PRESCRIBING INFORMATION

PrRAN™-MINOCYCLINE
(Minocycline Hydrochloride)

Capsules 50 mg and 100 mg minocycline (as minocycline hydrochloride)

USP

Antibiotic

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COMPLETE PRESCRIBING INFORMATION

[Pr]RAN™-MINOCYCLINE

(minocycline hydrochloride)

THERAPEUTIC CLASSIFICATION
Antibiotic

ACTIONS

Minocycline hydrochloride is a tetracycline with antibacterial activity against some Gram-negative and Gram-positive organisms. The action of RAN-MINOCYCLINE is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis.

INDICATION AND CLINICAL USES

RAN-MINOCYCLINE (minocycline hydrochloride) may be indicated for the treatment of the following infections due to susceptible strains of the designated organisms:

Gall bladder infections caused by *Escherichia coli*.

Urinary tract infections: cystitis, gonorrhea, pyelonephritis caused by *Escherichia coli*, *Proteus species, Klebsiella* species, *Enterobacter aerogenes*, *Neisseria gonorrhea.*

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, cellulitis, furunculosis, impetigo and pyoderma caused by: *Staphylococcus epidermidis. Staphylococcus aureus, Streptococcus pyogenes, Proteus species, Escherichia coli*. Although tetracyclines are not the drugs of choice in any staphylococcal or streptococcal infection minocycline could be useful in circumstances where these organisms are shown to be resistant to other agents but sensitive to minocycline. Bacterial evaluation of clinical cases involving proteus suggests a relatively lower success rate may be expected where these organisms are concerned.

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of RAN-MINOCYCLINE and other antibacterial drugs, RAN-MINOCYCLINE should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the Dosage Forms section.
- History of hypersensitivity to minocycline or any other tetracycline.
- Pregnancy and lactation (see WARNINGS, Pregnancy and Lactation)
- Children under 13 years (see WARNINGS, Newborns, Infants and Children)
- Complete renal failure
- Severe liver disease
- Myasthenia gravis

WARNINGS

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 REACTIONS). 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 s contraindicated in children under 13 years of age (see CONTRAINDICATIONS). The use of tetracycline 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 (yellow-grey-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 administered during the last trimester form a stable calcium complex throughout the human fetal skeleton. 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 appeared to be reversible when the drug was discontinued.

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

Pregnancy and lactation:

Tetracyclines including minocycline, are contraindicated during pregnancy and lactation (see CONTRAINDICATIONS) 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 embryotoxicity 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.

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.

Penicillins:

It is advisable to avoid giving minocycline in conjunction with penicillin since some bacteriostatic drugs may interfere with the bactericidal action of penicillin.

Treatment of Streptococcal Infections:

Minocycline should not be used for the treatment of streptococcal 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 REACTIONS). 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.

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.

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 REACTIONS).

Hyperpigmentation:

As with other tetracyclines, minocycline may cause hyperpigmentation at various body sites (see ADVERSE REACTIONS), 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 REACTIONS).

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 RAN-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 RAN-MINOCYCLINE 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 REACTIONS). 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 indicate that photosensitivity is rarely reported with minocycline.

Ability to Perform Tasks that Require Judgement, Motor, or Cognitive Skills:

Patients treated with minocycline may suffer from headaches, light-headedness, dizziness, tinnitus 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.

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 hydrochloride should be used with caution in patients with mild to moderate hepatic dysfunction and in conjunction with alcohol or other hepatotoxic drugs.

Laboratory Monitoring:

Periodic laboratory evaluation of organ system functions, including hematopoietic, renal and hepatic, should be performed.

Sucrose:

Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Diuretics:

Diuretics may aggravate nephrotoxicity by volume depletion.

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:

Food and/or milk reduce the absorption of tetracycline. Minocycline is not affected to the same extent.

In a study by Leyden, the absorption of a single 100 mg dose of minocycline was inhibited by the ingestion of solid food by 13% (as measured by a reduction in mean serum concentration), and the absorption of a single 250 mg dose of tetracycline was inhibited by 46% when that antibiotic was administered with solid food. When administered with milk, the mean serum concentration of minocycline was reduced by 27% and that of tetracycline, by 65%. The clinical significance of such declines in serum levels is not known. Laboratory Tests: Interference with laboratory and other diagnostic tests: False evaluations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Oral Contraceptives:

The concurrent use of tetracyclines with oral contraceptives may render oral contraceptives less effective.

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).

Ergot Alkaloids:

Increased risk of ergotism when ergot alkaloids or their derivatives are given with tetracyclines.

Adverse Reactions – Syndromes:

The following syndromes have been reported. In some cases involving these syndromes, death has been reported (see ADVERSE REACTIONS). 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, 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.

ADVERSE REACTIONS

The following adverse reactions have been reported with the tetracycline analogues including minocycline:

(a) Central Nervous System: increased intracranial pressure, 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, pancreatitis, 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: 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.

(f) Hypersensitivity reactions: urticaria, angioneurotic edema, polyarthralgia, anaphylaxis/anaphylactoid reactions (including shocks and fatalities), hypersensitivity, anaphylactoid purpura and pericarditis. Myalgia has also been reported.

(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 reactions 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

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. In cases of overdose, discontinue medication, treat symptomatically and with appropriate supportive measures. Minocycline is not removed in significant quantities by haemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

Children 13 Years of Age or Older:

The usual dosage of RAN-MINOCYCLINE (minocycline hydrochloride) is 4 mg/kg initially followed by 2 mg/kg every 12 hours. Tetracyclines is contraindicated in children under 13 years of age (see CONTRAINDICATIONS).

Adults:

The usual oral dosage of RAN-MINOCYCLINE is 100 mg or 200 mg initially, followed by 100 mg every 12 hours. Alternatively, 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. Therapy should be continued for 1 or 2 days beyond the time when characteristic symptoms or fever have subsided.

