Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
MINOCYCLINE 50 mg
MINOCYCLINE 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Minocycline 50 mg contains: 50 mg minocycline (as hydrochloride).
Minocycline 100 mg contains: 100 mg minocycline (as hydrochloride).

3. PHARMACEUTICAL FORM
Capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of infections caused by minocycline-sensitive micro-organisms including acne, gonorrhea and prophylaxis of asymptomatic meningococcal carrier.

4.2 Posology and method of administration
Posology
Unlike earlier tetracyclines, absorption of minocycline is not significantly impaired by food or moderate amounts of milk.

Adults:
Routine antibiotic use: 200mg daily in divided doses.

Acne: 50mg twice daily (or 100 mg once daily). Treatment should continue for a minimum of six weeks. If, after six months, there is no satisfactory response minocycline should be discontinued and other therapies considered. If minocycline is to be continued for longer than six months, patients should be monitored at least at three monthly intervals thereafter for signs and symptoms of hepatitis or SLE or unusual pigmentation of the skin**.** (See other special warnings and precautions).

Gonorrhoea: In adult males: 200mg initially followed by 100mg every 12 hours for a minimum of 4 days with post-therapy cultures within 2-3 days. Adult females may require more prolonged therapy.

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

Paediatric population:
Children over 12 years: 50mg every 12 hours (or 100 mg once daily).
Children under 12 years: Not recommended.

***Elderly*:**
Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment: minocycline may be used at the normal recommended dosage in mild to moderate renal impairment, however caution is advised in patients with severe renal impairment.

Method of Administration

For oral administration. To reduce the risk of oesophageal irritation and ulceration, the capsules should be swallowed whole with plenty of fluid, while sitting or standing. Unlike earlier tetracyclines, absorption of minocycline is not significantly impaired by food or moderate amounts of milk.

4.3 Contraindications

- Hypersensitivity to the active substance, to tetracyclines or to any of the excipients listed in section 6.1.
- Systemic Lupus Erythematosus
- Pregnancy and lactation.
- Children under 12 years.
- Complete renal failure.

4.4 Special warnings and precautions for use

• *Breathing difficulties:* Cases of breathing difficulties including dyspnoea, bronchospasm, exacerbation of asthma, pulmonary eosinophilia and pneumonitis (see section 4.8) have been reported with minocycline use. If patients develop breathing difficulties they should seek urgent medical advice and minocycline should be discontinued.

• *Paediatric population:* All tetracyclines form a stable calcium complex in any bone forming tissue. An increase in the fibula growth rate has been observed in premature babies administered oral tetracyclines.

Tetracyclines are known to cause a yellow to brown discoloration of the teeth and enamel hypoplasia in the developing child or foetus.

• *Hepatic impairment:* Minocycline should be used with caution in patients with hepatic dysfunction or in conjunction with potentially hepatotoxic drugs, including alcohol.

• *Auto–immune disorders:* Rare cases of auto-immune hepatotoxicity and isolated cases of systemic lupus erythematosus (SLE) and also exacerbation or pre-existing SLE have been reported. If patients develop signs or symptoms of SLE or hepatotoxicity, or suffer exacerbation or pre-existing SLE, minocycline should be discontinued.

• *Renal impairment:* Studies indicate there is no significant drug accumulation in patients with mild to moderate renal impairment when treated with the recommended dosages of minocycline. In cases of severe renal impairment a reduction of dosage and monitoring of renal function may be required.

• *Cross-sensitivities:* Micro-organisms can develop cross resistance to tetracyclines and patients can develop cross sensitivity. Minocycline should be discontinued if

there are signs/symptoms of overgrowth of resistant organisms, *e.g*. enteritis, glossitis, stomatitis, vaginitis, pruritus ani or staphylococcal enteritis.

• *Myasthenia Gravis:* Tetracyclines can cause weak neuromuscular blockade - use with caution in Myasthenia Gravis.

• Intracranial hypertension: As with other tetracyclines, bulging fontanelles in infants and benign intracranial hypertension in juveniles and adults have been reported. Presenting features were headache and visual disturbances including blurring of vision, scotoma and diplopia. Permanent vision loss has been reported. Treatment should cease if evidence of raised intracranial pressure develops.

• *Hyperpigmentation:* As with other tetracyclines, minocycline may cause hyperpigmentation at various body sites (see also section 4.8). Hyperpigmentation may present regardless of dose or duration of therapy but develops more commonly during long term treatment. Patients should be advised to report any unusual pigmentation without delay and minocycline should be discontinued. This is generally reversible on cessation of therapy.

• *Photosensitivity:* Tetracyclines are known to cause photosensitivity reactions. Such patients should be warned to avoid direct exposure to natural or artificial light and to discontinue therapy at the first sign of discomfort.

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants
Plasma prothrombin activity is depressed by tetracyclines. Reduced doses of any concomitant anticoagulants may be necessary.

