PRODUCT MONOGRAPH

[Pr]MINOCYCLINE

(Minocycline Hydrochloride Capsules USP)

50 mg & 100 mg
as minocycline base

Antibiotic

Sanis Health Inc.
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May 10, 2012

Control #: 154796

COMPLETE PRESCRIBING INFORMATION

PRODUCT MONOGRAPH

PrMINOCYCLINE

(Minocycline Hydrochloride Capsules, USP)

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION

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

The bioavailability study was performed on healthy volunteers using MINOCYCLINE 100 mg capsules. The rate and extent of absorption of Minocycline Hydrochloride after a single dose of 100 mg MINOCYCLINE and the marketed brand was measured and compared.

The pharmacokinetic data are presented in the table below:

Geometric Mean
Arithmetic Mean (C.V. %)

PARAMETER	MINOCYCLINE 100 mg capsules (Sanis Health Inc.)	MINOCIN® 100 mg capsules (Lederle Cyanamid, Canada)	RATIO OF MEANS %
AUC_{0-t} (ng hr/mL)	10013.46 10290.9 (22. 4%)	10274.29 10541.2 (23.0 %)	97.5 % (97.6%)** 97.6 %
AUC_{inf} (ng hr/mL)	12050.56 12292.1 (19.9 %)	10274.29 10541.2 (23.0 %)	97.6 % (97.7 %)** 97.6 %
C_{max} (ng/mL)	698.06 711.66 (19.6 %)	737.61 745.30 (14.6 %)	94.6% (94.7%)** 95.5 %
T_{max}* (h)	1.729 (47.5%)	1.901 (43.4 %)	N/A
$T_{½}$* (h)	14.70 (19.8 %)	15.00 (17.4 %)	N/A

* for Tmax and T½ arithmetic mean (C.V. %) are presented.
**the potency corrected ratio of means of the test product

INDICATIONS AND CLINICAL USE

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, bronchopneumonia, sinusitis and tonsillitis caused by: *Haemophilus influenzae, Klebsiella* species*, Enterobacter* species. Tetracyclines should not be prescribed for acute throat infections.

CONTRAINDICATIONS

History of hypersensitivity to Minocycline Hydrochloride or any other tetracycline.

WARNINGS

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:

The use of tetracyclines, including Minocycline Hydrochloride 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 Hydrochloride, 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. Minocycline should not be used in such patients unless other drugs are ineffective or are contraindicated.

Congenital anomalies including limb reductions have been reported in post-marketing experience.

Pregnancy and Lactation:

Tetracyclines, including Minocycline Hydrochloride, are not recommended 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 embryotoxicity has also been noted in animals treated early in pregnancy. The safety of Minocycline Hydrochloride for use during pregnancy has not been established.

Tetracyclines, including Minocycline Hydrochloride, are excreted in the milk of lactating women; therefore, a decision should be made whether to discontinue breast-feeding or to discontinue minocycline.

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

Minocycline Hydrochloride 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 Hydrochloride, then such treatment should be continued for at least ten days.

In the presence of significant renal impairment, usual oral doses may lead to excessive systemic accumulations of Minocycline Hydrochloride 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 Hydrochloride levels can lead to azotemia, hypophosphatemia and acidosis.

Renal failure, including interstitial nephritis, has been reported rarely.

Minocycline Hydrochloride is capable of aggravating the symptoms associated with lupus erythematosus. Therefore, caution should be taken when administering the drug to patients with this disease.

Minocycline Hydrochloride 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.

Cross-sensitization among the various tetracyclines is extremely common.

Pigmentation of skin, thyroid, bone and teeth have been reported occasionally in persons receiving Minocycline Hydrochloride usually for extended periods of time. The pigmentation may be irreversible.

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

PRECAUTIONS

The administration of MINOCYCLINE to children under 13 years of age is not recommended.

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.

Bulging fontanelles have been reported in young infants following full therapeutic dosage of tetracyclines including Minocycline Hydrochloride. Pseudotumor cerebri (benign intracranial hypertension) has been reported in adults. (See Adverse Reactions section). The usual clinical manifestations are headache and blurred vision. While both of these conditions and related symptoms usually resolve after discontinuation of the tetracycline, the possibility of permanent sequelae exists.

