SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Minocycline 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains minocycline hydrochloride equivalent to 50mg minocycline.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Brown-yellow, round, film-coated tablets with an approximate diameter of 7mm, embossed GL50.

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.

Minocycline is indicated for the treatment of the following infections:

- Gonorrhoea
- Non-gonococcal urethritis
- Prostatitis
- Moderate to severe acne; use in moderate acne only if topical treatment is ineffective, if acne is extensive or hard to reach and if there is a high risk of scarring.
- Acute and chronic bronchitis.
- Bronchiectasis.
- Lung abscess.
- Pneumonia.
- Ear, nose and throat infections.
- Urinary tract infections.
- Pelvic inflammatory disease (eg salpingitis, oophoritis).
- Skin and soft tissue infections caused by Minocycline-sensitive organisms.

- Ophthalmic infections.
- Nocardiosis.
- Prophylactic treatment of asymptomatic meningococcal carriers.
- Pre and post-operative prophylaxis of infection.
- Chlamydia (trachoma, epididymitis, lymphogranuloma venereum and psittacosis).
- Rickettsia (typhus, Q-Fever, Rocky mountain spotted fever).
- Mycoplasma (respiratory and genital).
- Brucella (normally in combination with other antibiotics such as streptomycin).
- Borrelia burgdorferi (Lyme disease).
- In cases of penicillin allergy
- Treatment of actinomycosis, leptospirosis and syphilis.

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

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

4.2 Posology and method of administration

Posology

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

Acne:
50mg twice daily. Treatment should continue for a minimum of 6 weeks. If, after 6 months, there is no satisfactory response Minocycline should be discontinued and other therapies considered. If Minocycline is to be continued for longer than 6 months, patients should be monitored at least at 3 monthly intervals thereafter for signs and symptoms of hepatitis or SLE or unusual pigmentation of the skin (see section 4.4).

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 5 days, usually followed by a course of rifampicin.

Paediatric population
Children over 12 years: 50mg every 12 hours.
Children under 12 years: Not recommended.

Elderly
Minocycline may be used at the normal recommended dosage in elderly patients,

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 tablets 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
- 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: The use of tetracyclines during tooth development in children under the age of 12 years may cause permanent discoloration (see section 4.3). 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 of pre-existing SLE have been reported. If patients develop signs or symptoms of SLE or hepatotoxicty, or suffer exacerbation of 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.

Cross-sensitivities: Cross-resistance between tetracyclines may develop in micro-organisms and cross-sensitisation in patients. Minocycline should be discontinued if there are signs or symptoms of overgrowth of resistant organisms, enteritis e.g. 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 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 taking oral contraceptives should be warned that if diarrhoea or breakthrough bleeding occur there is a possibility of contraceptive failure.

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 Adsorbents: absorption of Minocycline is impaired by the concomitant administration of antacids, iron, calcium, aluminium, magnesium, bismuth and zinc salts (interactions with specified salts, antacids and kaolin). Dosages should be maximally separated.

Antibacterials: Minocycline should not be used with penicillins or cephalosporins as it may antagonise the antibacterial effect of these agents.

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 - 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 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 Hungarty methods for measuring urinary catecholamines.

4.6 Fertility, Pregnancy and lactation

Pregnancy

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 unless considered essential.

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.

Breast-feeding

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

Light-headedness, visual disturbances, dizziness, tinnitus and vertigo have occurred with Minocycline and patients should be warned about the possible hazards of driving or operating machinery during treatment.

4.8 Undesirable effects

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)

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 (cannot be estimated from the available data): Agranulocytosis

Immune system disorders:
Rare: Anaphylaxis/anaphylactoid reaction (including shock and fatalities)
Not known (cannot be estimated from the available data): 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, hyperaesthesia, paraesthesia, intracranial hypertension, vertigo
Treatment should be stopped if evidence of raised intracranial pressure develops. Headache and visual disturbance can signify benign intracranial hypertension; treatment should cease if this develops.
Very rare: Bulging fontanelle
Not known (cannot be estimated from the available data): Convulsions, sedation

Ataxia may also occur.

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 (cannot be estimated from the available data): Pneumonitis

Pulmonary infiltration has also been reported.

Gastrointestinal disturbances:
Rare: Diarrhoea, nausea, stomatitis, discolouration of teeth, vomiting
Any diarrhoea must be differentiated from that due to bacterial overgrowth. Overgrowth with candida may also occur.
Very rare: Dyspepsia, dysphagia, enamel hypoplasia, enterocolitis, oesophagitis, oesophageal ulceration, glossitis, pancreatitis, pseudomembranous colitis, antibiotic-associated colitis

Hepato-biliary disorders:
Rare: Increased liver enzymes, hepatitis, auto-immune hepatoxicity (See section 4.4).
Very rare: Hepatic cholestatis, acute hepatic failure (including fatalities), hyperbilirubinaemia, jaundice
Not known: Autoimmune hepatitis (See section 4.4)

Skin and subcutaneous tissue disorders:
Rare: Alopecia, erythema multiforme, erythema nodosum, fixed drug eruption, hyperpigmentation of skin, photosensitivity, pruritus, 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 (including conjunctiva and lacrimal)
There are isolated cases of perspiration. (See section 4.6).

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 drug 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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. Gastric lavage and appropriate supportive treatment are recommended. Minocycline is not removed in significant quantities by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tetracycline

ATC code: J01A A08

Tetracyclines, including Minocycline, are broad spectrum antibiotics with a wide range of bacteriostatic activity including Chlamydia, Mycoplasmas, Rickettsias and Spirochaetes, and also any aerobic and anaerobic Gram-positive and Gram-negative pathogenic bacteria, and some protozoa.

Mechanism of action
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.

Tetracyclines penetrate bacterial cell walls as a result of both passive diffusion and an active transport process. Once within the cell they bind to the 30s subunit of the ribosome, preventing the binding of aminoacyl transfer RNA and inhibiting protein synthesis and hence cell growth.

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. Steady-state plasma concentrations of 2.3 to 3.5μg/ml are reported following doses of 100mg every 12 hours.

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. Though CSF penetration is still relatively poor, 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. 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.

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
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. Only 5-10% of a dose is excreted in the urine and up to 34% in the faeces.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:
Povidone (K-25)
Sodium starch glycollate
Microcrystalline cellulose (PH101)
Colloidal anhydrous silica
Magnesium stearate
Purified water

Film coating
Hydroxypropylmethylcelullose
Macrogol 6000
Titanium dioxide (E171)
Yellow ferric oxide (E172).

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25ºC in a dry place. Store in the original package in order to protectfrom light.

6.5 Nature and contents of container

Strips-Blister Packs

PVC (250 micrometres) heat sealed to aluminium foil (20 micrometres).
Packs Sizes: 2, 28, 56, 84, 98 tablets.

Not all packs sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
Key House, Sarum Hill, Basingstoke,
RG21 8SR,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0771

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19/07/1999
Date of latest renewal: 13/03/2009

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19/12/2022