For treatment of syphilis, RAN-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.

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.

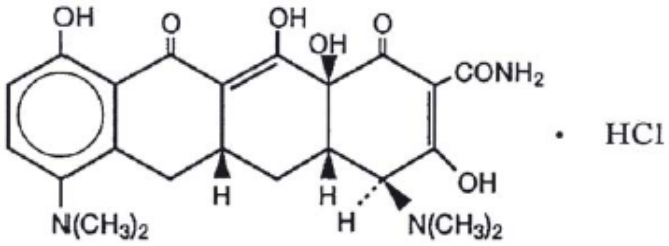
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: minocycline hydrochloride

Chemical Name: 4, 7-Bis(dimethylamino)-l, 4, 4a, 5, 5a, 6, 11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1, 11-dioxo-2-naphthacene-carboxamide monohydrochloride.

Structural Formula:



Molecular Formula: $C_{23}H_{27}N_30_7$.HCl Molecular Weight: 493.94 g/mol

Description:

Minocycline hydrochloride, USP is a yellow crystalline powder which is sparingly soluble in water; soluble in solutions of alkali hydroxides and carbonates, slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Composition In addition to the active ingredient minocycline, each capsule contains the non-medicinal ingredients, croscarmellose sodium, lactose, magnesium stearate and stearic acid. The capsule shell contains the non-medicinal ingredients FD&C yellow #6, gelatin, sodium lauryl sulfate and titanium dioxide. The 100 mg capsule, imprinted with edible white ink, also contains the non-medicinal ingredients black iron oxide, FD&C blue #1, FD&C red #3 and shellac. The 50 mg capsule, imprinted with edible black ink, also contains the non-medicinal ingredients D&C yellow #10, FD&C blue #1, FD&C blue #2, FD&C red #40 and shellac.

Stability and Storage Recommendations
Store at 15 to 30°C. Protect from moisture.

AVAILABILITY OF DOSAGE FORMS

Capsules - 50 mg

Light orange opaque cap/light orange opaque body, hard gelatin size ‘4’ capsules imprinted with ‘rbx’ on cap and ‘M 50’ on body in black ink containing yellow color powder.

Capsules –100 mg

Purple opaque cap/light orange opaque body, hard gelatin size ‘2’ capsules imprinted with ‘rbx’ on cap and ‘M 100’ on body in black ink containing yellow powder.

Package Sizes:

RAN-MINOCYCLINE 50 mg & 100 mg Capsules are available in bottles of 10 and 500.

CLINICAL TRIALS

A double-blind, balanced, randomized, two-sequence, two-treatment, two-period, single oral dose, crossover bioequivalence study of 1 x 100 mg RAN-MINOCYCLINE (minocycline hydrochloride) capsules (Ranbaxy Pharmaceuticals Canada Inc.) and 1 x 100 mg Minocin® (minocycline hydrochloride) capsules (Stiefel Canada Inc.) was conducted in 24 healthy, adult, male subjects under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Minocycline (1 x 100 mg) From measured data Geometric mean Arithmetic mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-T} (µg.h/mL)	31.99 32.77 (24.4)	29.08 29.91 (26.2)	110.0	105.54 – 114.62
AUC_I (µg.h/mL)	32.62 33.55 (27.2)	29.67 30.64 (28.8)	109.9	105.56 – 114.51
C_{max} (µg/mL)	1.90 1.93 (18.4)	1.70 1.74 (20.7)	111.5	104.90 – 118.45
T_{max} (h)§	1.75 (0.67 - 3.00)	1.75 (1.00 - 4.00)		
$T_{½}$€ (h)	16.48 (20.0)	16.60 (22.7)		

* RAN-MINOCYCLINE (minocycline hydrochloride) Capsules 100 mg (Ranbaxy Pharmaceuticals Canada Inc.)

† Minocin® (minocycline hydrochloride) Capsules 100 mg (Stiefel Canada Inc.) were purchased in Canada

§ Expressed as the median (range) only

€ Expressed as the arithmetic mean (CV %) only

MICROBIOLOGY

This survey of the *in vitro* activity of minocycline against clinical isolates was compiled from data presented in 130 articles published from 1967 to 1980. The MICs of minocycline against clinical isolates representing gram-positive, gram-negative, actinomycetes, acid-fast and anaerobic bacteria and mycoplasma, were recorded and entered into a computer data-base file. The percent of clinical isolates inhibited at various antibiotic concentrations was determined directly from the total number of isolates tested by a computer-assisted statistical analysis system program.

BACTERIA	No. of Strains Tested	Cumulative Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L)			
		≤1	≤4	≤8	≤16
GRAM-POSITIVE					
Staphylococcus aureus	3301	77	91	96	98
Staphylococcus aureus – methicillin resistant	13	38	100		
Staphylococcus aureus – penicillin resistant	100	100			
Staphylococcus aureus – tetracycline resistant	736	50	75	84	93
Staphylococcus epidermidis	577	89	94	95	98
Staphylococcus epidermidis – methicillin resistant	19	21	89	95	95
Staphylococcus species	775	82	89	96	99
Staphylococcus species – tetracycline resistant	46	48	100		
Staphylococcus beta hemolytic	654	73	83	95	99
Streptococcus – Enterococcus group	844	18	23	28	46
Streptococcus pneumonia	508	78	88	96	99
Streptococcus pneumoniae – tetracycline resistant	70	27	57	96	100

