AA-MINOCYCLINE 50MG AND 100MG

Name and Quantity of Active ingredient :
Minocycline Hydrochloride Capsules USP 50mg and 100mg.

Pharmacology : AA-MINOCYCLINE (minocycline hydrochloride) is a tetracycline with antibacterial activity against some Gram-negative and Gram-positive organisms. The action of **AA-MINOCYCLINE** is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis.
Following a 200mg oral loading dose of minocycline, serum levels are detectable within the first hour, reach 95% levels at 1 hour, and peak concentrations of 2-4 µg/mL at 2 hours. At the end of 24 hours the serum levels are approximately 1 µg/mL. Maintenance of levels in the 2.3 to 3.5 µg/mL range occurs when the loading dose is followed by a maintenance dose of 100mg every 12 hours.
When given 200mg once daily for three days the serum levels had fallen to approximately 1 µg/mL at 24 hours. After a single oral dose of 150mg, minocycline has a serum half-life of 16 hours.

Indications : AA-MINOCYCLINE (minocycline hydrochloride) may be indicated for the treatment of the following infections due to susceptible strains of the designated organisms :
Gallbladder infections caused by Escherichia coli;
Urinary tract infections : cystitis, gonorrhea, pyelonephritis caused by Escherichia coli, Proteus species, Klebsiella species, Enterobacter aerogenes, Neisseria gonorrhoeae.
When penicillin is contraindicated, minocycline may be employed as an alternative drug in the treatment of anal and pharyngeal gonorrhea and syphilis.
Skin and soft tissue infections : abscess cellulilitis, furunculosis, impetigo and pyoderma caused by : Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pyogenes, Proteus species, Escherichia coli. Respiratory tract infections : bronchitis, pharyngitis, pheumonia, bronchopneumonia, sinusitis and tonsillitis caused by : Haemophilus influenzae, Klebsiella species, Enterobacter species. Tetracyclines should not be prescribed for acute throat infections.

Adverse Effects : The following adverse effects have been reported with the tetracycline analogues including minocycline :

a) Central Nervous System : increased intracranial pressure, headaches, light-headedness, dizziness or vertigo and, rarely, fainting spells have been reported with a variable but overall incidence of approximately 7% in patients treated with minocycline. These symptoms usually disappear rapidly when the drug is discontinued. Impaired hearing, tinnitus, headache, convulsions, sedation, hypesthesia or paresthesia have also been reported.
b) Gastrointestinal system : anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritis ani, constipation, dyspepsia, dysphagia and inflammatory lesions (with monilial overgrowth) in the anogenital region, increases in liver enzymes, and rarely hepatitis and acute liver failure have been reported. Rare instances of esophagitis and esophageal 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. Very rare incidence of pseudomembranous colitis has been reported.
c) Teeth and Bone : dental staining (yellow-gray-brown) has been reported in children of mothers given tetracyclines, including minocycline, during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and childhood to age of 13 years. Enamel hypoplasia has also been reported. Discolouration of bones and teeth has been documented to occur rarely in adolescents and adults upon extended treatment with minocycline. The effects may be irreversible. At present the mechanism of staining, although not completely elucidated, appears to be mediated by the formation of a stable iron complex. Very rarely arthritis, joint stiffness and joint swelling have been reported.
d) Renal : rise in BUN has been reported and is apparently dose-related. Increased excretion of nitrogen and sodium has also been reported. Acute renal failure, including interstitial nephritis has been reported rarely.
e) Skin and subcutaneous : maculopapular and erythematous rashes. Rarely reported - alopecia, fixed drug eruption, photosensitivity, pruritus, rash, urticaria, onycholysis, discolouration of the nails, tongue, gum and lip, pigmentation of the skin and mucous membrane, erythema multiforme, erythema nodosum. Lesions occurring on the glans penis have caused balanitis. Very rare, serious events have occurred with minocycline hydrochloride including angioedema, exfoliative dermatitis, hyperpigmentation of nails, Stevens-Johnson syndrome, vasculitis and toxic epidermal necrolysis. Minocycline hydrochloride should be discontinued if either of these serious skin reactions is suspected. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) – discontinue minocycline if DRESS is suspected.
f) Hypersensitivity reactions : urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythematosus.

