New Zealand Data Sheet

1. PRODUCT NAME
Minomycin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Minocycline hydrochloride 100 mg

3. PHARMACEUTICAL FORM
Orange body and purple cap, shell size 2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
In the treatment of a variety of infections due to susceptible Gram-positive and Gram-negative organisms. These infections include:

Respiratory tract infections: Laryngotracheitis, tracheobronchitis, bronchitis, bronchiolitis, bronchiectasis, bronchopneumonia, pneumonia (single lobe and multilobe), lung abscess.

Genitourinary tract infections: Pyelonephritis, cystitis, prostatitis, gonococcal urethritis, nonspecific urethritis.

Skin and soft tissue infections: Abscess, acne (including cystic and pustular types), cellulitis, infected dermatitis, folliculitis, furunculosis, impetigo, lymphadenitis, suppurative hydradenitis, paronychia, infected wounds.

Ear, nose and throat infections: Otitis media and externa, bacterial rhinitis, sinusitis, tonsillitis, pharyngitis.

Ophthalmological infections: Dacryocystitis, internal hordeolum associated with susceptible staphylococci, streptococci, *Escherichia coli,* Aerobacter strains and *Haemophilus influenzae.*

Tetracyclines including minocycline are not the substances of choice in the treatment of staphylococcal infection. Culture and sensitivity studies should be performed whenever feasible and should be done routinely in suspected streptococcal infections.

In cases of acute gonococcal urethritis where a primary or secondary lesion of syphilis is suspected, proper diagnostic procedures including darkfield examination should be followed. In all other cases where concomitant syphilis is suspected, serological tests should be made monthly for at least four months.

4.2 Dose and method of administration

The usual dosage of minocycline for adults is 200 mg initially, followed by 100 mg every 12 hours. Therapy should continue for at least 24 to 48 hours after symptoms have subsided.

To reduce the risk of oesophageal irritation and ulceration, the capsules should be swallowed whole with plenty of fluid, while sitting or standing and to remain sitting or standing for at least 30 minutes afterwards.

ADULTS
Acne vulgaris: 100 mg daily, given as a single dose or 50 mg twice daily. Duration of therapy varies depending upon response. Acne patients have been safely treated with minocycline for periods over 6 months.

Non-gonococcal urethritis: 100 mg daily for 10-14 days.

Gonorrhoea: Adult males: 200 mg initially followed by 100 mg every 12 hours for a minimum of 4 days with post-therapy cultures within 2-3 days. Adult females may require therapy for 10-14 days at the same dosage indicated for males.

Systemic infections: The usual dosage of minocycline is 100 mg every 12 hours.

Prophylaxis of asymptomatic meningococcal carriers: 100 mg bid for five days, usually followed by a course of rifampicin.

CHILDREN ABOVE TWELVE YEARS OF AGE
(See section 4.4 Special Warnings And Precautions For Use)

Usual paediatric dose: 4 mg/kg (maximum dose 200 mg) followed by 2 mg/kg (maximum dose 100 mg) every 12 hours. Use sufficient liquids when taking medicine to prevent oesophageal irritation.

ELDERLY PATIENTS
Minocycline may be used at the normal recommended dosage in elderly patients even with mild to moderate renal impairment.

PATIENTS WITH RENAL IMPAIRMENT
(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.

TREATMENT OF STREPTOCOCCAL INFECTIONS
A therapeutic dose of minocycline should be administered for at least 10 days.

TREATMENT OF GONOCOCCAL INFECTIONS
Gonorrhoea patients sensitive to penicillin may be treated with minocycline administered as 200 mg initially followed by 100 mg every 12 hours for a minimum of 4 days, with post-therapy cultures within 2-3 days. In the treatment of

uncomplicated gonococcal urethritis in men, 100 mg twice a day orally for 5 days is recommended. Adult females with acute gonococcal infections require more extended therapy.

4.3 Contraindications

Patients with a history of hypersensitivity to any of the tetracycline antibiotics.