BACTERIA	No. of Strains Tested	Cumulative Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L)			
		≤1	≤4	≤8	≤16
GRAM-NEGATIVE					
Acinetobacter calcoaceticus	456	95	99	100	
Acinetobacter species	56	96	100		
Bordetella pertussis	23	100			
Brucella species	127	75	100		
Citrobacter species	37	8	81	81	84
Enterobacter aerogenes	130	0	13	35	61
Enterobacter cloacae	131	0	9	18	44
Enterobacter species	310	7	78	91	95
Escherichia coli	1538	33	56	69	78
Haemophilus influenzae	385	62	90	98	100
Haemophilus species	182	89	98	99	100
Klebsiella-Enterobacter group	309	30	48	59	68
Klebsiella pneumoniae	299	2	35	53	69
Klebsiella species	247	7	49	62	74
Legionella pneumophila	21	62	100		
Neisseria gonorrhoeae	1082	97	100		
Neisseria gonorrhoeae - beta lactamase positive	50	90	100		
Neisseria meningitidis	613	94	100		
Proteus-indole positive species	102	1	30	47	61
Proteus mirabilis	382	4	12	32	46
Providencia species	94	1	7	16	28
Pseudomonas aeruginosa	643	7	18	36	58
Pseudomonas cepacia	90	8	19	36	58
Pseudomonas maltophilia	81	89	99	99	99
Pseudomonas pseudomallei	157	10	77	89	9
Pseudomonas species	68	68	90	91	91
Salmonella species	128	2	59	76	80
Salmonella species - tetracycline resistant	123	0	73	92	100
Serratia species	341	0	23	37	55
Shigella species	90	28	66	80	86
Vibrio cholerae type Eltor	203	61	100		
Vibrio species	367	53	100		
Yersinia species	212	94	100		

BACTERIA	No. of Strains Tested	Cumulative Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L)			
		≤1	≤4	≤8	≤16
ACID-FAST BACTERIA					
Mycobacterium tuberculosis	5	0	0	80	100
Mycobacterium species	90	4	26	71	74
ACTINOMYCETES					
Actinomyces israeli	31	100			
Actinomyces species	110	89	95	100	
Nocardia asteroides	84	1	89	100	
Nocardia species	74	30	91	99	100
MYCOPLASMA					
Mycoplasma pneumoniae	14	100			
Mycoplasma species	223	85	91	92	93
CHLAMYDIA					
Chlamydia trachomatis	3	100			
ANAEROBIC					
Bacteroides fragilis	673	44	80	97	99
Bacteroides species	431	58	77	90	92
Campylobacter fetus	97	90	91	91	91
Clostridium species	297	69	81	91	98
Eubacterium species	144	53	87	99	100
Fusobacterium species	107	66	94	100	
Peptococcus species	375	46	81	97	99
Peptostreptococcus species	242	59	85	99	99
Propionibacterium -acnes	102	89	95	100	
Propionibacterium species	70	94	97	99	100
Veillonella species	13	69	92	100	

SUSCEPTIBILITY TESTING

Tube-Dilution Testing:

Microorganisms may be considered susceptible (likely to respond to minocycline therapy), moderately susceptible (harbouring partial resistance) or resistant (not likely to respond to minocycline therapy) depending on the minimum inhibitory concentration (M.I.C.) as follows:

Minocycline M.I.C. Interpretive Standards (mg/L)

Susceptible	Susceptible	Susceptible
≤4	<4	<4

Acceptable Quality Control Ranges of M.I.C. for Reference Strains:

Reference Strain	ATCC NUMBER	mg/L
Staphylococcus aureus	29213	0.12 - 0.5
Streptococcus faecalis	29212	2.0 - 8.0
Escherichia coli	25922	0.5 - 2.0

Plate Testing:

If the Kirby-Bauer method of susceptibility testing (using a 30 mcg tetracycline disc) gives a zone of 19 mm or greater, the bacterial strain is considered to be susceptible to any tetracycline. A zone of 14 mm or less is considered resistant.

Zone diameter Interpretive Standards (30 mcg disc)

Susceptible	Susceptible	Susceptible
≥ 19 mm	≥ 19 mm	≥ 19 mm

For *Staphylococcal* species, minocycline powder may be used for additional susceptibility testing.

Acceptable Quality Control Limits (Zone Diameter) for Disc Susceptibility testing of reference strains:

Reference Strain	ATCC NUMBER	mg/L
Escherichia coli	25922	19 - 25
Staphylococcus aureus	25923	25 - 30

PHARMACOLOGY

Animal Pharmacology:

Blood levels produced following oral dosing of minocycline to various animal species were: 21 mg/L at steady state in monkeys administered 30 mg/kg, and 6.5 mg/L at 3 hours post-dose in rats given a single 25 mg/kg dose, Minocycline was extensively distributed to all tissues examined in ^{14}C-labelled drug studies in dogs.

Clinical Pharmacology

Minocycline hydrochloride pellet-filled capsules are rapidly absorbed from the gastrointestinal tract following oral administration. Following a single dose of two 100 mg pellet-filled capsules of minocycline HCl administered to 18 normal fasting adult volunteers, maximum serum concentrations were attained in 1 to 4 hours (average 2.1 hours) and range from 2.1 to 5.1 mcg/mL (average 3.5 mcg/mL). The serum half-life in the normal volunteers ranged from 11.1 to 22.1 hours (average 15.5 hours).

When minocycline hydrochloride pellet-filled capsules were given concomitantly with a meal which included dairy products, the extent of absorption of minocycline hydrochloride pellet-filled capsules was not noticeably influenced. The peak plasma concentrations were slightly decreased (11.2) and delayed by one hour when administered with food, compared to dosing under fasting conditions.

When minocycline hydrochloride tablets are administered with a meal including milk, the extent of absorption (AUC) is reduced by approximately 33% while the peak serum concentrations are reduced by approximately 32% and delayed one hour. In previous studies with other dosage forms, the minocycline half-life ranged from 11 to 16 hours in 7 patients with hepatic dysfunction, and from 18 to 69 hours in 5 patients with renal dysfunction. The urinary and faecal recovery of minocycline when administered to 12 normal volunteers is one-half to one-third that of other tetracyclines.

