Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Minodene 50 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of minocycline (as minocycline hydrochloride dihydrate).

Excipients: Lactose monohydrate 10 mg.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, round, biconvex, film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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.

Minodene tablets are indicated for the treatment of ear, nose and throat infections, acute and chronic bronchitis, bronchiectasis, lung abscess, pneumonia, prostatitis, venereal diseases, urinary tract infections, salpingitis, skin and soft tissue infections, acne, ophthalmological infections, nocardiosis, and for the prophylactic treatment of asymptomatic meningococcal carriers.

4.2 Posology and method of administration

Adults:
Routine antibiotic use: 200 mg daily in divided doses.
Acne vulgaris: 50 mg twice daily. Treatment of acne should be continued for a minimum of six weeks and where possible limited to a maximum of six months. If, after six months, there is no satisfactory response Minodene should be discontinued and other therapies considered. If Minodene 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 4.4 Special warnings and precautions for use).
Gonorrhoea: In adult males, 200 mg initially followed by 100 mg every 12 hours for a minimum of four 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.
Prophylaxis of asymptomatic meningococcal carriers: 100 mg twice daily for five days, usually followed by a course of rifampicin.

Children:
Children over 12 years: One 50 mg tablet every 12 hours.
Children under 12 years: Not recommended.

Elderly:
No special dosing requirements.
Administration:
To reduce the risk of oesophageal irritation and ulceration, the tablets should be swallowed 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. In severe infections, treatment should be continued for up to three days after characteristic symptoms of the infection have subsided.

Because of the incidence of rheumatic fever or glomerulonephritis following streptococcal infection, therapy should be continued for 10 days even though symptoms have subsided.

4.3 Contraindications

Known hypersensitivity to tetracyclines or to any of the components of Minodene, use in pregnancy, lactation, children under the age of 12 years, complete renal failure. Severe liver disease.

4.4 Special warnings and precautions for use

Minodene 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, Minodene 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. Minodene 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 Minodene 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 Minodene. Unlike earlier tetracyclines, absorption of minocycline 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 or other systemic retinoids or retinol should be avoided shortly before, during and shortly after minocycline therapy. Each of these agents alone has been associated with pseudotumour cerebri (benign intracranial hypertension) (see 4.4 Special warnings and precautions for use).

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:
Minodene 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.

Minocycline, 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 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 foetus.

The use of drugs of the tetracycline class during tooth development (last half of pregnancy) 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 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 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, light-headedness, dizziness, tinnitus and vertigo (more common in women) and, rarely, impaired hearing have occurred with minocycline. Patients should be warned about the possible hazards of driving or operating machinery during treatment. These symptoms may disappear 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: $\geq 1\%$
Uncommon: $\geq 0.1\%$ and $< 1\%$
Rare: $\geq 0.01\%$ and $< 0.1\%$
Very rare: $< 0.01\%$

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.
Frequency undetermined: Agranulocytosis

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

Endocrine disorders:
Very rare: Abnormal thyroid function, brown-black discolouration of the thyroid.

Metabolism and nutrition disorders:
Rare: Anorexia.

Nervous system disorders:
Common: Dizziness (light-headedness).
Rare: Headache, hypaesthesia, paraesthesia, pseudotumour cerebri, vertigo.
Very rare: Bulging fontanelle.
Frequency undetermined: Convulsions, sedation.

Ear and Labyrinth disorders:
Rare: Impaired hearing, tinnitus.

Cardiac disorders:
Very rare: Myocarditis, pericarditis.

Respiratory, thoracic and mediastinal disorders:
Rare: Cough, dyspnoea.
Very rare: Bronchospasm, exacerbation of asthma, pulmonary eosinophilia.

Frequency undetermined: Pneumonitis.

Gastrointestinal disorders:
Rare: Diarrhoea, nausea, stomatitis, discolouration of teeth (including adult tooth discolouration), 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).

Hepatobiliary disorders:
Rare: Increased liver enzymes, hepatitis, rare cases of autoimmune toxicity (see Section 4.4 Special warnings and precautions for use).
Very rare: Hepatic cholestatis, hepatic failure (including fatalities), hyperbilirubinaemia, jaundice.
There are also reports of: Autoimmune hepatitis.

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.

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 precautions for use), joint stiffness, joint swelling.

Renal and urinary disorders:
Rare: Increased BUN
Very rare: Acute renal failure, interstitial nephritis.

Reproductive system and breast disorders:
Very rare: Balanitis.

General disorders and administration site conditions:
Uncommon: Fever.
Rare: Injection site erythema (injection only), injection site pain (injection only).
Very rare: Discolouration of secretions.

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.

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. 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: J01AA08
Minocycline hydrochloride, a semi-synthetic derivative of tetracycline, 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 has a long serum half-life and can be administered at 12 hour intervals.

Minocycline interferes with the third stage of bacterial protein synthesis. After amino acids are activated and attached to t-RNA (transfer RNA), the resulting amino acyl-t-RNA migrates to the bacterial ribosome for synthesis of proteins. Minocycline binds to the 30s subunit on the ribosome and inhibits binding of the aminoacyl-t-RNA molecules.

5.2 Pharmacokinetic properties

Minocycline hydrochloride is readily absorbed from the gastrointestinal 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. As minocycline hydrochloride is more lipid-soluble than doxycycline and other tetracyclines it is widely distributed in body tissues and fluids, including the cerebrospinal fluid. About 75% of minocycline hydrochloride in the circulation is bound to plasma proteins; its half life ranges from 11 to 23 hours. The plasma half life tends to be prolonged in patients with severe renal impairment.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Povidone K25
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

Film-coating:
Hypromellose 2910
Macrogol 6000
Iron oxide yellow (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/PVDC-Aluminium blisters.

Pack sizes: 4, 10, 28, 30, 50, 56, 60 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 126/177/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th June 2010

10 DATE OF REVISION OF THE TEXT