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.

Pregnancy and lactation.

Children under 12 years of age.

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.

Use with caution in the following circumstances:

Use in Renal Impairment

If renal impairment exists, even usual oral doses may lead to excessive systemic accumulation of the substance and possible liver toxicity. As with all tetracyclines, other than doxycycline, minocycline should be avoided in patients with renal failure.

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

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

Discolouration of Teeth

The use of tetracyclines during tooth development (last half of pregnancy, infancy and childhood to the age of 12 years) may cause permanent discolouration of the teeth (yellow/grey/brown). This adverse reaction is more common during long term use but has been observed following repeated short term courses. Enamel hypoplasia has also been reported.

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 to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracyclines 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.

Central Nervous System (CNS) Effects
CNS side effects including lightheadedness, dizziness or vertigo have been reported. 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 always disappear rapidly when the substance 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 are 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.

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 by 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 C. 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.

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 (*Strep. pyogenes*) (see INDICATIONS), treatment should continue for 10 days.

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

Syphilis
In venereal disease 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.

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 Newborns, Infants and Children
(See section 4.4 Special Warnings And Precautions For Use, 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 prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the substance was discontinued.

4.5 Interaction with other medicines and other forms of interaction

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

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 Products
Absorption of minocycline does not appear to be notably influenced by food and dairy products.

Penicillin
Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with 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 Minocycline therapy.

4.6 Fertility, pregnancy and lactation

Fertility
Segment I (fertility and general reproduction) studies have shown that at a dose level more than 50 times the highest human therapeutic dose, minocycline impairs fertility in male rats. There were no effects on fertility or reproduction in female rats or male or female rabbits.

Pregnancy
Minocycline should not be used in pregnancy (see section 4.3 Contraindications).

Safe use in pregnancy has not been established. Results of animal studies indicated that tetracyclines cross the placenta and are found in foetal tissues and can have toxic effects on the developing foetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

The use of tetracycline class during tooth development (last half of pregnancy) may cause permanent discoloration of teeth. Tetracyclines have been found in milk of lactation women. Permanent tooth discoloration may occur in the developing infant and enamel hypoplasia has been reported.

Large doses of tetracyclines have caused acute fatty necrosis of the liver in pregnant women, especially those with pyelonephritis.

Lactation
Tetracyclines have been shown to be present in the milk of lactating women.

Permanent tooth discoloration may occur in the developing infant and enamel hypoplasia has been reported.

Use in lactation is not recommended (see section 4.3 Contraindications).

4.7 Effects on ability to drive and use machines

Patients who experience CNS symptoms such as lightheadedness, dizziness or vertigo should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy.

4.8 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).

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. Rarely, oesophagitis and oesophageal ulceration.

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 exfoliative dermatitis have been reported rarely.

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Fixed drug eruptions have been rarely reported. Lesions occurring on the glans penis have caused balanitis. Fixed drug eruptions, erythema multiforme and rarely Stevens-Johnson syndrome have been reported. Pigmentation of the skin and mucous membranes, as well as nail discolouration, have been reported.

Photosensitivity (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 been reported in adults.

Renal toxicity: Rise in BUN 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 reactions: Urticaria, angioneurotic oedema, anaphylaxis, anaphylactoid purpura, pericarditis, polyarthralgia, and exacerbation of systemic lupus erythematosus. Pulmonary infiltrates with oesinophilia has been rarely reported. A reversible lupus-like syndrome has been reported.

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

Endocrine: 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.

CNS effects: Convulsions, hypesthesia, dizziness, paresthesia, sedation, and vertigo. Bulging fontanelles in infants and benign intracranial hypertension 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).

In long-term therapy, a periodic laboratory evaluation of organ systems, including haematopoietic, renal and hepatic studies, should be performed.

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://pophealth.my.site.com/carmreportnz/s/

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Microbiology

The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis.

Minocycline, like other tetracyclines, is also active against a wide range of Gram-negative and Gram-positive organisms. It is active against a proportion of *Staphylococcus aureus* organisms that 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.

