DIVAINE Tablets (Minocycline)

Composition

DIVAINE-50 Tablets
Each film-coated tablet contains
Minocycline Hydrochloride, BP
Equivalent to Minocycline ....................... 50 mg
DIVAINE -100 Tablets
Each film-coated tablet contains
Minocycline Hydrochloride, BP
Equivalent to Minocycline ....................... 100 mg

Dosage Form

Tablet

Pharmacology

Pharmacodynamics

Minocycline acts by inhibiting protein synthesis by blocking the binding of aminoacyl tRNA (transfer RNA) to the mRNA (messenger RNA) ribosome complex. Reversible binding occurs primarily at the 30S ribosomal subunit of susceptible organisms. Bacterial cell wall synthesis is not inhibited.

Antimicrobial Spectrum

While in vitro studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS section has not been documented:

**Gram-Negative Bacteria**
*Bartonella bacilliformis, Brucella species, Campylobacter fetus, Francisellatularensis, Haemophilus ducreyi, Haemophilus influenzae, Listeria monocytogenes, Neisseria gonorrhoeae, Vibrio cholerae* and *Yersinia pestis*. Because many strains of the following groups of Gram-negative microorganisms, i.e. *Acinetobacter* species, *Bacteroides* species, *Enterobacteraero genes, Escherichia coli*, *Klebsiella* species and *Shigella* species, have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recommended.

**Gram-Positive Bacteria**
Because many strains of the following groups of Gram-positive microorganisms, i.e. alpha-haemolytic streptococci (viridans group), *Streptococcus pneumoniae and Streptococcus pyogenes*, have been shown to be resistant to tetracyclines, culture and susceptibility testing are especially recommended. Tetracyclines should not be used for streptococcal diseases unless the organism has been demonstrated to be susceptible. Up to 44% of *Streptococcus pyogenes* strains have been found to be resistant to the tetracycline drugs.
Other Microorganisms

Actinomyces species, Bacillus anthracis, Balantidium coli, Borreliarecurrentis, Chlamydia psittaci, Chlamydia trachomatis, Clostridium species, Entamoeba species, Fusobacteriumfusiforme, Propionibacterium acnes, Treponema pallidum, Treponemapertene and Ureaplasmaurealyticum.

Pharmacokinetics

Minocycline is readily absorbed from the gastrointestinal tract and is not significantly affected by the presence of food or moderate amounts of milk. Oral doses of 200 mg followed by 100 mg every 12 hours are reported to produce plasma concentrations within the range of 2 to 4 µg/ml. It is more lipid soluble than doxycycline and the other tetracyclines and is widely distributed in body tissues and fluids, with high concentrations being achieved in the hepatobiliary tract, lungs, sinuses and tonsils, as well as in tears, saliva and sputum. Penetration into cerebrospinal fluid (CSF) is relatively poor, although a higher ratio of CSF to blood concentrations has been reported with minocycline than with doxycycline. It crosses the placenta and diffuses into the milk of nursing mothers. About 75% of minocycline in the circulation is bound to plasma proteins. It has a low renal clearance; only about 5% to 10% of a dose is excreted in the urine and up to about 34% is excreted in the faeces. However, in contrast to most tetracyclines, it appears to undergo some metabolism in the liver, mainly to 9-hydroxyminocycline. The plasma half-life is about 11 to 26 hours. Hepatic impairment does not appear to lead to accumulation.

Indications

DIVAINE Tablets is indicated in the treatment of the following infections due to susceptible microorganisms: acne, gonorrhoea, non-gonococcal urethritis, syphilis, prostatitis, acute and chronic bronchitis, bronchiectasis, lung abscess, pneumonia, ear, nose and throat infections, urinary tract infections, pelvic inflammatory disease, skin and soft tissue infections, ophthalmological infections, nocardiosis, prophylactic treatment of asymptomatic meningococcal carriers, pre- and post-operative prophylaxis of infection, trachoma, and inclusion conjunctivitis.

Dosage And Administration

The usual dosage and frequency of administration of DIVAINE Tablets differs from that of the other tetracyclines. Exceeding the recommended dosage may result in an increased incidence of side effects. DIVAINE Tablets may be taken with or without food.

Acne

50 mg twice daily for a minimum of 6 weeks. Treatment of acne should be continued for a minimum of 6 weeks. If, after 6 months, there is no satisfactory response, DIVAINE Tablets should be discontinued and other therapies considered. If DIVAINE Tablets are to be continued for longer than 6 months, patients should be monitored at least every 3 months thereafter for signs and symptoms of hepatitis or systemic lupus erythematosus (SLE) or unusual pigmentation.

