbances, permanent visual loss.

Vascular disorders:
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. 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)
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.
Not known: hepatotoxicity associated with fatty liver.

Skin and subcutaneous tissue disorders:
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 disorders:
Not known: increased muscle weakness in patients with myasthenia gravis (see section 4.4).

Renal & urinary disorders:
Rare: acute renal failure, nephritis.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

5.1 Pharmacodynamic properties

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

ATC code: J01AA07

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.

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for tetracycline and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

5.2 Pharmacokinetic properties

Absorption
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.

Distribution
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.

Elimination
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

None stated

6 PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

The tablet contains:

Sodium lauryl sulfate
Hydroxypropylcellulose (E463)
Colloidal silicon dioxide
Croscarmellose sodium
Magnesium stearate

The coating contains:

Methylhydroxypropylcellulose (E464)
Propylene glycol
Purified talc (E553)
Sunset yellow FCF aluminium lake (E110)
Titanium dioxide (E171)
Erythrosine (E127)

6.2. Incompatibilities

None known.

6.3. Shelf Life

36 months.

6.4. Special Precautions for Storage

Do not store above 25°C. Keep container tightly closed (polypropylene containers). Store in the original package (blisters).

6.5. Nature and Contents of Container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps.

The product may also be supplied in blister packs in cartons:
a) Carton: Printed carton manufactured from white folding box board.
b) Blister pack: (i) 250 µm white rigid PVC. (ii) Surface printed 20 µm hard temper aluminium foil with 5-7 g/M^2 PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack sizes: 7's, 10's, 14's, 21's, 28's, 30's, 50's, 56's, 60's, 84's, 100's, 112's, 250's, 500's and 1000's.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for temporary storage of the finished product before final packaging into the proposed marketing containers.
Pack size: 50000 (maximum)

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8. MARKETING AUTHORIZATION NUMBER

PL 00142/0373

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

25/10/1994

10 DATE OF REVISION OF THE TEXT

19/11/2024