PREScribing INFORMATION

PrTEVA-MINOCYCLINE
(Minocycline Hydrochloride)
50 mg and 100 mg Capsules
USP

Antibiotic

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Therapeutic Classification
Antibiotic

Action & Clinical Pharmacology
Preva-Minocycline (minocycline hydrochloride), a tetracycline antibiotic, has activity against some gram-negative and gram-positive organisms. The antibacterial effect of minocycline is primarily bacteriostatic and is thought to act by inhibiting protein synthesis.

Indications & Clinical Use
Preva-Minocycline (minocycline hydrochloride) may be indicated for the treatment of the following infections due to susceptible strains of the following organisms:
Gall bladder infections caused by Escherichia coli.
Urinary tract infections: cystitis, gonorrhea, pyelonephritis caused by Escherichia coli, Proteus species, Enterobacter aerogenes, Neisseria gonorrhoea, Klebsiella species.13(687)

Preva-Minocycline may be employed as an alternative drug in the treatment of anal and pharyngeal gonorrhea and syphilis when penicillin is contraindicated.
Skin and soft tissue infections: abscess, cellulitis, furunculosis, impetigo and pyoderma caused by: *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Proteus* species, *Escherichia coli*. TEVA-MINOCYCLINE could be useful in circumstances where staphylococcal or streptococcal organisms are shown to be resistant to other agents but sensitive to minocycline, even though tetracyclines are not the drugs of choice in these infections. Bacterial evaluation suggests that a relatively lower success rate may be expected in clinical cases involving proteus organisms.

Respiratory tract infections: pharyngitis, bronchitis, pneumonia, bronchopneumonia, sinusitis and tonsillitis caused by *Haemophilus influenzae*, *Klebsiella* species, *Enterobacter* species. For acute throat infections, tetracyclines should not be prescribed.

**CONTRAINDICATIONS**

TEVA-MINOCYCLINE (minocycline hydrochloride) is contraindicated in patients with a hypersensitivity to minocycline or any other tetracycline.

**WARNINGS**

Newborns, Infants and Children: Permanent tooth discolouration (yellow-gray-brown) has resulted from the use of tetracyclines, including minocycline, during tooth development (last half of pregnancy, infancy and childhood under the age of thirteen years). Although it has been observed following short-term courses, it is more common during long-term use. There have also been reports of enamel hypoplasia. A stable calcium complex is formed by all tetracyclines, including minocycline, in any bone forming tissue. The fibula growth rate has been observed to decrease in prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. Upon
discontinuation of the drug, this appeared to be reversible. Unless other drugs are ineffective or are contraindicated, minocycline should not be used in such patients.

**Pregnancy and Lactation:** Because of possible adverse effects on developing bones and teeth of the fetus and neonate, tetracyclines, including TEVA-MINOCYCLINE (minocycline hydrochloride), are not recommended during pregnancy and lactation. Animal study results have indicated 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).

Animals treated early in pregnancy have shown evidence of embryotoxicity. It has not been established if minocycline is safe for use during pregnancy.

Minocycline and other tetracyclines are excreted in the milk of lactating women.

Since some bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving TEVA-MINOCYCLINE in conjunction with penicillin.

As most streptococci have been found to be resistant to tetracycline drugs, minocycline should not be used for the treatment of streptococcal diseases unless the organism is demonstrated to be sensitive. Treatment of infections due to Group A beta-hemolytic streptococci should be continued for at least 10 days if it is deemed necessary to treat such infections with minocycline.

Usual oral doses may lead to excessive systemic accumulations of MINOCYCLINE and possible liver toxicity when significant renal impairment exists. Lower than
usual doses may be indicated under such conditions. Serum level determinations of
the drug are advisable after initial therapy and if therapy is prolonged.

The anti-anabolic action of tetracyclines also produce dose related increases in BUN;
therefore, in patients with significant renal impairment, higher serum minocycline
levels can lead to azotemia, hypophosphatemia and acidosis.