ACE inhibitors, antacids and adsorbants
Tetracyclines bind to di-/tri-valent cations. Absorption from the gastrointestinal tract is impaired by the concomitant administration of iron, calcium, aluminium, magnesium bismuth and zinc salts (interactions with specified salts, antacids, kaolin, bismuth containing ulcer-healing drugs, quinapril which contains a magnesium carbonate excipient). Dosages should be maximally separated. Absorption of tetracyclines is not significantly impaired by food, milk and milk products.

Diuretics
Diuretics may aggravate nephrotoxicity by volume depletion.

Antibacterials
Minocycline should not be used with penicillins.

Ergotamine and ergometrine
There is an increased risk of ergotism.

Oral Contraceptives
Both can induce hyperpigmentation.

Retinoids
Administration of isotretinoin should be avoided shortly before, during and shortly after minocycline therapy. Each drug alone has been associated with pseudotumor cerebri (benign intracranial hypertension) (see section 4.4).

Laboratory tests
Minocycline may affect urinary urobilinogen excretion tests by reducing bacterial converters of bilirubin to urobilinogen. Minocycline may also produce an interference fluorescence in the Hungarty methods for measuring urinary catecholamines.

4.6 Fertility, pregnancy and lactation

Minocycline use during pregnancy and lactation is contraindicated.

Pregnancy
Animal studies have indicated that tetracyclines cross the placenta. Tetracyclines have been found in foetal tissues and can have toxic effects on the developing foetus (related to retardation of skeletal development). Studies on animals treated during early pregnancy also indicate embryotoxicity.

The use of tetracyclines during the last half of pregnancy, when the teeth are developing, may cause permanent discoloration of the teeth (more common with long-term or repeated short-term use). Enamel hypoplasia has also been reported.

Breast-feeding
Tetracyclines have been detected in the milk of lactating women. Permanent tooth discoloration may occur in the developing infant and enamel hypoplasia has been reported.

4.7 Effects on ability to drive and use machines
Dizziness, vertigo, headache, light-headedness, visual disturbances, tinnitus and impaired hearing (rarely) have occurred following administration of minocycline. Patients should be warned of these effects and the possible hazard of driving or operating machinery, if affected.

4.8 Undesirable effects
Adverse reactions are listed in the Table in CIOMS frequency categories under MedDRA system/organ classes.
The frequency of adverse reactions is defined using the following convention:
Common: (≥1/100 to <1/10)
Uncommon: (≥1/1,000 to <1/100)
Rare: (≥1/10,000 to <1/1,000)
Very Rare: (<1/10,000)
Not known (cannot be estimated from the available data)

MedDRA system organ class	Adverse Drug Reaction
Infections and infestations	
Very rare	Oral and anogenital candidiasis, vulvovaginitis.
Blood and lymphatic system disorders	
Rare	Eosinophilia, leucopenia, neutropenia, thrombocytopenia
Very rare	Haemolytic anaemia, pancytopenia.
Not known	Agranulocytosis
Immune system disorders	
Rare	Anaphylaxis/anaphylactoid reaction (including shock and fatalities).
Not known	Hypersensitivity, pulmonary infiltrates, anaphylactoid purpura**,** polyarteritis nodosa.
Endocrine disorders	
Very rare	Abnormal thyroid function, brown-black discolouration of the thyroid.
Metabolism and nutrition disorders	
Rare	Anorexia.
Nervous system disorders	
Common	Dizziness (lightheadedness).
Rare	Headache, hypaesthesia, paraesthesia, intracranial hypertension, vertigo.
Very rare	Bulging fontanelle.
Not known	Convulsions, sedation.
Ear and labyrinth disorders	
Rare	Impaired hearing, tinnitus.
Cardiac disorders	
Rare	Myocarditis, pericarditis.
Respiratory, thoracic and mediastinal disorders	
Rare	Cough, dyspnoea.
Very rare	Bronchospasm, exacerbation of asthma, pulmonary eosinophilia.
Not known	Pneumonitis.
Gastrointestinal disorders	
Rare	Diarrhoea, nausea, stomatitis, discolouration of teeth, vomiting.
Very rare	Dyspepsia, dysphagia, enamel hypoplasia, enterocolitis, oesophagitis, oesophageal ulceration, glossitis, pancreatitis,

	pseudomembranous colitis.
Hepatobiliary disorders	
Rare	Increased liver enzymes, hepatitis, autoimmune hepatoxicity. (See Section 4.4).
Very rare	Hepatic cholestatis, hepatic failure (including fatalities), hyperbilirubinaemia, jaundice.
Not known	*Autoimmune hepatitis
Skin and subcutaneous tissue disorders	
Rare	Alopecia, erythema multiforme, erythema nodosum, fixed drug eruption, hyperpigmentation of skin, photosensitivity, pruritis, rash, urticaria, vasculitis.
Very rare	Angioedema, exfoliative dermatitis, hyperpigmentation of nails, Stevens-Johnson Syndrome, toxic epidermal necrolysis.
Not known	Drug rash with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	
Rare	Arthralgia, lupus-like syndrome, myalgia.
Very rare	Arthritis, bone discolouration, cases of or exacerbation of systemic lupus erythematosus (SLE) (See Section 4.4), joint stiffness, joint swelling.
Renal and urinary disorders	
Rare	Increased serum urea, acute renal failure, interstitial nephritis.
Reproductive system and breast disorders	
Very rare	Balanitis.
General disorders and administration site conditions	
Uncommon	Fever
Very rare	Discolouration of secretions.

