SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Acnamino™ MR 100mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100mg minocycline (as minocycline hydrochloride).

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

Minocycline 100 mg is a hard gelatin capsule, with an opaque-buff 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

Minocycline 100 mg capsules are indicated for the treatment of acne.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology:

Adults:	One 100 mg capsule every 24 hours
Children over 12 years:	One 100 mg capsule every 24 hours
Children under 12 years:	Minocycline is 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 insufficiency:	Minocycline must not be given to persons in renal failure. In lesser degrees of renal insufficiency, reduction of dosage and monitoring of renal function may be required (see sections 4.3 and 4.4).
Hepatic insufficiency:	Minocycline should be used with caution in patients with hepatic dysfunction (see section 4.4).

Treatment of acne should be continued for a minimum of 6 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 three monthly thereafter for signs and symptoms of hepatitis or SLE or unusual pigmentation (see section 4.4).

Method of Administration:

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

4.3 Contraindications

Hypersensitivity to minocycline or to any other of the tetracyclines or to any of the capsule excipients.

Pregnancy and lactation.

Children of less than 12 years of age.

Renal failure.

4.4 Special warnings and precautions for use

Minocycline should be used with caution in patients with 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, isolated cases of systemic lupus erythematosus (SLE) and 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, minocycline should be discontinued.

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.

Minocycline is contraindicated in persons with renal failure. Clinical studies have shown that there is no significant drug accumulation in patients with lesser degrees of renal impairment when they are treated with minocycline in the recommended doses. In the more severe cases of renal insufficiency, reduction of dosage and monitoring of renal function may be required.

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

Cross-hypersensitivity between tetracyclines may occur in patients (see section 4.3).

Cross-resistance between tetracyclines may develop in micro-organisms.

The use of minocycline may result in overgrowth of non-susceptible organisms and symptomatic super-infections may occur (e.g. due to fungi or to tetracycline-resistant bacteria). If a super infection occurs, minocycline should be discontinued and appropriate therapy instituted.

Minocycline may cause hyperpigmentation at various body sites (see 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.

If a photosensitivity reaction occurs (see section 4.8), patients should be warned to avoid direct exposure to natural or artificial light and to discontinue therapy at the first signs 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.

Minocycline is contraindicated in children of less than 12 years of age. The use of tetracyclines during tooth development in children under the age of 12 years may cause permanent discoloration. Enamel hypoplasia has also been reported.

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 depress plasma prothrombin activity and reduced doses of concomitant anticoagulants may be necessary.

Diuretics may aggravate nephrotoxicity by volume depletion.

Minocycline should not be used with beta-lactam antibacterial agents due to the possibility of antagonism.

Absorption of minocycline is impaired by the concomitant administration of antacids, iron, calcium, magnesium, aluminium, bismuth and zinc salts (interactions with specific salts, antacids, bismuth containing ulcer – healing drugs, quinapril which contains a magnesium carbonate excipient). It is recommended that any indigestion remedies, vitamins, or other products that contain these salts should be are taken at least 3 hours before or after a dose of Minocycline. However, the absorption of minocycline is not significantly impaired by food or moderate amounts of milk.

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 pseudotumor cerebri (benign intracranial hypertension) (see section 4.4 and 4.8).

Interference with laboratory and other diagnostic tests:

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

4.6 Pregnancy and lactation

Pregnancy:

Minocycline is contraindicated in pregnancy.

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.

In humans, 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.

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.

Lactation:

Minocycline is contraindicated during lactation.

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

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: ≥1%

Uncommon: ≥0.1% and < 1%

Rare: ≥0.01% and < 0.1%

Very Rare: < 0.01%

<u>Infections and Infestations</u>

Very Rare: Oral and anogenital candidiasis, vulvovaginitis.

<u>Blood and Lymphatic System Disorders</u>

Rare: Eosinophilia, leucopenia, neutropenia, thrombocytopenia.

Very Rare: Haemolytic anaemia, pancytopenia.

There are also reports of: Agranulocytosis

<u>Immune System Disorders</u>

Rare: Anaphylaxis /anaphylactoid reaction (including shock), including fatalities.

There are also reports of: Hypersensitivity, pulmonary infiltrates, anaphylactoid purpura.

<u>Endocrine Disorders</u>

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

<u>Metabolism and Nutrition Disorders</u>

Rare: Anorexia.

Nervous System Disorders

Common: Dizziness (lightheadedness).

Rare: Headache, hypaesthesia, paraesthesia, intracranial hypertension, vertigo.

Very Rare: Bulging fontanelle.

There are also reports of: 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.

There are also reports of: 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 Special warnings and precautions for use).

Very Rare: Hepatic cholestatis, hepatic failure (including fatalities), hyperbilirubinaemia, jaundice.

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.

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.

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.

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.

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 gastric lavage and appropriate supportive measures. Minocycline is not removed in significant quantities by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Therapeutic classification: Antibacterial for Systemic Use: J01AA08

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

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.

Breakpoints: The general MIC breakpoint to identify organisms susceptible to minocycline is ≤ 0.5 mg/l. All organisms for which the MIC of minocycline is ≥ 1 mg/l are considered resistant (European Committee on Antimicrobial Susceptibility Testing (EUCAST), 2004).

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

After a single 100 mg dose of Minocycline Capsules administered to fasting male subjects a maximum concentration of 608 (± 162) ng/ml was achieved at 3.2 (± 1.1) hours after dosing and was eliminated with a plasma half life of 18.4± 6.2 hours. When administered to male subjects in the fed state a maximum concentration of 750.9 (± 223.8) ng/ml was achieved at 3.7 (± 1.3) hours after dosing and was eliminated with a plasma half life of 18.8± 3.1 hours.

5.3 Preclinical safety data

There is no other relevant information from pre-clinical studies that has not already been mentioned in the preceding sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Croscarmellose sodium, Povidone, Red iron oxide, Ferric oxide yellow, Silica colloidal anhydrous, Magnesium stearate, Hypromellose phthalate, Triethyl citrate, Carnauba wax, Gelatin, Opadry OY-S-24932 pink (which contains Hypromellose 2910, Macrogol 6000, Titanium dioxide (E171), Talc, Iron oxide red (E172)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package

6.5 Nature and contents of container

The capsules are presented in aluminium/aluminium blisters, strips of which are contained within a printed cardboard carton. Each carton contains 56 capsules.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Dexcel®-Pharma Ltd.

7 Sopwith Way

Drayton Fields, Daventry

Northamptonshire NN11 8PB

UK

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