g) Autoimmune : autoimmune hepatotoxicity, lupus-like syndrome, cases of or exacerbation of systemic lupus erythematosus, and myocarditis.
h) Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanelles have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve soon after discontinuation of the tetracycline, the possibility for permanent sequelae exists.
i) Respiratory : rarely - cough and dyspnea, very rarely - bronchospasm, exacerbation of asthma and pulmonary eosinophilia and undetermined frequency of pneumonitis have been reported.
j) Other : fever, elevated liver enzymes including SGOT or SGPT values, hepatic cholestasis, hepatic failure (including fatalities) hyperbilirubinemia, jaundice, autoimmune hepatitis, hemolytic anemia, leukopenia, neutropenia, thrombocytopenia and eosinophilia and pancytopenia and agranulocytosis. When given over prolonged periods, minocycline, like other tetracyclines, has been reported to produce brown-black microscopic discolouration of the thyroid gland. Very rarely, abnormalities of thyroid function have been reported. If adverse effects or idiosyncrasy occur, the administration of minocycline should be discontinued and appropriate alternate therapy instituted. Very rare incidence of oral and anogenital candidiasis and vulvovaginitis have also been reported. Very rarely- Discoloration of secretions have been reported.

Warnings/Precautions

Anaphylactic/Anaphylactoid Reactions:

Rarely, anaphylactic/anaphylactoid reactions including shock and fatalities have been associated with the administration of minocycline hydrochloride.

Gastrointestinal: Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including minocycline (see ADVERSE EFFECTS). CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of Clostridium difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory, to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against Clostridium difficile. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against Clostridium difficile. Surgical evaluation should be instituted as clinically indicated since surgical intervention may be required in certain severe cases.

Newborns, Infants and Children : Minocycline is contraindicated in children under 13 years of age (see CONTRAINDICATIONS). The use of tetracyclines, including minocycline, during tooth development (last half of pregnancy, infancy and childhood under the age of thirteen years) has been shown to cause permanent tooth discolouration (yellowgrey-brown). This is more common during long-term use, but has been observed following short-term courses. Enamel hypoplasia has also been reported. All tetracyclines including minocycline form a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25mg/kg every 6 hours. This appeared to be reversible when the drug was discontinued.

Congenital anomalies including limb reductions have been reported in postmarketing experience.

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.

Treatment of Streptococcal Infections : Minocycline should not be used for the treatment of streptococal diseases unless the organism is demonstrated to be sensitive, since most streptococci have been found to be resistant to tetracycline drugs. If it is deemed necessary that infection due to Group A beta-hemolytic streptococci be treated with minocycline, then such treatment should be continued for at least ten days.

Renal Impairment : In the presence of significant renal impairment, usual oral doses may lead to excessive systemic accumulations of minocycline and possible liver toxicity. Under such conditions, lower than usual doses may be indicated. After initial therapy, and if therapy is prolonged, serum level determinations of the drug are advisable.

The anti-anabolic action of tetracyclines can also produce dose-related increases in BUN; consequently, in patients with significant renal impairment, elevated serum minocycline levels can lead to azotemia, hypophosphatemia and acidosis. Renal failure, including interstitial nephritis, has been reported rarely.

Auto-immune Disorders : Rare cases of auto-immune hepatotoxicity and isolated cases of systemic lupus erythematosus (SLE) have been reported (see ADVERSE EFFECTS). Also, Minocycline is capable of aggravating the symptoms associated with lupus erythematosus. Therefore, caution should be taken when administering the drug to patients with this disease. If patients develop signs or symptoms of SLE or hepatotoxicity, or suffer exacerbation or pre-existing SLE, minocycline should be discontinued.

Myasthenia Gravis : Minocycline is contraindicated in patients with myasthenia gravis as tetracyclines can cause weak neuromuscular blockade (see CONTRAINDICATIONS).

Cross-sensitivities : Cross-sensitization between tetracyclines may develop in micro-organisms and cross-sensitization among the various tetracyclines is extremely common. Minocycline should be discontinued if there are signs/symptoms of overgrowth of resistant organisms, enteritis, glossitis, stomatitis, vaginitis, pruritus ani or staphylococcal enteritis (see ADVERSE EFFECTS).

