

Name of Medicine

Tetralysal

Presentation

Yellow and red hard gelatin capsules containing lymecycline equivalent to 300mg tetracycline base.

Uses

Actions

ATC code: J01AA04

Tetracyclines provide bacteriostatic action at the available plasma and tissue concentrations and are effective against intracellular and extracellular organisms. Their mechanism of action is based on an inhibition of ribosomal protein synthesis. Tetracyclines block the access of the bacterial aminoacyl-tRNA to the mRNA-ribosome complex by binding to the 30S subunit of the ribosome, thus preventing the addition of amino acids to the growing peptide chain in protein synthesis. When given at therapeutically attainable concentrations their toxic effect is limited to the bacterial cells.

The exact mechanisms by which tetracyclines reduce lesions of acne vulgaris have not been fully elucidated; however, the effect appears to result in part from the antibacterial activity of the drugs. Following oral administration, the drugs inhibit the growth of susceptible organisms (mainly *Propionibacterium acnes*) on the surface of the skin and reduce the concentration of free fatty acids in sebum. The reduction in free fatty acids in sebum may be an indirect result of the inhibition of lipase-producing organisms which convert triglycerides into free fatty acids or may be a direct result of interference with lipase production in these organisms. Free fatty acids are comedogenic and are believed to be a possible cause of the inflammatory lesions, e.g. papules, pustules, nodules, cysts, of acne. However, other mechanisms also appear to be involved because clinical improvement of acne vulgaris with oral tetracycline therapy does not necessarily correspond with a reduction in the bacterial flora of the skin or a decrease in the free fatty acid content of sebum.

Mechanism of resistance

Tetracycline resistance in propionibacteria is usually associated with a single point mutation within the gene encoding 16S rRNA. Clinical isolates resistant to tetracycline were found to have cytosine instead of guanine at a position cognate with *Escherichia coli* base 1058. There is no evidence that ribosome mutations can be transferred between different strains or species of propionibacteria, or between propionibacteria and other skin commensals.

Resistance to the tetracyclines is associated with mobile resistance determinants in both staphylococci and coryneform bacteria. These determinants are potentially transmissible between different species and even different genera of bacteria.

In all three genera, cross-resistance with the macrolide-lincosamide-streptogramin group of antibiotics cannot be ruled out.

Strains of propionibacteria resistant to the hydrophilic tetracyclines are cross-resistant to doxycycline and may or may not show reduced susceptibility to minocycline.

Breakpoints

For tetracycline resistance in anaerobic and most aerobic bacteria, the breakpoints as set by the NCCLS are:

Susceptible MIC < 4 mg/L
 Intermediate MIC 8 mg/L
 Resistant MIC > 16 mg/L

In cutaneous propionibacteria, mutational resistance is associated with MICs of tetracycline > 2mg/L.

Susceptibility table

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Susceptibility to tetracyclines of species relevant to the approved indication

<i>Commonly susceptible species</i>
Gram-positive aerobes
None of relevance
Gram-negative aerobes
<i>None of relevance</i>
Anaerobes
Propionibacterium acnes (<i>clinical isolates</i>)*
Other
None of relevance
<i>Species for which acquired resistance may be a problem (defined as >10% resistant within any European country)</i>
Gram-positive aerobes
<i>S. aureus</i> (methicillin susceptible)
<i>S. aureus</i> (methicillin resistant) +
Coagulase-negative staphylococci (methicillin susceptible)
Coagulase-negative staphylococci (methicillin resistant) +
<i>Corynebacterium</i> spp

Species for which acquired resistance may be a problem (defined as >10% resistant within any European country)
Gram-negative aerobes
None of relevance
Anaerobes
Propionibacterium acnes (<i>isolates from acne</i>)* +
Other (microaerophile)
None of relevance
Inherently resistant species
None of relevance

However, even if resistance to cutaneous propionibacteria is detected, this does not automatically translate into therapeutic failure, since the anti-inflammatory activity of the tetracyclines is not compromised by resistance in the target bacteria.

Pharmacokinetics

Lymecycline is more readily absorbed from the gastro-intestinal tract than tetracycline, with a peak serum concentration of approximately 2mg/L after 3 hours following a 300 mg dose. In addition, similar blood concentrations are achieved with small doses. When the dose is doubled an almost correspondingly higher blood concentration has been reported to occur.

The serum half-life of lymecycline is approximately 10 hours.

Indications

Tetralysal is a broad spectrum antibiotic and is recommended for the treatment of all infections caused by tetracycline sensitive organisms and may be utilised in all conditions where tetracycline therapy is indicated. In common with other tetracyclines it is indicated in penicillin-sensitive patients for the treatment of staphylococcal infections.

Typical infections include: Ear, nose and throat infections; Acute and chronic bronchitis (including prophylaxis); Infections of the gastrointestinal and urinary tracts; Non-gonococcal urethritis of chlamydial origin; and other chlamydial infections such as trachoma; acne; rickettsial fevers; soft tissue infections.

