Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Minosil 100mg Modified-release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release capsule contains 100mg of minocycline (as minocycline hydrochloride).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release capsules, hard.

A hard gelatin capsule with an opaque cream body and an opaque brown cap; containing one pink film-coated tablet and one peach enteric-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Minosil capsules are indicated for the treatment of acne.

4.2 Posology and method of administration

Dosage:
Adults: One 100mg capsule every 24 hours.

Children over 12 years: One 100mg capsule every 24 hours.

Children under 12 years: Minosil is not recommended.

Elderly: No special dosing requirements.

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.

Treatment of acne should be continued for a minimum of 6 weeks and where possible limited to a maximum of six months. If, after six months, there is no satisfactory response Minosil should be discontinued and other therapies considered.

If Minosil is to be continued for longer than six months, patients should be monitored (including laboratory investigations) at least three monthly thereafter for signs and symptoms of hepatitis or SLE or unusual pigmentation (see Special warnings and precautions for use).

4.3 Contraindications

- Patients with known hypersensitivity to tetracyclines or to any of the components of Minosil 100mg modified release capsules
- use in pregnancy or lactation
- use in children under the age of 12years

- patients with complete renal failure
- patients with severe liver disease

4.4 Special warnings and precautions for use

Minosil should be used with caution in patients with mild to moderate hepatic dysfunction and in conjunction with alcohol and other hepatotoxic drugs. It is recommended that alcohol consumption should remain within the Government's recommended limits.
Rare cases of auto-immune hepatotoxicity (including acute liver failure), isolated cases of systemic lupus erythematosus (SLE) and also exacerbation of pre-existing SLE have been reported. If patients develop signs or symptoms of SLE or hepatotoxicity, or suffer exacerbation of pre-existing SLE, Minosil should be discontinued.

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 blood urea nitrogen (BUN). In patients with significantly impaired renal function, higher serum levels of tetracyclines may lead to azotaemia, 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.

Caution is advised in patients with myasthenia gravis as tetracyclines can cause weak neuromuscular blockade.

Cross-resistance between tetracyclines may develop in micro-organisms and cross-sensitisation in patients. Minosil should be discontinued if there are signs/symptoms of overgrowth of resistant organisms, e.g. enteritis, glossitis, stomatitis, vaginitis, pruritus ani or Staphylococcal enteritis.

Patients taking oral contraceptives should be warned that if diarrhoea or breakthrough bleeding occur there is a possibility of contraceptive failure.

Minocycline may cause hyperpigmentation at various body sites (see administration and side effects). 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 Minosil should be discontinued.

If photosensitivity reaction occurs, patients should be warned to avoid direct exposure to natural or artificial light and to discontinue therapy at the first sign of skin discomfort.

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.

Use in the elderly:
Clinical studies of Minocycline did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Use in children:
The use of tetracyclines during tooth development in children under the age of 12 years may cause permanent discolouration. Enamel hypoplasia has also been reported.

Laboratory monitoring:
Periodic laboratory evaluations of organ system function, including haematopoietic, renal and hepatic, should be conducted.

4.5 Interaction with other medicinal products and other forms of interaction

Tetracyclines have been shown to depress plasma prothrombin activity and reduced doses of concomitant anticoagulants may be necessary.

Diuretics may aggravate nephrotoxicity by volume depletion.

Bacteriostatic drugs may interfere with the bactericidal action of penicillin. Avoid giving tetracycline-class drugs in conjunction with penicillin. Absorption of minocycline is impaired by the concomitant administration of antacids, iron, calcium, magnesium, aluminium, bismuth and zinc salts (interactions with specific salts and antacids, bismuth containing ulcer-healing drugs, quinapril which contains a magnesium carbonate excipient). It is recommended that any indigestion remedies, vitamins, or other supplements containing these are taken at least 3 hours before or after a dose of Minosil. Unlike earlier tetracyclines, absorption of Minosil is not significantly impaired by food or moderate amounts of milk.

There is an increased risk of ergotism when ergot alkaloids or their derivatives are given with tetracyclines.

The concomitant use of tetracyclines may reduce the efficacy of oral contraceptives.

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

Interference with laboratory and other diagnostic tests:
False evaluations of urinary catecholamine levels may occur due to interference with the fluorescence test.

4.6 Fertility, pregnancy and lactation

Use in pregnancy:
Minosil should not be used in pregnancy unless considered essential.

Results of animal studies indicate that tetracyclines cross the placenta, 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.

Minosil, like other tetracycline-class antibiotics, crosses the placenta and may cause foetal harm when administered to a pregnant woman. In addition, there have been post-marketing reports of congenital abnormalities including limb reduction. If Minosil 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 foetus.

The use of drugs of the tetracycline class during tooth development (last half of pregnancy) may cause permane 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 shc term courses. Enamel hypoplasia has also been reported.

Tetracyclines administered during the last trimester form a stable calcium complex throughout the human skeleton. A growth-rate has been observed in premature human infants given oral tetracyclines in doses of 25mg/kg every 6 hours. Changes in fibula growth-rate were shown to be reversible when the drug was discontinued.

Use in lactation:
Tetracyclines have been found in the milk of lactating women who are taking a drug in this class.
Permanent tooth discolouration may occur in the developing infant and enamel hypoplasia has been reported.

