# AUSTRALIAN PRODUCT INFORMATION

# AKAMIN®

*(minocycline hydrochloride dihydrate) tablet*

## 1 NAME OF THE MEDICINE

Minocycline hydrochloride dihydrate

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each AKAMIN 50 tablet contains minocycline hydrochloride dihydrate equivalent to 50 mg of minocycline as the active ingredient.

Excipients with known effect: sulfites and sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS**.**

## 3 PHARMACEUTICAL FORM

AKAMIN 50 tablets: Gold coloured, convex, film coated tablet 6mm in diameter, debossed with "MC" on one side and the greek alpha symbol on the other.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Infections due to the following organisms, provided that they have been shown by bacteriological testing to be susceptible to minocycline: *Escherichia coli; Enterobacter aerogenes; Haemophilus influenzae;* Klebsiella and Proteus.In addition, infections due to *Streptococcus pyogenes* (group A β-haemolytic) and *Streptococcus faecalis*, however, because a large proportion of these organisms are resistant to tetracyclines, minocycline should be used only if the organisms have definitely been shown to be sensitive.

Tetracyclines, including minocycline, are not the drugs of choice in the treatment of Staphylococcal infections. Minocycline may be considered for the treatment of such infections only if other suitable agents are not available and the organism has been shown to be sensitive to minocycline.

Minocycline may be used in the treatment of tetracycline resistant acne.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

The usual dosage of minocycline for adults is 200 mg initially followed by 100 mg every twelve hours.Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided.

In tetracycline resistant acne the dosage is 100 mg daily, given preferably as 50 mg twice daily.Most cases are likely to resolve within 3 months.

*Impaired Renal Function.*(see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

*Streptococcal Infections.*If tetracycline is used for streptococcal infections, therapeutic doses should be administered for at least 10 days.

### 4.3 CONTRAINDICATIONS

Hypersensitivity to any of the tetracyclines.Severe renal insufficiency.Systemic lupus erythematosus.

Rare cases of benign intracranial hypertension have been reported after tetracyclines and after vitamin A or retinoids such as isotretinoin or etretinate.Concomitant treatment of tetracyclines and vitamin A or retinoids

is therefore contraindicated (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with other antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi.If superinfection occurs, the antibiotic should be discontinued and appropriate therapy should be instituted.

### Discolouration of Teeth

The use of tetracyclines during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discolouration of the teeth (yellow-grey-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses.Enamel hypoplasia has also been reported. Tetracyclines also accumulate in the growing skeleton.Tetracycline drugs, therefore, should not be used in this age group, unless other drugs are unlikely to be effective or are contraindicated.

### Hyperpigmentation

Minocycline use has been associated with blue-black cutaneous hyperpigmentation.Most areas of the body may be affected, including the face.It has also been reported in nails, mucous membranes, hard palate and bone.The incidence varies but appears more likely to occur in patients with certain immunological conditions (rheumatoid arthritis, pemphigus and pemphigoid in particular), acne vulgaris and with prolonged use and/or higher doses.In many cases the cutaneous pigmentation is reversible or partially reversible on discontinuation of minocycline.Complete resolution may take several months or years.

### Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines.Patients prone to exposure to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

Patients should be advised to avoid direct sunlight or ultraviolet light exposure if possible. Some reports suggest that, compared with other tetracyclines, minocycline may be less likely to produce photosensitivity.

### Enterocolitis

The use of tetracyclines can cause severe enterocolitis due to resistant staphylococci.

### Colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including minocycline.A toxin produced with *Clostridium difficile* appears to be the primary cause.The severity of the colitis may range from mild to life threatening.It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy).Mild cases usually respond to drug discontinuation alone.However, in moderate to severe cases, appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered.Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

### Central Nervous System Effects

Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with minocycline therapy.Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy.These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

***Other CNS***

*Pseudotumour cerebri* (benign intracranial hypertension) in adults has been associated with the use of tetracyclines including minocycline.The usual clinical manifestations are headache and blurred vision.Bulging fontanelles have been associated with the use of tetracyclines in infants.While both of these conditions and related symptoms usually resolve soon after discontinuation of the tetracycline, the possibility for permanent sequelae exists.Headache (not related to *Pseudotumour cerebri*) has also been reported.Decreased hearing has been reported in patients on minocycline therapy.

## Anticoagulant Therapy

Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage, because tetracyclines have been shown to depress plasma prothrombin activity.In long-term therapy, periodic laboratory evaluation of organ systems, including haematopoietic, renal and hepatic studies, should be performed.

## Syphilis

In venereal diseases when coexistent syphilis is suspected, darkfield examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

## Staphylococcal Infection

Tetracycline is not the drug of choice in the treatment of any type of staphylococcal infection.