Hyperpigmentation : As with other tetracyclines, minocycline may cause hyperpigmentation at various body sites (see ADVERSE EFFECTS), including the skin, nails, teeth, oral mucosa, bones, thyroid, eyes (including sclera and conjunctiva), breast milk, lacrimal secretions and perspiration. The black/blue/grey or muddy-brown discolouration may be localized or diffuse. The most frequently reported site is in the skin (see ADVERSE EFFECTS). Hyperpigmentation may present regardless of dose or duration of therapy but develops more commonly during long term treatment. 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.

Patients should be advised to report any unusual pigmentation without delay and minocycline should be discontinued.

Oral Contraceptives : Reduced efficacy and increased incidence of breakthrough bleeding has been suggested with concomitant use of tetracycline and oral contraceptive preparations.

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

Susceptibility/Resistance : Development of Drug Resistant Bacteria

Prescribing MINOCYCLINE in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Precautions :

Children : The administration of **AA-MINOCYCLINE** (minocycline hydrochloride) to children under 13 years of age is contraindicated.

Skin and Subcutaneous Tissue Disorders : Very rare, serious events have occurred with minocycline hydrochloride including Stevens-Johnson Syndrome and toxic epidermal necrolysis. Minocycline hydrochloride should be discontinued if either of these serious skin reactions is suspected.

Intracranial Hypertension : Bulging fontanelles have been reported in young infants following full therapeutic dosage of tetracyclines including minocycline. Pseudotumor cerebri (benign intracranial hypertension) has been reported in juveniles and adults. (See ADVERSE EFFECTS). The clinical manifestations were headache and visual disturbances including blurring of vision, scotoma and diplopia. While these conditions and related symptoms usually resolved after discontinuation of the tetracycline, permanent vision loss has been reported. Treatment should cease if evidence of raised intracranial pressure develops.

Photosensitivity : Patients should be warned to avoid exposure to direct sunlight and/or ultraviolet light while under treatment with minocycline or other tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema or discomfort. Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Studies to date indicated that photosensitivity is rarely reported with minocycline.

Overgrowth of Non-susceptible Organisms : As with other antibiotics, minocycline therapy may result in overgrowth of non-susceptible organisms (including fungi). If super infection occurs, minocycline should be discontinued and appropriate therapy instituted.

Cross-sensitivities : The development of cross-resistance to many antibiotics can develop rapidly in several species of micro-organisms. The clinician should bear this in mind if therapy with minocycline is not achieving expected results.

The frequency of resistance to minocycline in hemolytic streptococci is highest in strains from infections of the ear, wounds and skin. Culture and sensitivity studies should be performed whenever feasible and routinely in suspected streptococcal infections. Since sensitivity reactions are more likely to occur in persons with a history of allergy, asthma, hay fever, or urticaria, minocycline should be used with caution in such individuals.

Treatment of Gonorrhea : Before treating patients with gonorrhea, a darkfield examination should be made from any lesion suggestive of concurrent syphilis. Serological tests for syphilis should be repeated monthly for at least 4 months.

Hepatic Dysfunction : Hepatotoxicity has been reported with minocycline hydrochloride; therefore, minocycline should be used with caution in patients with hepatic dysfunction and in conjunction with alcohol or other hepatotoxic drugs.
Laboratory monitoring : In long-term therapy with minocycline, periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed.
Sucrose : Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
Adverse Reactions – Syndromes : The following syndromes have been reported. In some cases involving these syndromes, death has been reported (see ADVERSE EFFECTS). As with other serious adverse effects, 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, 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.
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) : Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) including fatal cases have been reported with minocycline use. DRESS, which often occurs several weeks after initiation of treatment, consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy, and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis.
Discontinue minocycline if DRESS is suspected.