Patients should be warned to avoid exposure to direct sunlight and/or ultraviolet light while under treatment with Minocycline Hydrochloride 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 Hydrochloride.

Patients treated with Minocycline Hydrochloride may suffer from headaches, light-headedness, dizziness or vertigo. Decreased hearing has been rarely reported in patients on minocycline hydrochloride. Administration of Minocycline Hydrochloride 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 Hydrochloride therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

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

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.

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.

Hepatotoxicity has been reported with Minocycline Hydrochloride; therefore, Minocycline Hydrochloride should be used with caution in patients with hepatic dysfunction and in conjunction with alcohol or other hepatotoxic drugs.

Periodic laboratory evaluation of organ systems including haematopoietic, renal and hepatic studies, should be performed.

Minocycline Hydrochloride 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.

Antacids containing aluminum, calcium or magnesium and oral iron preparations impair absorption and should not be given to patients taking oral Minocycline Hydrochloride.

Food and/or milk reduce the absorption of tetracycline. Minocycline Hydrochloride 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.

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

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.

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

The following syndromes have been reported. In some cases involving these syndromes, death has been reported. As with other serious adverse reactions, if any of these syndromes are recognized, the drug should be discontinued immediately:

- Hypersensitivity syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, 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 Hydrochloride:

(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

Hydrochloride. 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, 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 Hydrochloride, 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 Hydrochloride. 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, pericarditis and exacerbation of systemic lupus erythematosus. Myalgia and Myocarditis have also been rarely reported.

(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 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.

(h) Respiratory: rarely – cough and dyspnea, very rarely – bronchospasm, exacerbation of asthma and pulmonary eosinophilia and undetermined frequency of pneumonitis have been reported.

(i) 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, eosinophilia and pancytopenia and agranulocytosis. When given over prolonged periods, Minocycline Hydrochloride, like other tetracyclines, has been reported to produce brown-black microscopic discolouration of the thyroid gland. Abnormalities of thyroid function have not been shown to date. If adverse reactions or idiosyncrasy occur, the administration of Minocycline Hydrochloride 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.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- **Fax toll-free to 1-866-678-6789, or**
- **Mail to: Canada Vigilance Program**
  Health Canada
  Postal Locator 0701 E
  Ottawa, ON
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

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 Hydrochloride. (Calcium Solution 5%: 50 gm calcium carbonate or lactate dissolved in 1000 mL water, yields a 5% solution). Gastric lavage, if necessary.

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

DOSAGE AND ADMINISTRATION

Children 13 Years of Age or Older:

The usual dosage of MINOCYCLINE (minocycline hydrochloride) is 4 mg/kg initially followed by 2 mg/kg every 12 hours. Tetracyclines are not recommended in children under 13 years of age (see WARNINGS).

Adults:

The usual oral dosage of 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, 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

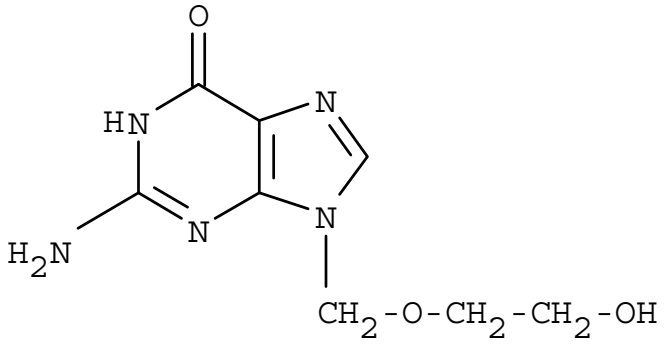
CHEMISTRY:

Trade Name MINOCYCLINE

Proper Name Minocycline Hydrochloride

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

Structural Formula:



Molecular Formula C23H27N307. HCl

Molecular Weight 493.94

Description

Minocycline hydrochloride is a yellow crystalline powder which is slightly hydroscopic and slightly sensitive to light and oxidation.