## Streptococcal Infection

If a tetracycline is used for the treatment of infections due to group A β-haemolytic streptococci (*S. pyogenes*) (see Section 4.1 THERAPEUTIC INDICATIONS), treatment should continue for 10 days.

## Use in Hepatic Impairment

***Hepatotoxicity.***Hepatotoxicity has been reported with minocycline, therefore, minocycline should be used with caution in patients with hepatic dysfunction and in conjunction with other hepatotoxic drugs.

## Use in Renal Impairment

If renal impairment exists, even usual doses may lead to excessive systemic accumulation of the drug and possible hepatic toxicity.As with all tetracyclines, (except doxycycline), minocycline should be avoided in patients with renal failure.

The antianabolic action of tetracyclines may cause an increase in serum urea.This effect may be enhanced by diuretics.

In patients with significantly impaired renal function, higher serum levels of tetracyclines may lead to azotaemia, hyperphosphatemia and acidosis.

## Use in the Elderly

No data available.

## Paediatric Use

(See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy about use during tooth development).All tetracyclines form a stable calcium complex in any bone forming tissue.A decrease in the fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every six hours.This reaction was shown to be reversible when the drug was discontinued.

## Effects on Laboratory Tests

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

### Anticoagulants

Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage, as tetracyclines have been shown to depress plasma prothrombin activity.

### Aluminium, Calcium, Magnesium, Iron

Antacids containing aluminium, calcium or magnesium and preparations containing iron impair absorption and should not be given to patients taking oral tetracycline.

### Etretinate and Isotretinoin

Administration of etretinate and isotretinoin should be avoided shortly before, during, and shortly after minocycline therapy.Each drug alone has been associated with *Psuedotumour cerebri* (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

### Methoxyflurane

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

### Food and Dairy

Food and dairy products do not appear to significantly influence the absorption of minocycline.

### Penicillin

It is advisable to avoid giving tetracyclines concomitantly with penicillin, as bacteriostatic drugs may interfere with the bactericidal action of penicillin.

### Oral Contraceptives

Reduced efficacy and increased incidence of breakthrough bleeding has been suggested with concomitant use of tetracycline and oral contraceptive preparations. Consideration should therefore be given to using an additional mechanical form of contraception whilst on AKAMIN therapy.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on Fertility

No data available.

### Use in Pregnancy (Category D)

Safe use in pregnancy has not been established.Tetracyclines are safe for use during the first 18 weeks of pregnancy after which they cause discolouration of the baby's teeth.These products should be avoided during the second and third trimesters of pregnancy.

*Australian categorisation definition of Category D.*Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.Accompanying texts should be consulted for further details.

### Use in Lactation

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse reactions profile of minocycline is generally similar to that of tetracyclines, except for a significantly higher incidence of vestibular adverse effects, e.g. dizziness, vertigo and ataxia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

***Gastrointestinal***

Anorexia, nausea, vomiting, diarrhoea, glossitis, dysphagia, enterocolitis, pancreatitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region.These reactions have been caused by both the oral and parenteral administration of tetracyclines.Oesophagitis and oesophageal ulceration have been reported rarely.

***Hepatic***

Increases in liver enzymes, hepatitis and acute liver failure have been reported.Autoimmune hepatitis with lupus-like symptoms and acute hypersensitivity hepatitis associated with eosinophilia and dermatitis have been reported rarely.

***Dermatological***

Maculopapular and erythematous rashes.Exfoliative dermatitis has been reported but is uncommon.Photosensitivity (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Lesions occurring on the glans penis have caused balanitis. Fixed drug eruptions, erythema multiforme and Stevens-Johnson Syndrome have been reported.Pigmentation of the skin and mucous membranes, as well as nail discolouration, have been reported (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

***Dental***

Discolouration of teeth (yellow-grey-brown) and/or enamel hypoplasia have been reported in infants and children to the age of 8 years.Tooth discolouration has also been reported in adults.

***Renal***

Rise in serum urea has been reported, and is apparently dose related (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Tetracyclines may aggravate pre-existing renal failure.Nephrotoxicity has also occurred in association with "acute fatty liver" related to the use of tetracycline in high doses.Degraded tetracycline may result in renal tubular damage and a "Fanconi-like" syndrome.Reversible acute renal failure has been reported.

***Hypersensitivity***

Urticaria, angioneurotic oedema, anaphylaxis, anaphylactoid purpura, pericarditis, polyarthralgia, pulmonary infiltrates with eosinophilia and exacerbation of systemic lupus erythrematosus have been reported.A reversible lupus-like syndrome has been reported.

***Haematological***

Agranulocytosis, haemolytic anaemia, thrombocytopenia, neutropenia and eosinophilia have been reported.

