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.

- **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
- Known hypersensitivity to tetracyclines or to any of the excipients.
- 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.
- **Use in Children:** The use of tetracyclines during tooth development in children under the age of 12 years may cause permanent discoloration (see above). Enamel hypoplasia has been reported.
- **Use in Hepatic Dysfunction:** Minocycline should be used with caution in patients with hepatic dysfunction and in conjunction with alcohol and other hepatotoxic drugs.
- **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:** Clinical studies have shown that there is no significant drug accumulation in
patients with renal impairment when they are treated with minocycline in the recommended doses. In cases of severe renal insufficiency, reduction of dosage and monitoring of renal function may be required. The anti-anabolic action of the tetracyclines may cause an increase in serum urea. In patients with significantly impaired renal function, higher serum levels of tetracyclines may lead to uraemia, hyperphosphataemia and acidosis. If renal impairment exists, even usual oral and parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity.

- **Cross-sensitivities**: Cross-resistance between tetracyclines may develop in micro-organisms and cross-sensitisation in patients. Minocycline should be discontinued if there are signs/symptoms of overgrowth of resistant organisms, e.g. enteritis glossitidis, 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 sections 4.2 and 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**: If photosensitivity occurs, patients should be warned to avoid direct exposure to natural or artificial light and to discontinue therapy at the first sign of discomfort.
- **Contraceptive failure**: Patients should be warned that minocycline may reduce the efficacy of combined oral contraceptives if diarrhoea or breakthrough bleeding occurs.
- **Laboratory monitoring**: Periodic laboratory evaluations of organ system function, including hematopoietic, renal and hepatic should be conducted.

### 4.5 Interaction with other medicinal products and other forms of interaction

- **ACE Inhibitors**: Absorption of minocycline decreased by quinapril tablets (which contains magnesium carbonate).
- **Antacids and Adsorbants**: Absorption of minocycline is impaired by the concomitant administration of antacids, iron, calcium, aluminium, magnesium and zinc salts (interactions with specified salts, antacids and kaolin). Dosages should be maximally separated. It is recommended that any indigestion remedies, vitamins, or other supplements containing these salts are taken at least 3 hours before or after a dose of Minocycline.
- **Antibacterials**: Minocycline should not be used with penicillins.
- **Anticoagulants**: Tetracyclines depress plasma prothrombin activity and reduced dosages of concomitant anticoagulants may be necessary.
- **Diuretics**: May aggravate nephrotoxicity by volume depletion.
- **Ergotamine and ergometrine**: Increased risk of ergotism.
- **Oral Contraceptives**: Minocycline may reduce the efficacy of combined oral contraceptives. Both can induce hyperpigmentation.
- **Retinoids**: Administration of isotretinoin or other systemic retinoids or retinol should be avoided shortly before, during and shortly after minocycline therapy. Each drug alone has been associated with pseudotumor cerebri (benign intracranial hypertension) (see 4.4 Special warnings and precautions).
- **Ulcer healing Drugs**: Absorption of minocycline decreased by sucralfate and bismuth salts.
- **Laboratory tests**: May affect urinary urobilinogen excretion tests by reducing bacterial converters of bilirubin to urobilinogen. May also produce an interference fluorescence in the Hungary methods for measuring urinary catecholamines.

### 4.6 Pregnancy and lactation

Results of animal studies indicate 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. Minocycline should not therefore be used in pregnancy.

In humans, minocycline, like other tetracycline-class antibiotics, crosses the placenta and may cause fetal harm when administered to a pregnant woman. In addition, there have been post marketing reports of congenital abnormalities including limb reduction. If minocycline is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus.