The symptoms associated with lupus erythematosus may be aggravated by
minocycline. Therefore, when administering the drug to patients with this disease,
caution should be taken.

Depressed plasma prothrombin activity has occurred with minocycline use.
Therefore, patients should be monitored regularly if they receive anticoagulant
therapy. Their anticoagulant dosage may require downward adjustment. There have
been reports of interference with vitamin K synthesis by microorganisms in the gut.

It is extremely common to have cross-sensitization among the various tetracyclines.

In persons receiving minocycline, usually for extended periods of time, there have
been occasional reports of pigmentation of skin, thyroid, bone and teeth which may
be irreversible.

Reduced efficacy and increased incidence of breakthrough bleeding has been
suggested with concomitant use of tetracycline and oral contraceptives.
PRECAUTIONS

It is recommended that TEVA-MINOCYCLINE (minocycline hydrochloride) not be administered to children under 13 years of age.

Following full therapeutic dosage of tetracyclines, including minocycline, bulging fontanels have been reported in young infants. Very rarely, pseudotumor cerebri have been reported in adults. Upon discontinuation of the drug, these signs disappeared rapidly (see ADVERSE REACTIONS).

While under treatment with TEVA-MINOCYCLINE or other tetracycline drugs, patients should be warned to avoid exposure to direct sunlight and/or ultraviolet light. Treatment should be discontinued at the first evidence of skin erythema or discomfort. In some individuals taking tetracyclines, photosensitivity manifested by an exaggerated sunburn reaction has been observed. Studies to date have rarely reported photosensitivity in association with minocycline.

Headaches, lightheadedness, dizziness or vertigo may occur in patients treated with TEVA-MINOCYCLINE. The frequency and severity of these CNS symptoms can be increased when TEVA-MINOCYCLINE is administered in excess of the recommended dosage. While on TEVA-MINOCYCLINE therapy, patients should be cautioned about driving vehicles or using hazardous machinery. These symptoms usually disappear when the drug is discontinued, but may disappear during therapy.

TEVA-MINOCYCLINE therapy may result in overgrowth of non-susceptible organisms (including fungi), as with other antibiotics. TEVA-MINOCYCLINE should be discontinued if superinfection occurs, and appropriate therapy instituted.
Cross-resistance to many antibiotics can develop rapidly in several species of microorganisms. The clinician should consider this if therapy with TEVA-MINOCYCLINE is not achieving the expected results.

Strains of hemolytic streptococci from infections of the ear, wounds and skin have the highest frequency of resistance to minocycline. Whenever feasible, culture and sensitivity studies should be performed. In suspected streptococcal infections, these studies should be performed routinely.

TEVA-MINOCYCLINE should be used with caution in patients with a history of allergy, asthma, hay fever or urticaria since sensitivity reactions are more likely to occur in such individuals.

A darkfield examination should be made from any lesion suggestive of concurrent syphilis before treating patients with gonorrhea. Monthly serological tests for syphilis should be repeated for at least 4 months.

TEVA-MINOCYCLINE should be used cautiously in patients with hepatic dysfunction and when used in conjunction with alcohol or other hepatotoxic drugs.

Periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies, should be performed when TEVA-MINOCYCLINE is used in long-term therapy.

Plasma prothrombin activity has been depressed with minocycline. Patients on anticoagulant therapy should, therefore, be monitored regularly. Their anticoagulant
dosage may require downward adjustment. The interference of vitamin K synthesis by microorganisms in the gut has been reported.

Patients taking oral minocycline should not be given oral iron preparations and antacids containing aluminum, calcium or magnesium since they impair absorption.

Absorption can be delayed by dairy products. However, studies to date have not indicated that food notably influences minocycline absorption.

