SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tetralysal 300mg Hard Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 408mg of Lymecycline equivalent to 300mg tetracycline base

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard capsule
Hard gelatin capsule, red cap and yellow body

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tetralysal is indicated for the treatment of infections caused by tetracycline sensitive organisms (please see section 4.4 and 5.1) including the following:

- Acne
- Ear, nose and throat infections
- Acute exacerbation of chronic bronchitis
- Gastro-intestinal infection
- Urinary tract infection
- Non-gonococcal urethritis
- Trachoma
- Rickettsial fever
- Soft tissue infection

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Adults:
The usual dosage for the chronic treatment of acne is 1 capsule daily (300 mg/day): treatment should be continued for at least 8 weeks.
For other infections, the usual dosage is 1 capsule b.d. (600 mg/day). If higher doses are required, 3-4 capsules (900-1200 mg) may be given over 24 hours. Lower doses may be given for prophylaxis.
In the management of sexually transmitted disease both partners should be treated.

Elderly:
As for other tetracyclines, no specific dose adjustment is required.

Paediatric population:

The safety and efficacy of Tetralysal in children aged under 12 years of age have not been established. No data are available.
For children over the age of 12 years, the adult dosage may be given.
For children under the age of 8 years, see section 4.3.

Methods of administration
The capsules should be taken with a glass of water in order to reduce the risk of oesophageal irritation and ulceration (see section Special warnings and precautions for use).

4.3 Contraindications

Hypersensitivity to the active substance or any other tetracycline or to any of the excipients listed in section 6.1.
Its use is contraindicated in patients with overt renal insufficiency and in children less than 8 years due to a risk of permanent dental staining and enamel hypoplasia.

Concurrent treatment with oral retinoids (see Interaction with other Medications).

4.4 Special warnings and precautions for use

Oesophageal irritation and ulceration
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 Posology and method of administration).

Caution should be exercised if the product is administered to patients with impaired renal or hepatic functions.

Hepatotoxicity
Overdosage could result in hepatotoxicity

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

Phototoxicity
Due to the risks of photosensitivity, it is recommended to avoid exposure to direct sunlight and ultraviolet light during the treatment which should be discontinued if erythematous cutaneous manifestations occur.

Expired medication
The use of expired tetracyclines can lead to renal tubular acidosis (Pseudo-Fanconi syndrome) readily reversible when treatment is discontinued altogether.

Systemic lupus erythematosus
May cause exacerbation of systemic lupus erythematosus.

Myasthenia Gravis
Can cause weak neuromuscular blockade so should be used with caution in Myasthenia Gravis.

Hepatic impairment
Care should be exercised in administering tetracyclines to patients with hepatic impairment.

Paediatric population
The product should not be used in children below 12 years of age due to the risk of permanent dental staining and enamel hypoplasia (see Contraindications).

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous administration of iron preparations and anti-acids, magnesium/aluminium and calcium hydroxides, oxides, salts, cholestyramine, bismuth chelates, sucralfate and quinapril may decrease cycline absorption. 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. These products should not be taken within two hours before or after taking Tetralysal 300.

Some adverse effects are reported with tetracycline therapy in general in case of combination with lithium; an interaction between lithium and the tetracycline class is a recognised interaction. A combination of lymecycline with lithium may cause an increase in serum lithium levels.

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 anticoagulants may occur with tetracyclines with an increased risk of haemorrhage. Concomitant use of diuretics should be avoided.

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.

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Tetracyclines are selectively absorbed by developing bones and teeth and may cause dental dyschromia and enamel hypoplasia (see section 4.3).

Pregnancy
Tetracyclines readily cross the placental barrier. Therefore, Tetralysal 300 should not be administered to pregnant women.

Breastfeeding
Tetracyclines are distributed into milk. Therefore, Tetralysal 300 should not be administrated to breast-feeding women (risk of enamel hypoplasia or dental dyschromia in the infant) (see section 4.3).

Fertility
No data on the effect on fertility is available.

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

Tabulated list of adverse reactions

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 (≥1/100 and <1/10)	Nausea Abdominal pain Diarrhoea
	Unknown	Epigastralgia Glossitis Vomiting Enterocolitis
General disorders and administration site conditions	Unknown	Pyrexia
Hepatobiliary disorders	Unknown	Jaundice Hepatitis
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 subcutaneus tissues disorders	Unknown	Erythematous rash Photosensitivity Pruritus Stevens Johnson syndrome
Psychiatric disorders,	Unknown	Depression Nightmare

Description of selected adverse reactions

*The manifestation of clinical symptoms, including vision disorders, or headache, must suggests the possibility of a cranial hypertension diagnosis. If increased intracranial pressure is suspected during treatment with Tetralysal, administration should be stopped.

Benign intracranial hypertension and bulging fontanelles in infants were reported with tetracyclines with possible symptoms of headaches, vomiting, 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, systemic lupus erythematosus, 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 staphyloccocal enterocolitis.

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
Acute overdosage is rare with antibiotics and there is no specific treatment.

Management
Supportive measure should be instituted as required and a high fluid intake maintained.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tetracyclines

ATC code: J01AA04

Mode of action
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 $\leq$ 4 mg/L
Intermediate	MIC 8 mg/L
Resistant	MIC $\geq$ 16 mg/L

In cutaneous propionibacteria, mutational resistance is associated with MICs of tetracycline $\geq$ 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 antiinflammatory activity of the tetracyclines is not compromised by resistance in the target bacteria.

5.2 Pharmacokinetic properties

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.

5.3. Pre-clinical 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) and indigotine (E132).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years (unopened)

6.4 Special precautions for storage

Aluminium and polyethylene strips: Do not store above 25ºC.
Store in the original container.
Aluminium-PVC/PVDC calendar blister strips: Do not store above 25ºC.
Keep container in the outer carton.

As with all medicines, Tetralysal 300 should be kept out of the sight and reach of children.

6.5 Nature and contents of container

Aluminium-PVC/PVDC calendar blister strips of 14 capsules; two strips per carton, pack size = 28 capsules or Aluminium and polyethylene strips 28 or 56 capsule pack size.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Galderma (U.K.) Limited,
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8. MARKETING AUTHORISATION NUMBER(S)

PL 10590/0019

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

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04/10/2022