TOXICOLOGY

Minocycline has been tested in acute experiments in mice and rats, sub-chronic and chronic experiments in rats and dogs following oral and parenteral routes of administration.

Dietary administration of minocycline hydrochloride in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. In the rat, chronic treatment with minocycline hydrochloride has resulted in goiter accompanied by elevated radioactive iodine uptake and evidence of thyroid tumor production. Minocycline hydrochloride has been observed to cause a dark discoloration of the thyroid in animals (rats, mice, dogs, and monkey). Minocycline hydrochloride has also been found to produce thyroid hyperplasia in rats and dogs.

In addition, there has been evidence of oncogenic activity in rats in studies with a related antibiotic, oxytetracycline (ie, adrenal and pituitary tumors). Likewise, although mutagenicity studies of minocycline hydrochloride have not been conducted, positive results in *in vitro* mammalian cell assays (ie, mouse lymphoma and Chinese hamster lung cells) have been reported for related antibiotics (tetracycline hydrochloride and oxytetracycline).

Segment I (fertility and general reproduction) studies have provided evidence that minocycline hydrochloride impairs fertility in male rats.

The LD_{50} of intravenous and intraperitoneal injections of minocycline in mice was 95 mg/kg and 280 mg/kg, respectively. The oral LD50 in mice was 3100 mg/kg.

Minocycline has been given orally each day to dogs for six months at doses of 0, 4, 20 and 60 mg/kg/day (100 mg/kg/day for the first month) equally divided each day. At 20 mg/kg/day, there were no apparent drug-related findings except yellow discoloration of the skeleton and teeth in some animals, occasional emesis and black discoloration of the thyroid gland. At a dose of 4 mg/kg/day, there were no drug related findings during the six month period, with the exception of discoloration of the thyroid gland and possibly some yellowing of the bones. Peak serum drug concentrations ranging from 8.5 to 100 mg/L were obtained with 60 and 100 mg/kg/day doses, 2.1 to 9.7 mg/L with the 20 mg/kg/day dose and 0.4 to 1.5 mg/L with the 4 mg/kg/day dose.

Minocycline was also given intravenously to dogs at doses of 5, 10, 20 and 40 mg/kg/day, a very similar dose range to that of the oral study, but administered for 1 month. Untoward findings such as body weight loss, reduced food consumption, erythema of the skin and of visible mucous membranes of varying duration, intensity and incidence, were associated primarily with the high dose (40 mg/kg/day). These findings were similar, except for erythema, to those obtained after the same dose of tetracycline. These drug-related findings with minocycline hydrochloride were associated with serum concentrations of 95 mg/L, three times those found with tetracycline (31 mg/L). Dogs that received 5, 10 and 20 mg/kg/day intravenously gave serum concentrations of 412 and 38 mg/L, respectively, and were found essentially to be without toxicity. These serum values are in considerable excess of those necessary for therapeutic effectiveness in man. In these experiments, minocycline hydrochloride appeared to be tolerated as well intravenously as it was orally.

Similar results were found following chronic oral administration of minocycline hydrochloride to rats for one year.

These animals were given a drug diet containing 0.008, 0.04, 0.2 and 1.0% minocycline, which corresponded to ranges of 4.4 to 8.5, 21.3 to 44.0,108 to 122 and 593 to 812 mg/kg/day drug intake; these doses gave early morning plasma drug concentrations of 0.07 to 0.16, 0.36 to 0.51, 2.9 to 6.5 and 17 to 50 mg/L respectively. With the exception of the discoloration of the teeth (dose 0.04% drug diet or greater), femur and thyroid gland, there were no significant drug-related signs of toxicity at doses less than 1% drug diet.

As with other tetracyclines, minocycline has been found to produce discoloration of the thyroid gland in the rat, dog, monkey and human but not in the mouse. There was no evidence, however, from these investigations that thyroid function or bone growth was affected. A 23-month carcinogenicity study in the rat has shown that minocycline was not carcinogenic and that the black pigment in the thyroid gland did not cause neoplastic changes.

Biopsy specimens of thyroid tissue following the administration of minocycline and tetracycline to man revealed an intraepithelial lipofuscin deposition of both drugs, considered to be within normal variation. Thyroid function studies in man displayed a decrease within the normal range of thyroxine, indicating a tendency toward relative hypothyroidism.

Other than the tooth and bone discoloration that also occurs with other tetracyclines and the thyroid pigmentation seen in rats, dogs and monkeys, toxic effects of minocycline were observed only where serum concentrations were in excess of the therapeutic concentrations. It is concluded from the chronic safety evaluation studies that minocycline has a good margin of safety between therapeutic blood concentrations and concentrations producing toxic effects.

Reproduction studies performed in rats, rabbits and dogs have shown, as with other tetracyclines in animal studies that minocycline crosses the placenta, is found in fetal tissues and can produce toxic effects on the developing embryo, fetus or neonate when present in sufficient amounts.

The effects observed on the conceptus in rats and rabbits ranged from a low incidence of slight retardation of ossification and slight angulation of ribs at oral doses of 70 mg/kg/day in rats and 25 mg/kg/day in rabbits during pregnancy, to more extensive retardation of ossification and generalized morphologic changes and death at doses of 150 mg/kg/day and higher in the rat fetus. On other experiments, no deleterious effects were reported in rats or rabbits with oral doses as high as 100 and 75 mg/kg/day respectively. No adverse effects due to minocycline were seen in the newborn of 2 dogs given 20 mg/kg in 2 equally divided daily doses from days 35 to 62 of pregnancy.