Uncomplicated Gonococcal Infections Other Than Urethritis and Anorectal Infections

In men, 200 mg initially, followed by 100 mg every 12 hours for a minimum of 4 days, with post-therapy cultures within 2 to 3 days. Adult females may require more prolonged therapy.

Uncomplicated Gonococcal Urethritis in Men

100 mg, every 12 hours, for 5 days is recommended.

Uncomplicated Non-Gonococcal Urethral Infection in Adults Caused by Chlamydia trachomatis or Ureaplasmaurealyticum

100 mg orally, every 12 hours, for at least 7 days.

Syphilis

The usual dosage of DIVAINE Tablets should be administered over a period of 10 to 15 days. Close follow-up, including
laboratory tests, is recommended.

Pneumonia Caused By Susceptible organisms

The usual dosage of DIVAINE Tablets is 200 mg initially, followed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg tablets may be given initially, followed by one 50 mg four times daily. Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided.

Meningococcal Carrier State

The recommended dosage is 100 mg, every 12 hours, for 5 days.

Note: For children (above 8 years of age) the usual dosage of DIVAINE Tablets is 50 mg every 12 hours. Minocycline is not recommended for children below 8 years of age.

### Contraindications

DIVAINE Tablets are contraindicated in individuals with a known hypersensitivity to tetracyclines.

### Warnings And Precautions

#### General

Minocycline hydrochloride tablets, like other tetracycline-class antibiotics, can cause foetal harm when administered to a pregnant woman. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the foetus. The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow to grey-brown). This adverse reaction is more common during long-term use of the drug, but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

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 been noted in animals treated early in pregnancy.

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

Drug rash with eosinophilia and systemic symptoms (DRESS), including fatal cases, have been reported with minocycline use. If this syndrome is recognized, the drug should be discontinued immediately.

Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

Clostridium difficile-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including minocycline hydrochloride, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of C. difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is
necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

### Drug Interactions

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage. Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin. Absorption of tetracyclines is impaired by antacids containing aluminium, calcium or magnesium, and iron-containing preparations. The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity. Concurrent use of tetracyclines may render oral contraceptives less effective. Administration of isotretinoin should be avoided shortly before, during and shortly after minocycline therapy. Each drug alone has been associated with pseudotumourcerebri (benign intracranial hypertension). There is an increased risk of ergotism when ergot alkaloids or their derivatives are given with tetracyclines. Absorption of minocycline is decreased by ACE inhibitors (quinapril tablets, which contain magnesium carbonate). The concurrent use of diuretics may aggravate nephrotoxicity by volume depletion. Absorption of minocycline is decreased by ulcer healing drugs like sucralfate and bismuth salts.

### Laboratory Tests

Tetracyclines may affect urinary urobilinogen excretion tests by reducing bacterial converters of bilirubin to urobilinogen and also produce interference fluorescence in the Hungarty methods for measuring urinary catecholamines.

### Breathing Difficulties

Cases of breathing difficulties, including dyspnoea, bronchospasm, exacerbation of asthma, pulmonary eosinophilia and pneumonitis, have been reported with minocycline use. If patients develop breathing difficulties, they should seek urgent medical advice and minocycline should be discontinued.

### Renal Impairment

The anti-anabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotaemia, hyperphosphataemia, and acidosis. If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be necessary. The total dosage should be decreased by either reducing the recommended individual doses and/or by extending the time intervals between doses.

### Hepatic Impairment

Hepatotoxicity has been reported with minocycline; so, minocycline should be used with caution in patients with hepatic dysfunction and in conjunction with alcohol and other hepatotoxic drugs.

### Autoimmune Disorders

Rare cases of autoimmune hepatotoxicity and isolated cases of SLE as well as 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.

Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported with minocycline. 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.

Cross-sensitivities

Cross-resistance between tetracyclines may develop in microorganisms and cross-sensitization in patients. Minocycline should be discontinued if there are signs/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.

Pseudotumour cerebri (Intracranial Hypertension)

Pseudotumour cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and visual disturbances, including blurring of vision, scotoma and diplopia. Permanent vision loss has been reported. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve after discontinuation of the tetracycline, the possibility for permanent sequelae exists. Treatment should cease if evidence of raised intracranial pressure develops.

Contraceptive Failure

Patients should be warned that minocycline may reduce the efficacy of combined oral contraceptives if diarrhoea or breakthrough bleeding occurs.

Hyperpigmentation

As with other tetracyclines, minocycline may cause hyperpigmentation at various body sites. 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.