Interactions with Other Medicaments :
Penicillins : It is advisable to avoid giving minocycline in conjunction with penicillin since some bacteriostatic drugs may interfere with the bactericidal action of penicillin.
Retinoids : Administration of isotretinoin or other systemic retinoids or retinol should be avoided shortly before, during, and shortly after minocycline therapy. Each of these agents used alone has been associated with pseudotumor cerebri (benign intracranial hypertension).
Anticoagulants : Minocycline has been shown to depress plasma prothrombin activity. Therefore patients who are on anticoagulant therapy should be monitored regularly and may require downward adjustment of their anticoagulant dosage. Interference with vitamin K synthesis by micro-organisms in the gut has been reported.
Oral Contraceptives : The concurrent use of tetracyclines with oral contraceptives may render oral contraceptives less effective.
Diuretics : Diuretics may aggravate nephrotoxicity by volume depletion.
Ergot Alkaloids : Increased risk of ergotism when ergot alkaloids or their derivatives are given with tetracyclines.
Drugs Impairing Minocycline Absorption : Absorption of minocycline is impaired by antacids containing aluminum, calcium or magnesium, and oral iron preparations, as well as bismuth and zinc salts - interactions with specific salts and antacids, bismuth containing ulcer-healing drugs, quinapril which contains a magnesium carbonate excipient. These should not be given to patients taking oral minocycline.
Food Interactions : Dairy products can delay absorption. Studies to date have indicated that the absorption of minocycline is not notably influenced by foods.

Pregnancy and Lactation : Tetracyclines, including minocycline, are contraindicated during pregnancy and lactation because of possible adverse effects on developing bones and teeth of the fetus and neonate. Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). If minocycline hydrochloride is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
Evidence of embryo-toxicity has also been noted in animals treated early in pregnancy. The safety of minocycline for use during pregnancy has not been established.
Tetracyclines, including minocycline, are excreted in the milk of lactating women; therefore, a decision should be made whether to discontinue breast-feeding or to discontinue minocycline.
Fertility : There are no relevant data available.

Effects on Ability to Drive and Use Machine :
Ability to Perform Tasks that Require Judgement, Motor, or Cognitive Skills : Patients treated with minocycline may suffer from headaches, light-headedness, dizziness or vertigo (more common in women). Decreased hearing has been rarely reported in patients on minocycline hydrochloride. Administration of minocycline in excess of the

recommended dosage can increase the frequency and severity of these CNS symptoms. Patients 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.

Contraindications :

- Patients who are sensitive to this drug or to any ingredient in the formulation
- History of hypersensitivity to minocycline or any other tetracycline.
- Pregnancy and lactation (see WARNINGS)
- Children under 13 years (see WARNINGS)
- Complete renal failure
- Severe liver disease
- Myasthenia gravis

Dosage : Children 13 years of Age or Older :
The usual dosage of **AA-MINOCYCLINE** (minocycline hydrochloride) is 4mg/kg initially followed by 2mg/kg every 12 hours. Tetracyclines are not recommended in children under 13 years of age (See **WARNINGS**).
Adults :
The usual oral dosage of **AA-MINOCYCLINE** is 100mg or 200mg initially, followed by 100mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50mg doses may be given initially, followed by one 50mg dose every 6 hours. Therapy should be continued for 1 or 2 days beyond the time when characteristic symptoms or fever have subsided.
For treatment of syphilis, **AA-MINOCYCLINE** therapy should be administered over a period of 10 or 15 days.
Close follow-up, including laboratory tests, is recommended. Concomitant therapy :
Antacids containing aluminum, calcium or magnesium and/or iron preparations impair absorption and should not be given to patients taking minocycline.

Symptoms and Treatment of Overdosage : Symptoms and Signs **:**
Dizziness, nausea, vomiting, abdominal pain, intestinal hemorrhage, hypotension, lethargy, coma, acidosis, azotemia without a concomitant rise in creatinine.
Treatment : Specific antidote : None.
General antidotes : Antacids (e.g., calcium carbonate or lactate, milk of magnesia, aluminium hydroxide) which form relatively insoluble complexes with minocycline.
(Calcium Solution 5% : 50g calcium carbonate or lactate dissolved in 1000mL water, yields a 5% solution). Gastric lavage, if necessary.

Availability of Dosage Forms :
AA-Minocycline Capsules 50mg :
Each Light orange opaque body, light orange opaque cap, hard-gelatin capsule. Imprinted APO 50. Yellow powder fill, contains minocycline hydrochloride equivalent to 50mg minocycline.
Available in bottles of 100's.
AA-Minocycline Capsules 100mg :
Each Light orange opaque body, purple opaque cap, hard-gelatin capsule. Imprinted APO 100. Yellow powder fill, contains minocycline hydrochloride equivalent to 100mg minocycline. Available in bottles of 100's.

Storage Conditions : Store below 30°C.

Manufacturer : Apotex Inc, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3.

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