BIBLIOGRAPHY

1. Anthony JR. Effect on deciduous and permanent teeth of tetracycline deposition in utero. Postgrad Med 1970;48(4):165-8.

2. Bach MC, Zinner SH, Wilcox C, Finland M. Efficacy of standard disc-diffusion test as applied to susceptibility of Staphylococcus aureus to tetracycline and minocycline. J Lab Clin Med 77(2), 1972

3. Bacon JF, Shenfield GM. Pregnancy attributable to interaction between tetracycline and oral contraceptives. Br Med J 1980;1:293.

4. Benitz KF, Roberts GKS, Yusa A. Morphologic effects of minocycline in laboratory animals. Toxicol Appl Pharm 1967;11:150-70.

5. Bernard B, Yin EJ, Simon HJ. Clinical pharmacologic studies with minocycline. J Clin Pharm 1971;332-48.

6. Bevelander G, Cohlan SQ. The effect on the rat fetus of transplacentally acquired tetracyclines. Bio Neonatorum 1962;4:365-70.

7. Bhattacharjee SB, Pal B, Bhaumik G. Further studies on tetracycline-induced mutation in V79 Chinese hamster cells. Mutat Res 1984;135:211-7.

8. Boucher D, Delost P. Développement post-natal de la souris après traitement de la mère gestante et des descendants par les tétracyclines. Compt Rend Soc Biol 161:300-305,1967.

9. Boudreaux JP, Hayes DH, Mizrahi S, Hussey J, Regenstein F, Balart L. Fulminant hepatic failure, hepatorenal syndrome, and necrotizing pancreatitis after minocycline hepatotoxicity. Transplant Proc 1993;25(2):1873.

10. Burette A, Finet C, Prigogine T, De Roy G, Deltenre M. Acute hepatic injury associated with minocycline. Arch Intern Med 1984;144:1491-2.

11. Carney S, Butcher RA, Dawborn JK, Pattison G. Minocycline excretion and distribution in relation to renal funtion in man. Clin Exp Pharm Physiol 1974;1:299-308.

12. Cartwright AC, Hatfield HL, Yeadon A, London E. A comparison of the bioavailability of minocycline capsules and film-coated tablets. J Antimicrob Chemother 1975;1:317-22.

13. Chiu AM, Chuenkongkaew WL, Cornblath WT, Trobe JD, Digre KB, Dotan SA, et al. Minocycline treatment and pseudotumor cerebri syndrome. Am J Ophthalmol 1998;126(1):116-21.

14. Cohlan SQ, Bevelander G, Tiamsic T. Growth inhibition of prematures receiving tetracycline. Am J Dis Child 1963;105:453-61.

15. Corcoran R, Castles JM. Tetracycline for acne vulgaris and possible teratogenesis. Br Med J 1977;2:807-8.

16. Cunha BA, Comer JB, Jonas M. The Tetracyclines. Med Clin of Nort Am 1982;66(1):293-302.

17. Danos EA. Apparent potentiation of warfarin activity by tetracycline. Clin Pharm. 1992;11:806-8.

18. Data on file: Wyeth-Ayerst Pharmaceuticals. Periodic Safety Update Report (PSUR); February 1996-December 1998.

19. Davies MG, Kersey PJW. Acute hepatitis and exfoliative dermatitis associated with minocycline. BMJ 1989;298(6686):1523-4.

20. Delaney RA, Wee D, Narayanaswamy TR. Pseudo-tumor cerebri and acne. Milit Med 1990;155(10):511.

21. Fedorke J, Katz S, Allnoch H. *In Vitro* activity of minocycline, a new tetracycline. Am J Med Sci 255:252-258 1968.

22. Fields JP. Bulging fontanel: a complication of tetracycline therapy in infants. J Pediatr 1961;58(1):74-6.

23. Frisk AR, Tunevall G. Minocycline: Clinical evaluation, abstract of papers. Eighth Interscience Conference on Antimicrobial Agents and Chemotherapy. New York (Oct.) 1968 p. 49

24. George CRP, Guinness MDG, Lark DJ, Evans RA. Minocycline toxicity in renal failure. Med J Aust 1973;1:640-1.

25. Graber CD, Jervey LP, Martin F, Boltjes BH. In Vitro and In Vivo sensitivity of staphylococci and selected bacteria to minocycline and doxycycline. Abstracts of Papers, Eighth Interscience Conference on Antimicrobial Agents and Chemotherapy. New York (Oct.) 1968 p. 49.

26. Grove Donald C, Randall WA. Assay methods of antibiotics: A laboratory manual. New York, 1955 Med Encyclopedia, (Follow the method for chlortetracycline.)

27. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs. An update. Clin Pharmacokinet 1990;18(3):210-19.

28. Halme J, Aer J. Inhibition of collagen synthesis and bone calcification in foetal rat by tetracycline. Scand J Clin Lab Invest 21:4(Suppl 101)1968.

29. Jao RL, Finland M. Susceptibility of Mycoplasma Pneumoniae to 21 antibiotics In Vitro. Amer J Med Sci 253:639-650 June 1967.

30. Kasamaki A, Urasawa S. Induction of mutagenic activity by synergistic action of multiple chemicals. J Toxicol. Sci 1979;4:310-1.

31. Kelly RG, Kanegis LA. Metabolism and tissue distribution of radioisotopically labeled minocycline. Toxicol Appl Pharmacol 11:171-183,1967.

32. Kline AH, Blattner RJ, Lunin M. Transplacental effect of tetracyclines on teeth. JAMA 1964;188(2):178-80.

33. Kasamaki A, Urasawa S. Induction of mutagenic activity by synergistic action of multiple chemicals. J Toxicol. Sci 1979;4:310-1.