The use of drugs of the tetracycline class during tooth development (last half of pregnancy) may cause permanent discoloration 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 administered during the last trimester form a stable calcium complex throughout the
human skeleton. A decrease in fibula growth rate has been observed in premature human infants given oral tetracyclines in doses up to 25mg/kg every 6 hours. Changes in fibula growth rate were shown to be reversible when the drug was discontinued. Tetracyclines have been found in the milk of lactating women who are taking a drug in this class. 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
Lightheadedness, headache, visual disturbances, dizziness, tinnitus, vertigo and rarely, impaired hearing have occurred with minocycline and patients should be warned about the possible hazards of driving or operating machinery during treatment.

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: (≥1/10 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)

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Oral and anogenital candidiasis, vulvovaginitis.</td>
</tr>
<tr>
<td>Very rare</td>
<td>Eosinophilia, leucopenia, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Haemolytic anaemia, pancytopenia.</td>
</tr>
<tr>
<td>Rare</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Very rare</td>
<td>Anaphylaxis/anaphylactoid reaction (including shock and fatalities).</td>
</tr>
<tr>
<td>Not known (cannot be estimated from the available data)</td>
<td>Hypersensitivity, pulmonary infiltrates, anaphylactoid purpura, polyarteritis nodosa.</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Abnormal thyroid function, brown-black discolouration of the thyroid.</td>
</tr>
<tr>
<td>Rare</td>
<td>Anorexia.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness (lightheadedness).</td>
</tr>
<tr>
<td>Common</td>
<td>Headache, hypaesthesia, paraesthesia, intracranial hypertension, vertigo.</td>
</tr>
<tr>
<td>Very rare</td>
<td>Bulging fontanelle.</td>
</tr>
<tr>
<td>Not known (cannot be estimated from the available data)</td>
<td>Convulsions, sedation.</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Impaired hearing, tinnitus.</td>
</tr>
<tr>
<td>Rare</td>
<td>Myocarditis, pericarditis.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cough, dyspnoea.</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchospasm, exacerbation of asthma, pulmonary eosinophilia.</td>
</tr>
<tr>
<td>Very rare</td>
<td>Pneumonitis.</td>
</tr>
<tr>
<td>Disorder Category</td>
<td>Frequency</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
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<tr>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Rare</td>
</tr>
<tr>
<td>disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Musculoskeletal and connective</td>
<td>Rare</td>
</tr>
<tr>
<td>tissue disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Rare</td>
</tr>
<tr>
<td>Reproductive system and breast</td>
<td>Very rare</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
</tbody>
</table>

* Autoimmune hepatitis: See Section 4.4 Special warnings and precautions for use.

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

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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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system at: adr@MOH.HEALTH.GOV.IL.

4.9 Overdose
Dizziness, nausea and vomiting are the adverse effects most commonly seen with overdose. There is no specific antidote. In cases of overdose, discontinue medication, treat symptomatically and with appropriate supportive measures. Minocycline is not removed in significant quantities by haemodialysis or peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties
ATC code: J01A A08
Minocycline hydrochloride has a spectrum of activity and mode of action similar to that of tetracycline hydrochloride, but it is more active against many species. In addition, it is reported to be effective in vitro, against some tetracycline resistant staphylococci, streptococci and certain strains of tetracycline-resistant Escherichia coli and Haemophilus influenzae.

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 although absorption is 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: It is more lipid-soluble than doxycycline and the other tetracyclines and is widely distributed in body tissues and fluids, including the cerebrospinal fluid. 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. It penetrates well into thyroid, lung and liver tissues and in most instances tissue levels exceed serum levels. It also appears in tears and saliva.
Metabolism: 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, silicon dioxide colloidal, magnesium stearate, indigo carmine (FD&C blue 2), erythrosine (FD&C red 3), red iron oxide, titanium dioxide, yellow iron oxide, gelatin.

6.2 Incompatibilities
None known.

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

6.5 Presentation
Minocycline 50 mg: 30, 60 or 100 capsules in blisters.
Minocycline 100 mg: 10 capsules in blisters.
Not all pack sizes may be marketed.

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

The format of this leaflet was determined by the Ministry of Health that checked and approved its content in November 2014.