**ADVERSE REACTIONS**

Adverse reactions which have been reported with tetracycline analogues, including minocycline, follow:

a) **Central Nervous System**: Increased intracranial pressure, headaches, lightheadedness, dizziness or vertigo and fainting spells (rare) have been reported with an overall incidence of approximately 7% in patients treated with minocycline. This is variable, however. When the drug is discontinued, these symptoms usually disappear rapidly.

b) **Gastrointestinal System**: Nausea, vomiting, anorexia, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani, constipation, dysphagia and inflammatory lesions (with monilial overgrowth) in the anogenital region.

c) **Teeth and Bone**: There have been reports of dental staining (yellow-gray-brown) 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 the age of 13 years. Enamel hypoplasia has been reported also. Rarely, upon extended treatment with
minocycline, discolouration of bones and teeth has been documented to occur. The mechanism of staining, although not completely elucidated at present, appears to be mediated by the formation of a stable iron complex. The effects may be irreversible.

d) **Renal**: An apparently dose related rise in BUN has been reported. There have also been reports of increased excretion of nitrogen and sodium.

e) **Skin**: Maculopapular and erythematous rashes. Exfoliative dermatitis, onycholysis, discolouration of the nails, pigmentation of the skin and mucous membrane, erythema multiforme and Stevens–Johnson syndrome.

f) **Hypersensitivity Reactions**: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, polyarthritis and exacerbation of systemic lupus erythematosus.

g) **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 fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve soon after stoppage of the tetracycline, the possibility for permanent consequences exists.

h) **Other**: Elevated SGOT or SGPT values, hepatic cholestasis, hemolytic anemia, neutropenia, thrombocytopenia and eosinophilia. Minocycline, like other tetracyclines, has been reported to produce brown-black microscopic discolouration of the thyroid gland when given over prolonged periods. Abnormal–ities of thyroid function in humans, however, have not been shown to date. The administration of TEVA-MINOCYCLINE should be discontinued and appropriate alternate therapy instituted if adverse reactions or idiosyncrasy occur.
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:
There is no specific antidote. Antacids (e.g., calcium carbonate or lactate, milk of magnesia, aluminum hydroxide) are general antidotes as they form relatively insoluble complexes with minocycline. (Calcium solution 5%: 50 g calcium carbonate or lactate dissolved in 1000 mL water yields a 5% solution.) Gastric lavage may be used, if necessary.

DOSAGE AND ADMINISTRATION

Children 13 Years of Age or Older:
TEVA-MINOCYCLINE (minocycline hydrochloride) should usually be initiated at 4 mg/kg, followed by 2 mg/kg every 12 hours. The administration of tetracyclines to children under 13 years of age is not recommended (see WARNINGS).

Adults:
Initially, the usual oral dosage of TEVA-MINOCYCLINE is 100 mg or 200 mg, followed by 100 mg every 12 hours. If more frequent doses are preferred, two or four 50 mg doses may be given initially, followed by one 50 mg dose every 6 hours. TEVA-MINOCYCLINE therapy should be continued for 1 or 2 days beyond the time when characteristic symptoms or fever have subsided.
MINOCYCLINE should be administered over a period of 10 or 15 days for the treatment of syphilis. In these patients, close follow-up, including laboratory tests, is recommended.

Concomitant therapy: Patients taking TEVA-MINOCYCLINE should not be given antacids containing aluminum, calcium or magnesium and/or iron preparations because they impair absorption.

**AVAILABILITY**

TEVA-MINOCYCLINE (minocycline hydrochloride) is available in orange, hard gelatin capsules containing 50 mg of minocycline base, and orange and purple, hard gelatin capsules containing 100 mg of minocycline base. Both strengths are packaged in bottles of 100 and 500 and in unit dose strips of 10.

**STABILITY AND STORAGE RECOMMENDATIONS**

Bottles should be stored between 15–30°C in tight, light-resistant containers. Unit dose boxes should be stored between 15–25°C and protected from light and high humidity.