34. Krevsky S. The bulging fontanelle syndrome following tetracycline administration. Mich Med 1968;67(9):597-8.

35. Kuck NA, Redin GS, Forbes M. Activity of minocycline and other tetracyclines against tetracycline-sensitive and resistant staphylococci. Pro Soc Exp Biol Med 136:479-481,1971.

36. Lander CM. Minocycline-induced benign intracranial hypertension: Clin Exp Neurol. 1989;26:161-7.

37. Lee AG. Pseudotumor cerebri after treatment with tetracycline and isotretinoin for acne. Cutis® 1995;55:165-8.

38. Lepper MH, Dowling HF. Treatment of pneumococcic meningitis with penicillin compared with penicillin plus aureomycin. Arch Intern Med 1951;88:489-94.

39. Lester MR. Sulfite sensitivity: significance in human health. J Amer Coll Nutr 1995;14(3):229-32.

40. Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride. Effect of food, milk, and iron. J Am Acad Dermatol 1985;12:308-312.

41. Lewis PA, Kearney PJ. Pseudotumor cerebri induced by minocyline treatment for acne vulgaris. Acta Dermato Venereologica 1997;77(1):83.

42. Little PJ, Bailey RR. Tetracyclines and renal failure. N Z Med J 1970;72(460):183-4.

43. Macdonald H. Effect of food and milk on absorption of minocycline. American Cyanamid Company Clinical Study 66-37, 168-79, 1967.

44. Macdonald H, Kelly RG, Allen ES, Noble JF, Kanegis LA. Pharmacokinetic studies on minocycline in man. Clin Pharmcol Ther 1973;14(5):852-61.

45. Malcolm A, Heap TR, Eckstein RP, Lunzer MR. Minocycline-induced liver injury. Amer J Gastroenterol 1996;91(8):1641-3.

46. McGregor DB, Brown AG, Howgate S, McBride D, Riach C, Casprary WJ. Responses of the L5178Y mouse Lymphoma cell forward mutation assay. V:27 coded chemicals. Environ Mol Mutagen 1991;17:196-219.

47. McHenry MC, Gavan TL, Vidt DG, Jameson S, Wagner JG. Minocycline in renal failure. Clin Pharmacol Ther 1972:13:146.

48. Min DI, Burke PA, Lewis WD, Jenkins RL. Acute Hepatic Failure Associated with Oral Minocycline: A case report. Pharmacotherapy 1992;12(1):68-71.

49. MINOCIN® Product Monograph, Professional Services Lederle Laboratories, 1990.

50. Minutello JS, Dimayuga RG, Carter J. Pseudotumor cerebri, a rare adverse reaction to tetracycline therapy: A case report. J Periodontol 1988;59(12):848-51.

51. Naline E, Sanceaume M, Toty L, Bakdach H, Pays M, Advenier C. Penetration of Minocycline into lung tissues. Br J Clin Pharmacol 1991;32:402-4.

52. Neuvonen PJ, Pentikainen PJ, Gothoni G. Inhibition of iron absorption by tetracycline {letter}. Br J Clin Pharmacol 1975;2(1):94-6.

53. Nishijima S, Namura S, Kawai S, Akamatsu H, Asada Y, Kawabata S. Sensitivity of Staphylococcus aureus and Streptococcus pyogenes isolated from skin infections in 1992 to antimicrobial agents. J Dermatol 1994;21:233-8.

54. Noble JF, Kanegis LA, Hallesy OW. Short-term toxicity and observations on certain aspects of the pharmacology of a unique tetracycline - minocycline. Toxicol Appl Pharmacol 1967; 11: 128-149.

55. Pellagali GV, d'Angelo A. Effetto della tetracycline cloridrato sulla comparsa dei nuclei di ossificazione di embrioni di ratto. Bull Soc ltal Sper 40:13211324,1964.

56. Posner AC, Prigot A, Konicoff NG. Further observations on the use of tetracycline hydrochloride in prophylaxis and treatment of obstetric infections. In Welch, H, and Morti-Ibanex, F, eds. Antibiotics Annual 1954-1955. New York Medical Encyclopedia, Inc. 1955:594-8.

57. Redin GS. Antibacterial activity in mice of minocycline, a new tetracycline. Antimicrob Ag Chemother 1966; pp 371-376.

58. Renzini G, Bevilacqua RL, Boemi G, Ravagnan L. Antimicrobial *In Vitro* and *In Vivo* activity of a new tetracycline: CL 59806. Antibioti 1967; 5:241- 261.

59. Sadowski DC. Drug interactions with antacids: mechanisms and clinical significance. Drug Saf 1994; 11:395-407.

60. Saito K, Jujio T, Hashizume I, Yamada T, Onaya T, Uehara T, et al. Studies on goitrogenic action of minocycline and related compounds. Endocrinology 1972;90(5):1192-201.

61. Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. Clin Pharmacokinet 1988;15:355-66.

62. Saxen L. Effect of tetracycline on osteogenesis In Vitro. J Exp Zool 1966; 162: 269-294.

63. Schlegal PN, Chang TSK, Marshall FF. Antibiotics: potential hazards to male fertility. Fertil Steril 1991;55(2):235-42.

64. Searcy RL, Craig RG, Foreman JA, Berqquist LM. Blood clotting anomalies with intensive tetracycline therapy. Clin Res 1965;12:230.

65. Segal BM. Photosensitivity, nail discoloration, and onycholysis: side effects of tetracycline therapy. Arch Intern Med 1963;112:165-7.

66. Shils ME. Renal disease and the metabolic effects of tetracycline. Ann Intern Med 1963;58:389-408.

67. Steigbigel NH, McCall CE, Reed CW, Finland M. Antibacterial action of "broad spectrum" penicillins, cephalosporins and other antibiotics against Gram-negative bacilli isolated from bacteremic patients. Ann N Y Acad Sci 1967; 145: 224-236.