* Autoimmune hepatitis: See Section 4.4.

The following syndromes have been reported. In some cases involving these syndromes, death has been reported. As with other serious adverse reactions, if any of these syndromes are recognised, the drug should be discontinued immediately:
• Hypersensitivity syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, pericarditis. Fever and lymphadenopathy may be present.

• Lupus-like syndrome consisting of positive antinuclear antibody, arthralgia, arthritis, joint stiffness or joint swelling, and one or more of the following: fever, myalgia, hepatitis, rash, vasculitis.
• Serum sickness-like syndrome consisting of fever, urticaria or rash, and arthralgia, arthritis, joint stiffness or joint swelling. Eosinophilia may be present.

Hyperpigmentation of various body sites including the skin, nails, teeth, oral mucosa, bones, thyroid, eyes (including sclera and conjunctiva), breast milk, lacrimal secretions and perspiration has been reported. This blue/black/grey or muddy-brown discolouration may be localised or diffuse. The most frequently reported site is in the skin. Pigmentation is often reversible on discontinuation of the drug, although it may take several months or may persist in some cases. The generalised muddy-brown skin pigmentation may persist, particularly in areas exposed to the sun.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Dizziness, nausea and vomiting are the adverse effects most commonly seen with overdose. Gastric lavage plus appropriate supportive treatment. Antacids and calcium salts will reduce absorption of minocycline but there is no specific antidote. Minocycline is not removed in significant quantities by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, tetracyclines,
ATC code: J01A A08

Minocycline is a broad spectrum antibiotic used for the treatment of infections caused by tetracycline-sensitive organisms. Some tetracycline-resistant strains of Staphylococci are also sensitive.

Minocycline should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Mechanism of action

Minocycline inhibits protein synthesis in susceptible bacteria. In common with other tetracyclines it is primarily bacteriostatic and has a similar spectrum of activity to other tetracyclines.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for minocycline and are listed here:

https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Susceptibility
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable. Minocycline is usually active *in vitro* against *Propionibacterium acnes*, which is implicated in the pathogenesis of acne.

Resistance
Bacterial resistance to the tetracyclines is now common in some species and usually involves cross-resistance between the different tetracyclines.

5.2 Pharmacokinetic properties
Absorption:
Minocycline is readily absorbed from the GI tract and is not significantly affected by the presence of food or moderate amounts of milk as other tetracyclines. Absorption may be impaired by the concomitant administration of iron salts or antacids containing calcium, magnesium or aluminium salts. Normal doses of 200mg followed by 100mg every 12 hours produced plasma concentrations within the range of 1-4µg/ml.

Distribution:
Minocycline is reported to be more lipid-soluble than doxycycline and the other tetracyclines and to be widely distributed in body tissues and fluids. High concentrations being achieved in the hepatobiliary tract, lungs, sinuses and tonsils, as well as in tears, saliva, and sputum. Penetration into cerebrospinal fluid is relatively poor, although a higher ratio of CSF to blood concentrations has been reported with minocycline than with doxycycline. It crosses the placenta and diffuses into milk of nursing mothers. About 75% of minocycline in the circulation is bound to plasma proteins. The plasma half-life tends to be prolonged in patients with severe renal impairment. It has a lower renal clearance than doxycycline and its plasma half-life ranges from 11-23 hours.

Biotransformation:
In contrast to most tetracyclines, minocycline appears to undergo some metabolism in the liver, mainly to 9-hydroxyminocycline. It is also excreted in bile.

Elimination:
About a third of the drug may be excreted unchanged and although figures vary widely, about a third of this unchanged drug may appear in the urine and two thirds in the faeces.

5.3 Preclinical safety data
Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
The capsules also contain:

Pregelatinized maize starch, magnesium stearate, silicon dioxide colloidal, gelatin, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), erythrosine (FD&C red 3), indigo carmine (FD&C blue 2).

6.2 Incompatibilities
None known.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C in the original package.

6.5 Nature and contents of container
Minocycline 50 mg: 30 capsules in blisters.
Minocycline 100 mg: 10 capsules in blisters.

6.6 Special precautions for disposal and other handling
Not applicable.

7. REGISTRATION HOLDER:
Rafa Laboratories Ltd., P.O. Box 405, Jerusalem 9100301.

8. MARKETING AUTHORISATION NUMBERS:
Minocycline 50 mg: 064 98 27129
Minocycline 100 mg: 116 73 27128

Revised in January 2025.