Susceptibility Testing

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (eg. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microoganisms 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.

5.2 Pharmacokinetic properties

Minocycline is rapidly absorbed after oral administration and absorption is not significantly impaired by ingestion of food or milk. After single oral doses of 150 mg in humans, minocycline yields serum levels that are generally 2 to 4 times higher

than those of most other tetracyclines at all time intervals. When serum activity is determined against a standard of tetracycline, 150 mg of minocycline gives activity levels 16 or more times higher than 250 mg of tetracycline at 24 to 48 hours, this difference being largely due to the much longer serum half life of minocycline.

Minocycline is widely distributed in body tissues, with higher concentrations being found in cerebrospinal fluid and sputum than with other tetracycline analogues. As in blood, the concentration in tissues is generally 2 to 4 times higher with minocycline than with tetracycline.

Following a single dose of two 100 mg minocycline HCL capsules administered to ten normal adult volunteers, serum levels ranged from 0.74 to 4.45 mg/mL in one hour and attained peak levels between 2 and 3 hours; after 12 hours, they ranged from 0.34 to 2.36 mg/mL. Therapeutic levels are 1-2 mg/mL. The serum half life following a 200 mg dose in 12 normal volunteers ranged from 11 to 17 hours, in 7 patients with hepatic dysfunction ranged from 11 to 16 hours and in 5 patients with renal dysfunction ranged from 18 to 69 hours. Between 55% and 76% of an administered dose is bound by serum proteins.

Minocycline is excreted via the faeces primarily and via the urine at a low rate. High serum protein binding and the lipophylic properties contribute to this low excretion rate. The urinary and faecal recovery of minocycline when administered to 12 normal volunteers is one half to one third that of tetracycline.

5.3 Preclinical safety data

Carcinogenesis and Mutagenesis
Minocycline has been found to produce thyroid hyperplasia in rats and dogs. Dietary administration of minocycline in a long-term tumourgenicity study in rats resulted in evidence of thyroid tumour production. Minocycline causes goitre in rats and this species appears to be uniquely susceptible to developing thyroid tumours following long-term administration of agents that cause goitre.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Brilliant blue FCF, erythrosine, gelatin, magnesium stearate, opaspray white K-1R-7000, pregelatinised maize starch, sunset yellow FCF, titanium dioxide.

6.2 Incompatibilities
No data available.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
100 mg capsules: Plastic bottles containing 100 capsules.

6.6 Special precautions for disposal (and other handling)
No data available.

7. MEDICINE SCHEDULE
Prescription medicine

8. SPONSOR
Pharmacy Retailing (NZ) Limited Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

9. DATE OF FIRST APPROVAL
September 2009

10. DATE OF REVISION OF TEXT
6 December 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Minor editorial changes.
4.2	Included additional information relating to method of administration. Added maximum dose for children over 12 years of age.
4.4	Added Hyperpigmentation. Added additional information to photosensitivity. Added subtitles, Use in Renal Impairment, Discolouration of Teeth, Photosensitivity, Central Nervous System (CNS) Effects, Other CNS, Enterocolitis, Colitis, Staphylococcal Infection, Streptococcal Infection, Anticoagulant Therapy, Syphilis, Hepatotoxicity. Revised Use in Discolouration of Teeth, Renal Impairment, Photosensitivity. Deleted Carcinogenesis and Mutagenesis.
4.5	Added additional information to oral contraceptives. Added subtitles, Anticoagulants, Aluminium, Calcium, Magnesium, Iron, Food and Dairy Products, Penicillin, Oral Contraceptives.
4.6	Revised Pregnancy and Lactation.
4.8	Added fixed drug eruptions, enamel hypoplasia, decreased hearing, headache not related to benign intracranial

	hypertension. Updated the link for reporting of suspected adverse drug reactions in New Zealand.
5.3	Added Carcinogenesis and Mutagenesis.