68. Steigbigel NH, Reed CW, Finland M. Susceptibility of common pathogenic bacteria to seven tetracycline antibiotics In Vitro. Amer J Med Sci 1968; 255: 296-312.

69. Steiner G, Bradford W, Craig JM. Tetracycline-induced abortion in the rat. Lab Invest 1965;14(8):1456-63.

70. Traub WH, Leonhard B. Comparative susceptibility of clinical group A, B, C, F, and G ß-hemolytic streptococcal isolates to 24 antimicrobial drugs. Chemother 1997;43:10-20.

71. Wallman IS, Hilton HB. Teeth pigmented by tetracycline. Lancet 1962;1:827-9.

72. Walters BNJ, Gubbay SS. Tetracycline and benign intracranial hypertension: report of five cases. BMJ 1981;282(6257):19-20.

73. Weller M, Klockgether T. Minocycline-induced benign intracranial hypertension. J. Neurology 1998;245(1):55.

74. Welling PG, Shaw WR, Uman SJ, Tse FLS, Craig WA. Pharmacokinetics of minocycline in renal failure. Antimicrob Ag Chemother 1975;8:532-537.

75. Williams DN, Laughlin LW, Lee YH. Minocycline: possible vestibular sideeffects. Lancet 1974;2:744-6.

76. Zachariasen RD. Loss of oral contraceptive efficacy by concurrent antibiotic administration. Women Health. 1994;22(1):17-26.

77. PRESCRIBING INFORMATION, APO-MINOCYCLINE (minocycline hydrochloride); APOTEX Inc.; Date of Revision: August 14, 2018; Submission Control no.: 210873.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE PATIENT MEDICATION INFORMATION

RAN-MINOCYCLINE

Minocycline Hydrochloride Capsules

Read this carefully before you start taking RAN-MINOCYCLINE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about RAN -MINOCYCLINE.

What is RAN-MINOCYCLINE used for?

RAN -MINOCYCLINE is used for the treatment of infections caused by certain bacteria in many different parts of the body.

Antibacterial drugs like RAN -MINOCYCLINE treat only bacterial infections. They do not treat viral infections.

How does RAN -MINOCYCLINE work?

RAN-MINOCYCLINE is an antibiotic that belong to a class of drugs called tetracyclines. RAN - MINOCYCLINE works by slowing the growth or reproduction of bacteria that causes the infection.

What are the ingredients in RAN -MINOCYCLINE?

Medicinal Ingredient: minocycline hydrochloride
Nonmedicinal ingredients: Corn Starch, FD&C Yellow # 6, Gelatin, Iron Oxide Black, Magnesium Stearate, Propylene Glycol, Shellac Glaze, Titanium dioxide, 100 mg capsule:All ingredients of the 50 mg capsule, FD&C Blue #1, FD&C Red #3, Potassium Hydroxide, Shellac

RAN -MINCOCYCLINE comes in the following dosage forms:

Capsules: 50 mg and 100 mg.

Do not use RAN -MINOCYCLINE if you:

- are allergic to minocycline or to any of the other ingredients in RAN-MINOCYCLINE
- are allergic to other tetracycline antibiotics
- are pregnant or planning to become pregnant. RAN-MINOCYCLINE can cause damage to your unborn babies bones and teeth. If you get pregnant while taking RAN-MINOCYCLINE contact to your healthcare professional immediately.
- are breastfeeding or planning to breastfeed. RAN-MINOCYCLINE passes into human milk and can cause damage to your babies bones and teeth. You should not breastfeed while taking RAN - MINOCYLCINE.
- have liver or kidney problems
- have the autoimmune disease myasthenia gravis
- are lactose intolerant or have one of the following rare hereditary diseases:

- Galactose intolerance
- Fructose intolerance
- Sucrose-isomaltase insufficiency
- Lapp lactase deficiency
- Glucose-galactose malabsorption

Because lactose is a non-medicinal ingredient in RAN -MINOCYCLINE. RAN -MINOCYCLINE is not recommended for children under 13 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RA –MINOCYCLINE. Talk about any health conditions or problems you may have, including if you:

- have liver or kidney problems
- have the autoimmune disease systemic lupus erythematosus
- suffer from allergies, asthma, hay fever or itchy skin rashes. You may be more likely to experience side effects while taking RAN-MINOCYCLINE.
- are also taking a penicillin antibiotic
- are taking birth control pills. RAN-MINOCYLCINE may make your birth control pills less effective. Talk to your healthcare professional about using a back-up method of birth control, such as condoms, while you are taking RAN-MINOCYCLINE.

Other warnings you should know about: Sensitivity to Sunlight

RAN-MINOCYCLINE can make your skin more sensitive to the sun. While you are taking RAN-MINOCYCLINE avoid direct sunlight, sunlamps and tanning beds. If you develop any skin redness or discomfort while taking RAN-MINOCYCLINE, contact your healthcare professional immediately.

Driving and Using Machines

RAN-MINOCLYCLINE can cause headaches, light-headedness, dizziness, ringing in the ears and vertigo (feeling like you're spinning). Use caution when driving or using dangerous machinery while taking RAN-MINOCYCLINE.

Serious Side Effects

Serious side effects, in some cases causing death, have been seen in people taking RAN-MINOCYLCINE. If you have any of the following symptoms stop taking RAN -MINOCYLCINE and seek immediate medical help.