Pregnancy

Pregnancy Category D

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. The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood up to the age of 12 years) may cause permanent discoloration of the teeth (yellow to 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. DIVAINE Tablets, therefore, should not be used in pregnancy unless considered essential.

Lactation

Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Paediatric Patients

The use of tetracyclines during tooth development in children below the age of 8 years may cause permanent discolouration. Enamel hypoplasia has been reported. DIVAINE Tablets should not be used in children below 8 years of age.

Geriatric Patients

Clinical studies of oral minocycline did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, 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.

Others

Central nervous system side effects, including light-headedness, dizziness or vertigo, have been reported with minocycline therapy.

In venereal disease, when co-existent syphilis is suspected, a dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months. In long-term therapy, periodic laboratory evaluations of organ systems, including haematopoietic, renal and hepatic studies, should be performed.

As with other antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy when indicated.

Prescribing minocycline hydrochloride tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Undesirable Effects

Due to oral minocycline’s virtually complete absorption, side effects in the lower bowel, particularly diarrhoea, have been infrequent.

The following adverse reactions have been observed in patients receiving tetracyclines:

Body as a Whole: Fever, and discolouration of secretions.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhoea, dyspepsia, stomatitis, glossitis, dysphagia, enamel hypoplasia, enterocolitis, pseudomembranous colitis, pancreatitis, inflammatory lesions (with monilial overgrowth) in the oral and anogenital regions. Instances of oesophagitis and oesophageal ulcerations have been reported in patients taking the tetracycline-class antibiotics in capsule and tablet form. Most of these patients took the medication immediately before going to bed.

Genitourinary: Vulvovaginitis.

Hepatic Toxicity: Hyperbilirubinaemia, hepatic cholestasis, increases in liver enzymes, fatal hepatic failure, and jaundice. Hepatitis, including autoimmune hepatitis and liver failure have been reported.

Skin: Alopecia, erythema nodosum, hyperpigmentation of nails, pruritus, photosensitivity toxic epidermal necrolysis, and vasculitis. Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported. Fixed drug eruptions have been reported. Lesions occurring on the glans penis have caused balanitis. Erythema multiforme and Stevens-Johnson syndrome have been reported. Pigmentation of the skin and mucous membranes has been reported.

Respiratory: Cough, dyspnoea, bronchospasm, exacerbation of asthma, and pneumonitis.
Renal Toxicity: Interstitial nephritis. Elevations in BUN have been reported and are apparently dose-related. Reversible acute renal failure has been reported.

Musculoskeletal: Arthralgia, arthritis, bone discolouration, myalgia, joint stiffness, and joint swelling.

Hypersensitivity Reactions: Urticaria, angioneurotic oedema, polyarthralgia, anaphylaxis/anaphylactoid reaction (including shock and fatalities), anaphylactoid purpura, myocarditis, pericarditis, polyarteritis nodosa, exacerbation of systemic lupus erythematosus and pulmonary infiltrates with eosinophilia have been reported. A transient lupus-like syndrome and serum sickness-like reactions also have been reported.

Blood: Agranulocytosis, haemolytic anaemia, thrombocytopenia, leucopenia, neutropenia, pancytopenia and eosinophilia have been reported.

Central Nervous System: Convulsions, dizziness, hypaesthesia, paraesthesia, sedation, and vertigo. Bulging fontanels in infants and benign intracranial hypertension (pseudotumourcerebri) in adults have been reported. Headache has also been reported.

Infections and infestations: Oral and anogenital candidiasis, vulvovaginitis.

Other: Thyroid cancer has been reported in the postmarketing setting in association with minocycline products. When minocycline therapy is given over prolonged periods, monitoring for signs of thyroid cancer should be considered. When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discolouration of the thyroid gland. Cases of abnormal thyroid function have been reported.

Tooth discolouration in children less than 8 years of age, and also in adults, has been reported.

Oral cavity discolouration (including tongue, lips and gums) have been reported.

Tinnitus and decreased hearing have been reported in patients on minocycline hydrochloride.

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 recognized, 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, and 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, and vasculitis.
- Serum sickness-like syndrome consisting of fever; urticaria or rash; and arthralgia, arthritis, joint stiffness, or joint swelling.

**Overdosage**

The adverse events more commonly seen in overdose are dizziness, nausea, and vomiting. No specific antidote for minocycline is known.

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures. Minocycline is not removed in significant quantities by haemodialysis or peritoneal dialysis.

**Shelf-Life**

30 months

**Storage And Handling Instructions**

Store in a cool, dry place.
Protect from light.

Packaging Information

DIVAINE-50: Blister pack of 10 tablets
DIVAINE-100: Blister pack of 10 tablets

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DIVAINE Tablets

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