# New Zealand Datasheet

## 1 PRODUCT NAME
TETRALYSAL

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Lymecycline capsules 300 mg

## 3 PHARMACEUTICAL FORM
Yellow and red hard gelatin capsules containing lymecycline equivalent to 300mg tetracycline base.

## 4 CLINICAL PARTICULARS
### 4.1 Therapeutic 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.

### 4.2 Dose and method of administration
**Adults**
One capsule morning or night with or without milk or food. The usual recommended dose for indications other than acne in the adult is 600 mg/day. Lower doses may be given for prophylaxis and for the treatment of recalcitrant acne; The recommended dose for acne is 300 mg/day. The usual duration of treatment is 12 weeks In the management of sexually transmitted diseases both partners should be treated.

It should be taken with an adequate amount of fluid in order to reduce the risk of esophageal irritation and ulceration (see section 4.4).

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

### 4.3 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.

Tetralysal should not be used concurrently with oral retinoids (see Interactions).

### 4.4 Special warnings and precautions for use

Solid dosage forms of the tetracyclines may cause oesophageal irritation and ulceration. To avoid oesophageal irritation and ulceration, adequate fluids (water) should be taken with this medicinal product (see section 4.2).

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 renal or hepatic impairment. Overdosage could result in hepatotoxicity.

Tetracyclines may cause photosensitivity reactions; however, very rare cases have been reported with lymecycline. It is recommended to avoid exposure to direct sunlight and ultraviolet light during the treatment which should be discontinued if erythematous cutaneous manifestations occur.

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

The use of expired tetracyclines can lead to renal tubular acidosis (Pseudo-Fanconi syndrome) readily reversible when treatment is discontinued altogether.
Treatment should cease if any evidence of raised intracranial pressure develop during treatment with Tetralysal.

## 4.5 Interaction with other medicines and other forms of interaction

The absorption of tetracyclines may be affected by the simultaneous administration of iron preparations and antacids, magnesium/aluminium and calcium, , hydroxides, oxides, salts, and activated charcoal, cholestyramine, bismuth chelates and sucralfate may decrease cycline absorption.
Medicinal products which increase gastric pH may reduce the absorption of tetracyclines. Enzyme inducers such as barbiturates, carbamazepine, phenytoin may accelerate the decomposition of tetracycline due to enzyme induction in the liver thereby decreasing its half-life. Consequently, a minimum of 2-hour gap is necessary between the two treatments.

Unlike earlier tetracyclines, absorption of Tetralysal 300 is not significantly impaired by moderate amounts of milk.

Concomitant use of oral retinoids and Vitamin A (above 10 000 IU/day) should be avoided as this may increase the risk of benign intracranial hypertension.

An increase in the effects of coumarin-type anticoagulants may occur with tetracyclines.

Bacteriostatic medicinal products including lymecycline may interfere with the bacteriocidal action of penicillin and beta-lactam antibiotics. It is advisable that tetracycline-class drugs and penicillin should not therefore be used in combination.

Laboratory tests: Lymecycline could cause false-positive urine glucose determinations. It could also interfere with fluorometric determinations of urine catecholamines resulting in falsely increased values (Hingerty's method).

Tetracyclines and methoxyflurane used in combination have been reported to result in fatal renal toxicity.

Didanosine: the digestive absorption of cyclines is decreased due to the increase of the gastric pH by the association of an anti-acid in the DDI tablet.

## 4.6 Fertility, 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 are distributed into milk. Therefore Tetralysal 300 mg should not be given to pregnant or lactating women (risk of enamel hypoplasia or dental dyschromia in the infant).

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable 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<br>Thrombocytopenia |
| Eye disorders | Unknown | Visual disturbance |
| Gastrointestinal disorders | Common (≥1/100 and <1/10) | Nausea<br>Abdominal pain<br>Diarrhoea |
| | Unknown | Epigastralgia<br>Glossitis<br>Vomiting<br>Enterocolitis |
| General disorders and administration site conditions | Unknown | Pyrexia |
| Hepatobiliary disorders | Unknown | Jaundice<br>Hepatitis |
| Immune system disorder | Unknown | Anaphylactic reaction<br>Hypersensitivity<br>Urticaria<br>Angioneurotic oedema |
| Investigations | Unknown | Transaminases increased<br>Blood alkaline phosphatase increased<br>Blood bilirubin increased |
| Nervous system disorders | Common (≥1/100 and <1/10) | Headache |
| | Unknown | Dizziness<br>Intracranial hypertension |
| Skin and subcutaneus tissues disorders | Unknown | Erythematous rash<br>PhotosensitivityPruritus<br>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. Treatment should cease if any evidence of raised intracranial pressure develop during treatment with Tetralysal.

The following adverse effects were reported with tetracyclines in general and may occur with Tetralysal: teeth discolouration, haemolytic anaemia, eosinophilia and other hematologic disorders. Dental dyschromia and/or enamel hypoplasia may occur if the product is administered in children younger than 8 years of age

Extra-renal hyperazotemia linked to an anti-anabolic effect which may be intensified by the association with diuretics has been reported with tetracycline therapy.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

## 4.9 Overdose

Acute overdosage is rare with antibiotics and 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.

In case of overdose, immediately contact the Poisons Information Centre for advice, in New Zealand, call 0800 764 766.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tetracyclines. 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

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

## 5.2 Pharmacokinetic properties

Absorption: Absorption is rapid, effective plasma levels are reached within the first hour following drug intake.

The peak plasma level is reached within 3 to 4 hours after oral administration. Concurrent milk intake has not been shown to significantly modify the absorption of lymecycline.

Distribution: Oral administration of 300 mg, in the adult, gives rise to:

- a peak plasma level of 1.6 to 4 µg/ml,
- a highly variable residual concentration (0.29 to 2.19 µg/ml),
- a plasma half-life of approximately 10 hours.

Repeated administration results in a steady mean plasma concentration between 2.3 and 5.8 µg/ml. Wide intra- and extra-cellular diffusion, under normal dosage conditions, results in effective concentrations in most body tissues and fluids, and notably in the lungs, bones, muscles, liver, bladder, prostate, bile and urine.

Excretion/elimination: The product is principally excreted in urine and secondarily in the bile. About 65% of the administered dose are eliminated within 48 hours.

## 5.3 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.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Magnesium stearate
Colloidal hydrated silica

The capsule shells contain:
gelatin
titanium dioxide (E171)
erythrosine (E127)
quinoline yellow (E104)
indigotine (E132)

### 6.2 Incompatibilities
Not applicable

### 6.3 Shelf life
36 months.

### 6.4 Special precautions for storage
Tetralysal 300mg should be stored at or below 25°C protected from light.

### 6.5 Nature and contents of container
PE/Al blister packs of 28 capsules.

### 6.6 Special precautions for use or disposal
No special requirements.

## 7 MEDICINE SCHEDULE
Prescription Medicine.

## 8 SPONSOR
Sponsor and distributor in New Zealand
Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand
Ph (09) 918 5100
Fax (09) 918 5101

For:
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Suite 4, 13B Narabang Way,
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## 9 DATE OF FIRST APPROVAL
6 April 1973

## 10 DATE OF REVISION OF THE TEXT
19 November 2018

# SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| 8.0 | Correction of sponsor details |