COMPOSITION

Each MINOCYCLINE capsule contains: Lactose Monohydrate (Spray Dried), Starch Corn, Magnesium Stearate, Capsule #3 CS Med Orange OP "G"/Med Orange OP "M50"*, Capsule #2 CS Lavender OP "G"/Med Orange OP "M100"**, ink***.

* The capsule shell body (Medium Orange Opaque) contains: D&C Yellow #10, FD&C Red #40, Titanium Dioxide, Gelatin-NF.

** The capsule shell cap (Lavender Opaque) contains: FD&C Blue #1, FD&C Red #40, D&C Red #28, Titanium Dioxide, Gelatin-NF.

*** The ink contains: Pharmaceutical Glaze (Modified) in SD-45, Synthetic Black Iron Oxide, SDA-3A Alcohol, FD&C Blue No.2 Aluminum Lake, FD&C Red No.40 Aluminum Lake, FD&C Blue No.1 Aluminum Lake, D&C Yellow No.10 Aluminum Lake, n-Butyl Alcohol and Propylene Glycol.

Stability and Storage Recommendations: Store at 15-30 °C. Protect from light.

DOSAGE FORMS

Availability:

MINOCYCLINE is available in 50 mg and 100 mg capsules.

Potency is calculated in terms of minocycline base.

Description:

50 mg Capsules: Hard gelatin capsules with medium orange body and medium orange opaque cap. The body has “M50" and the cap has “G” both printed in black.

100 mg Capsules: Hard gelatin capsules with medium orange body and lavender orange opaque cap. The body has “M100" and the cap has “G” both printed in black.

Package Sizes:

MINOCYCLINE 50 mg Capsules: Bottles of 100 and 250.

MINOCYCLINE 100 mg Capsules: Bottles of 100 and 250.

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		
Streptococcus beta hemolytic	654	73	83	95	99
Streptococcus - Enterococcus group	844	18	23	28	46
Streptococcus pneumoniae	508	78	88	96	99
Streptococcus pneumoniae - tetracycline resistant	70	27	57	96	100
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

BACTERIA	**No. of Strains Tested**	**Cumulative Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L)**			
		≤ 1	**≤ 4**	**≤ 8**	**≤ 16**
Haemophillus influenzae	385	62	90	98	100
Haemophillus 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 pneumohila	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	83	97
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	Moderately Susceptible	Resistant
≤ 4	**8**	**≥ 16**

Acceptable Quality Control Ranges of M.1.C. for Reference Strains:

Reference Strain	ATCC NUMBER	mg/mL
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	Moderately Susceptible	Resistant
≥ 19 mm	15 - 18 mm	≤ 14 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 Hydrochloride 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 Hydrochloride was extensively distributed to all tissues examined in $_{14}$C-labelled drug studies in dogs.

Clinical Pharmacology

Minocycline Hydrochloride capsules are rapidly absorbed from the gastrointestinal tract following oral administration. Following a single dose of two 100 mg capsules of minocycline hydrochloride 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 µg/mL (average 3.5 µg/mL). The serum half-life in the normal volunteers ranged from 11.1 to 22.1 hours (average 15.5 hours).

When Minocycline Hydrochloride capsules were given concomitantly with a meal which included dairy products, the extent of absorption of Minocycline Hydrochloride 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 capsules 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 Hydrochloride 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 LD5Q in mice was 3100 mg/kg.

Minocycline Hydrochloride 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 discolouration of the skeleton and teeth in some animals, occasional emesis and black discolouration 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 discolouration 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 Hydrochloride 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 4, 12 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 Hydrochloride, 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 discolouration 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 Hydrochloride has been found to produce discolouration 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 Hydrochloride 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 Hydrochloride 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 discolouration that also occurs with other tetracyclines and the thyroid pigmentation seen in rats, dogs and monkeys, toxic effects of Minocycline Hydrochloride were observed only where serum concentrations were in excess of the therapeutic concentrations. It is concluded from the chronic safety evaluation studies that Minocycline Hydrochloride 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 Hydrochloride 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 Hydrochloride 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.

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