Dosage and Administration

Adults

One capsule morning or night with or without milk or food. If higher doses are required 3-4 capsules of 300 mg may be given over 24 hours. Lower doses may be given for prophylaxis and for the treatment of recalcitrant acne; in such cases

treatment should be continued for at least eight weeks. In the management of sexually transmitted diseases both partners should be treated.

Children

Tetralysal should not be administered to children under the age of 8 years.

Contraindications

Hypersensitivity to lymecycline or any other tetracycline or to any of the excipients.

Tetracyclines are selectively absorbed by developing bones and teeth and may cause dental staining and enamel hypoplasia. In addition these compounds readily cross the placental barrier and therefore Tetralysal should not be administered to pregnant women or children below the age of 8 years. As Tetralysal is mainly excreted by the kidneys it should not be administered to patients with overt renal insufficiency.

Warnings and Precautions

Prolonged use of broad spectrum antibiotics may result in the appearance of resistant organisms and superinfection.

Care should be exercised in administering tetracyclines to patients with hepatic impairment. Tetracyclines may cause photosensitivity reactions; however, very rare cases have been reported with lymecycline.

May cause exacerbation of systemic lupus erythematosus. Can cause weak neuromuscular blockade so should be used with caution in Myasthenia Gravis.

Use in Pregnancy and Lactation

Tetracyclines are selectively absorbed by developing bones and teeth and may cause dental staining and enamel hypoplasia. In addition these compounds readily cross the placental barrier and therefore Tetralysal 300 should not be given to pregnant or lactating women.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed

Adverse Effects

The most frequently reported adverse events with Tetralysal are gastrointestinal disorders of nausea, abdominal pain, diarrhoea and nervous system disorder of headache. The most serious adverse events reported with Tetralysal are Stevens Johnson syndrome, anaphylactic reaction, angioneurotic oedema and intracranial hypertension.

System Organ Class	Frequency	Adverse Reaction
Blood and lymphatic system disorders	Unknown	Neutropenia Thrombocytopenia
Eye disorders	Unknown	Visual disturbance
Gastrointestinal disorders	Common	Nausea

	(≥1/100 and <1/10)	Abdominal pain Diarrhoea
	Unknown	Epigastralgia Glossitis Vomiting Enterocolitis
General disorders and administration site conditions	Unknown	Pyrexia
Hepatobiliary disorders	Unknown	Jaundice
Immune system disorder	Unknown	Anaphylactic reaction Hypersensitivity Urticaria Angioneurotic oedema
Investigations	Unknown	Transaminases increased Blood alkaline phosphatase increased Blood bilirubin increased
Nervous system disorders	Common (≥1/100 and <1/10)	Headache
	Unknown	Dizziness Intracranial hypertension
Skin and subcutaneous tissues disorders	Unknown	Erythematous rash Photosensitivity Pruritus Stevens Johnson syndrome

General tetracyclines adverse events:

Benign intracranial hypertension and bulging fontanelles in infants were reported with tetracyclines with possible symptoms of headaches, visual disturbances including blurring of vision, scotomata, diplopia or permanent visual loss.

The following adverse effects were reported with tetracyclines in general and may occur with Tetralysal: dysphagia, oesophagitis, oesophageal ulceration, pancreatitis, teeth discolouration, hepatitis, hepatic failure. Dental dyschromia and/or enamel hypoplasia may occur if the product is administered in children younger than 8 years of age

As with all antibiotics overgrowth of non-susceptible organisms may cause candidiasis, pseudomembranous colitis (Clostridium Difficile overgrowth), glossitis, stomatitis, vaginitis or staphylococcal enterocolitis.

Interactions

The absorption of tetracyclines may be affected by the simultaneous administration of calcium, aluminium, magnesium, bismuth and zinc salts, antacids, Bismuth containing ulcer-healing medicines, iron preparations and quinapril. Unlike earlier tetracyclines, absorption of Tetralysal 300 is not significantly impaired by moderate amounts of milk.

Concomitant use of oral retinoids should be avoided as this may increase the risk of benign intracranial hypertension. An increase in the effects of anticoagulants may occur with tetracyclines. Concomitant use of diuretics should be avoided.

Although not reported for Tetralysal 300, a few cases of pregnancy or breakthrough bleeding have been attributed to the concurrent use of tetracycline or oxytetracycline with oral contraceptives.

Overdosage

There is no specific treatment but gastric lavage should be performed as soon as possible. Supportive measures should be instituted as required and a high fluid intake maintained.

Pharmaceutical Precautions

Tetralysal 300mg should be stored at or below 25°C protected from light.

Medicine Classification

Prescription Medicine.

Package Quantities

Capsule, 300mg, 28's.

Further Information

Excipients

Magnesium stearate
Colloidal hydrated silica

The capsule shells contain:

gelatin
titanium dioxide (E171)
erythrosine (E127)
quinoline yellow (E104)
indigotine (E132)

Preclinical safety data

No specific information is presented given the vast experience gained with the use of tetracyclines in humans over the last forty years.

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