- **Allergic reaction (hypersensitivity) with skin rashes:** rash, skin redness, peeling skin, blisters on your nose, mouth, eyes or genitals, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, fever, swollen lymph nodes combined with any of the following: liver problems (yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite), lung problems (flu-like symptoms, cough, shortness of breath), kidney problems (decreased urination, nausea, vomiting, swelling of extremities, fatigue), heart problems (chest pain, fast or irregular heartbeat, shortness of breath, swelling in the legs, ankles or feet, fatigue)
- **Lupus-like syndrome:** joint and muscle pain, fatigue, fever, swollen lymph nodes, inflammation around the lungs or heart that causes pain or discomfort
- **Serum-sickness syndrome:** fever, generally feeling unwell, hives, itching, rash, joint pain, swollen lymph nodes

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RAN-MINOCYCLINE:

- penicillin antibiotics, used to treat infections
- acne medicines known as retinoids
- quinapril, used to treat heart problems and high blood pressure
- blood thinners, used to prevent blood clots
- birth control pills, RAN -MINOCYCLINE may make your birth control pills less effective.
- diuretics or "water pills" used to treat high blood pressure
- medicines used to treat migraines called ergot alkaloids
- antacids containing aluminum calcium, magnesium, bismuth or iron containing products
- magnesium or zinc salts

How to take RAN -MINOCYCLINE:

- Although you may feel better early in treatment, RAN-MINOCYCLINE should be used exactly as directed.
- Misuse or overuse of RAN -MINOCYCLINE could lead to the growth of bacteria that will not be killed by RAN -MINOCYCLINE (resistance).This means that RAN-MINOCYCLINE may not work for you in the future.
- Do not share your medicine.

Usual Dose:

Children 13 years of age and older: Your healthcare professional will tell you how much RAN-MINOCYCLINE to give your child and how often based on their body weight.

Adults: 100 mg or 200 mg to start followed by 100 mg every 12 hours.

Overdose:

If you think you have taken too much RAN-MINOCYCLINE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose of RAN -MINOCYCLINE take it as soon as you remember.

What are possible side effects from using RAN -MINOCYCLINE?

These are not all the possible side effects you may feel when taking RAN -MINOCYCLINE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- light-headedness, dizziness, vertigo (feeling like you're spinning or losing your balance)
- headache

- loss of appetite, constipation
- nausea, vomiting, diarrhea
- indigestion
- trouble swallowing
- inflammation or sores in the mouth, lips and/or tongue
- joint swelling, pain and stiffness, aching muscles
- rash, itching
- cough
- sleepiness
- fever

RAN -MINOCYCLINE can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Fainting		√	
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite			√
Inflammation or ulcers of the food pipe (esophagus): trouble swallowing, pain when swallowing, sore throat, hoarse voice, heartburn, chest pain that is worse with eating, nausea			√
Kidney problems: decreased urination, nausea, vomiting, swelling of extremities, fatigue			√
Unusual hair loss or thinning	√		
Increased sensitivity of the skin to sun		√	
Discolouration of the nails, skin, tongue, gums, lips or teeth	√		
Shortness of breath		√	
VERY RARE			
Pseudomembranous colitis: watery, bloody diarrhea, mucus in the stool, abdominal cramps and pain, fever			√
Angioedema: swelling of the face, eyes, lips, tongue, throat, arms or legs, trouble breathing or swallowing, hoarseness, itching, hives, rash on the hands, arms and feet, fever, abdominal cramps			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Allergic reaction (hypersensitivity) **with skin rashes:** rash, skin redness, peeling skin, blisters on your nose, mouth, eyes or genitals, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, fever, swollen lymph nodes combined with any of the following: liver problems (yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite), lung problems (flu-like symptoms, cough, shortness of breath), kidney problems (decreased urination, nausea, vomiting, swelling of extremities, fatigue), heart problems (chest pain, fast or irregular heartbeat, shortness of breath, swelling in the legs, ankles or feet, fatigue)			√
Thyroid problems: weight changes, fatigue, heart palpitations, constipation, dry skin, joint or muscle pain			√
Yeast infections: **Oral:** creamy white bumps on the tongue, cheeks, gums or throat that bleed when scraped, pain, trouble swallowing, bad taste in the mouth **Genital and Anal:** genital (vagina or penis) or anal itching, burning during intercourse or urination, pain, redness, swelling, discharge			√
Bronchospasm: pain, tightness and a feeling of constriction in the chest and back, trouble breathing, wheezing, coughing, dizziness			√
NOT KNOWN			
Hearing problems: buzzing, ringing or other persistent noise in ear, loss of hearing	√		
Tingling or numbness of the hands or feet √	√		

Lupus-like syndrome: joint and muscle pain, fatigue, fever, swollen lymph nodes, inflammation around the lungs or heart that causes pain or discomfort			√
High blood pressure in the brain: headache, blurred vision, nausea, vomiting, confusion			√
Respiratory disorder:			√
Pneumonitis: flu-like symptoms, cough, shortness of breath, fever, chills, fatigue			√
Nervous system disorder:			√
Seizures or fits			
Gastrointestinal disorder:			
Inflammation of the pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting	√		
Immune system disorder:			
Serum-sickness syndrome: fever, generally feeling unwell, hives, itching, rash, joint pain, swollen lymph nodes			√
Blood disorder:			
Hemolytic anemia: pale skin, yellow skin, eyes and mouth (jaundice), dark-coloured urine, fever, weakness, dizziness, confusion, reduced ability to exercise	√		
Low levels of white blood cells: infection, fatigue, fever, aches, pain, flu-like symptoms	√		
Low levels of blood platelets: bruising, bleeding, fatigue, weakness	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting(https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html)) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at 15 to 30°C. Protect from moisture.
Keep out of reach and sight of children.

If you want more information about RAN-MINOCYCLINE:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs- health-products/drug-products/drug-product-database.html) or by calling Ranbaxy Pharmaceuticals Canada Inc. at: 1-866-840-1340

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