4.7 Effects on ability to drive and use machines

Headache, lightheadedness, dizziness, tinnitus and vertigo (more common in women) and, rarely, impaired hearing have occurred with Minosil. Patients should be warned about the possible hazards of driving or operating machinery during treatment. These symptoms may appear during therapy and usually disappear when the drug is discontinued.

4.8 Undesirable effects

Adverse reactions are listed in the Table in CIOMS frequency categories under MedDRA system/organ classes:

Common:	≥ 1%
Uncommon:	≥ 0.1% and < 1%
Rare:	≥ 0.01% and < 0.1%
Very Rare:	< 0.01%

Blood and Lymphatic System Disorders
Rare: Eosinophilia, leucopenia, neutropenia, thrombocytopenia.
Very Rare: Haemolytic anaemia, pancytopenia.
Frequency undetermined: Agranulocytosis

Cardiac Disorders
Very Rare: Myocarditis, pericarditis.

Ear and Labyrinth Disorders
Rare: Impaired hearing, tinnitus.

Endocrine Disorders
Very Rare: Abnormal thyroid function, brown-black discolouration of the thyroid.

Gastrointestinal Disorders
Rare: Diarrhoea, nausea, stomatitis, discolouration of teeth, vomiting.
Very Rare: Dyspepsia, dysphagia, enamel hypoplasia, enterocolitis, oesophagitis, oesophageal ulceration, glossitis, pancreatitis, pseudomembranous colitis.

There are also reports of: Oral cavity discolouration (including tongue, lip and gum).

General Disorders and Administration Site Conditions
Uncommon: Fever.
Rare: Injection site erythema (injection only), injection site pain (injection only).
Very Rare: Discolouration of secretions.

Hepatobiliary Disorders
Rare: Increased liver enzymes, hepatitis, rare cases of autoimmune toxicity. (See Section 4.4 Special warnings and Special precautions for use).
Very Rare: Hepatic cholestatis, hepatic failure (including fatalities), hyperbilirubinaemia, jaundice.

There are also reports of: Autoimmune hepatitis.

Immune System Disorders
Rare: Anaphylaxis /anaphylactoid reaction (including shock),including fatalities.
Frequency undetermined: Hypersensitivity.

Infections and Infestations
Very Rare: Oral and anogenital candidiasis, vulvovaginitis.

Metabolism and Nutrition Disorders
Rare: Anorexia.

Musculoskeletal, Connective Tissue and Bone 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 Special warnings and Special precautions for use), joint stiffness, joint swelling.

Nervous System Disorders
Common: Dizziness (lightheadedness).
Rare: Headache, hypaesthesia, paraesthesia, pseudotumour cerebri, vertigo.
Very Rare: Bulging fontanelle.
Frequency undetermined: convulsions, sedation.

Renal and Urinary Disorders
Rare: Increased BUN
Very Rare: Acute renal failure, interstitial nephritis.

Reproductive System and Breast Disorders
Very Rare: Balanitis.

Respiratory, Thoracic and Mediastinal Disorders
Rare: Cough, dyspnoea.
Very Rare: Bronchospasm, exacerbation of asthma, pulmonary eosinophilia.
Frequency undetermined: Pneumonitis.

Skin and Subcutaneous Tissue Disorders
Rare: Alopecia, erythema multiforme, erythema nodosum, fixed drug eruption, hyperpigmentation of skin, photosensitivity, pruritis, rash, urticaria.
Very Rare: Angioedema, exfoliative dermatitis, hyperpigmentation of nails, Stevens-Johnson Syndrome, toxic epidermal necrolysis, vasculitis.

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 black/blue/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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 with supportive measures. Minosil is not removed in significant quantities by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:	Tetracyclines
ATC code:	J01AA08

Minosil capsules contain the active ingredient minocycline as minocycline hydrochloride, a semi-synthetic derivative of tetracycline.

5.2 Pharmacokinetic properties

Minosil capsules have been formulated as a "double pulse" delivery system in which a portion of the minocycline dose is delivered in the stomach, and a second portion of the dose is available for absorption in the duodenum and upper GI tract.

5.3 Preclinical safety data

None stated

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Povidone
Croscarmelose sodium
Magnesium stearate
Red iron oxide (E 172)
Silica colloidal anhydrous
Ferric oxide yellow
Hypromellose phthalate
Triethyl citrate
Opadry OY-S-24932 Pink
- Hypromellose 2910
- Macrogol 6000
- Titanium dioxide (E171)
- Talc
- Iron oxide, red (E172)

Carnauba wax
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

The blister strips are made of aluminium foil and are formed as follows: the aluminium Formpack layer is a stiff sheet coated on one side with an oriented polyamide (OPA) film and on the other side with a hard polyvinyl chloride (PVC) film. The Lidding aluminium foil layer is a thin, flexible sheet and is coated on one side with a clear, heat-resistant print primer and on the other with a lacquer capable of heat-sealing to PVC.

Pack sizes: 2, 7, 28, 56 & 96
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited
Trading as Pinewood Healthcare
Ballymacarbry
Clonmel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA0281/132/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th June 2007

Date of last renewal: 8th June 2012

10 DATE OF REVISION OF THE TEXT

March 2015