***Central Nervous System***

Convulsions, hypesthesia, dizziness, paresthesia, sedation, and vertigo.Bulging fontanelles in infants and benign intracranial hypertension (the usual clinical manifestations are headache and blurred vision) in adults have been reported.Decreased hearing and headache (not related to benign intracranial hypertension) have also been reported (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

***Other***

When given over prolonged periods, tetracyclines have been reported to produce brown/black microscopic discolouration of thyroid glands.No abnormalities of thyroid function studies are known to occur, but the potential for such an effect cannot be excluded.

### Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

## 4.9 OVERDOSE

Maximum dosage should not exceed 400 mg/day.

*Symptoms and Signs of Acute Overdosage.*May include nausea, vomiting, abdominal pain, hypotension, lethargy, coma, acidosis and azotaemia without a concomitant rise in creatinine.

*Treatment of Acute Overdose.*No specific antidote.General supportive care includes maintenance of clear airway, adequate respiration, circulation and renal function.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

### Mechanism of Action

Minocycline hydrochloride dihydrate is a semisynthetic derivative of the broad spectrum antibiotic, tetracycline.

***Microbiology***

Like other tetracyclines, minocycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by protein synthesis inhibition.

Minocycline is active against a wide range of Gram-negative and Gram-positive organisms.It is active against a proportion of *Staphylococcus aureus* organisms which are resistant to other tetracyclines.Except for this difference, it shares the antimicrobial spectra and cross resistance common to other tetracyclines.

Because many strains of the Gram-negative and Gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recommended.Resistance levels in an individual may also be influenced by previous antibiotic exposure.

***Microbiology, Susceptibility Tests***

*Dilution or Diffusion Techniques.*Either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS).Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated.This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used.This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major

discrepancies in interpretation.A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

### Clinical Trials

No data available.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

Following oral administration of a single minocycline 200 mg dose, mean peak plasma levels of approximately 4 microgram/mL were achieved in one to four hours.

With oral doses of 100 mg twice daily, it has been reported that steady state levels were achieved in approximately five days; mean peak serum levels were higher in women (3.4 microgram/mL) than in men (2.45 microgram/mL).

### Distribution

Minocycline is widely distributed in body tissues. Approximately 75% of the minocycline in plasma is protein bound.

### Metabolism

A number of metabolites of minocycline have been isolated from urine. Therefore, metabolism appears to be a significant mechanism of clearance of minocycline in contrast to other tetracycline derivatives.

The plasma half-life of minocycline is approximately 13 hours.

### Excretion

Less than 10% of the administered dose is excreted in the urine.Minocycline is excreted in the bile and undergoes enterohepatic circulation.Approximately 35% of an administered dose is excreted in the faeces.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

No data available.

### Carcinogenicity

No data available.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

lactose monohydrate, sodium starch glycollate, povidone, microcrystalline cellulose, sodium lauryl sulfate, magnesium stearate and Opadry Orange OY-23022 (ARTG PI No. 2215).

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

## 6.5 NATURE AND CONTENTS OF CONTAINER

Container type: HDPE bottle, PP screw cap.

### Australian Register of Therapeutic Goods (ARTG)

AUST R 70852 - AKAMIN 50 minocycline (as hydrochloride) 50mg tablet bottle

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

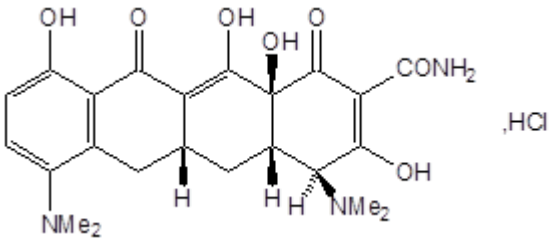
## 6.7 PHYSICOCHEMICAL PROPERTIES

Minocycline hydrochloride dihydrate is a yellow crystalline powder which is sparingly soluble in water, slightly soluble in alcohol. It dissolves in solutions of alkali hydroxides and carbonates.

### Chemical Structure

Chemical name : (4*S*,4a*S*,5a*R*,12a*S*)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide

Structural formula :




Molecular formula : $C_{23}H_{27}N_3O_7.HCl$

Molecular weight : 493.95

### CAS Number

13614-98-7

# 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

# 8 SPONSOR

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# 9 DATE OF FIRST APPROVAL

18/08/2005

# 10 DATE OF REVISION

29/04/2024

**Summary Table of Changes**

| Section Changed | Summary of New Information |
|---|---|
| **All** | Minor editorial changes |
| **3, 6.1** | Minor editorial changes to match ARTG details |
| **6.5** | Minor editorial change to update packaging details, added ARTG entry |
| **8** | Updated Sponsor details |



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