PRODUCT MONOGRAPH

RIVA-MINOCYCLINE
(Minocycline Hydrochloride)

50 mg and 100 mg Capsules

Antibiotic

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PRODUCT MONOGRAPH

NAME OF DRUG

RIVA-MINOCYCLINE

(Minocycline Hydrochloride Capsules USP)

50 mg and 100 mg capsules

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION & CLINICAL PHARMACOLOGY

RIVA-MINOCYCLINE (minocycline hydrochloride capsules USP), a tetracycline antibiotic, has activity against some gram-negative and gram-positive organisms. The antibacterial effect of minocycline is primarily bacteriostatic and is thought to act by inhibiting protein synthesis.

Two comparative, two–way bioavailability studies were conducted in 13 normal volunteers on two 50 mg minocycline capsule products, RIVA-MINOCYCLINE 50 mg capsules and MINOCIN 50 mg capsules and two 100 mg minocycline capsule products. The pharmacokinetic data calculated for the RIVA-MINOCYCLINE and MINOCIN capsule formulations is tabulated below.

50 mg Formulation:

	GEOMETRIC MEAN ARITHMETIC MEAN (C.V.) RIVA-MINOCYCLINE 4 x 50 mg	MINOCIN® 4 x 50 mg	Percentage of MINOCIN®
AUC_T (ng• h/mL)	48533 49008 (14)	54176 54762 (18)	90
AUC_I (ng• h/mL)	51021 51552 (15)	56954 57848 (18)	90
C_{max} (ng/mL)	2697 2714 (14)	2835 2875 (17)	95
T_{max}* (h)	2.00 (0.79)	2.04 (0.75)	—
$t_{1/2}$* (h)	16.6 (1.5)	17.2 (1.8)	—

*These are arithmetic means (Standard Deviation)

100 mg Formulation:

	GEOMETRIC MEAN ARITHMETIC MEAN (C.V.) RIVA-MINOCYCLINE 2 x 100 mg	MINOCIN® 2 x 100 mg	Percentage of MINOCIN®
AUC_T (ng• h/mL)	49021 49931 (22)	51022 51955 (18)	96
AUC_I (ng• h/mL)	52052 53145 (23)	54721 55479 (19)	95
C_{max} (ng/mL)	2697 2743 (22)	2752 2776 (16)	98
T_{max}* (h)	2.04 (0.75)	2.25 (0.69)	—
$t_{1/2}$* (h)	17.9 (2.9)	18.3 (2.4)	—

*These are the arithmetic means (Standard Deviation)

INDICATIONS AND CLINICAL USE

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

Gall bladder infections caused by Escherichia coli.

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

RIVA-MINOCYCLINE may be employed as an alternative drug in the treatment of anal and pharyngeal gonorrhoea and syphilis when penicillin is contraindicated.

Skin and soft tissue infections: abscess, cellulitis, furunculosis, impetigo and pyoderma caused by: Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pyogenes, Proteus species, Escherichia coli. RIVA-MINOCYCLINE could be useful in circumstances where staphylococcal or streptococcal organisms are shown to be resistant to other agents but sensitive to minocycline, even though tetracyclines are not the drugs of choice in these infections. Bacterial evaluation suggests that a relatively lower success rate may be expected in clinical cases involving proteus organisms.

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

CONTRAINDICATIONS

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

WARNINGS

Newborns, Infants and Children: Permanent tooth discoloration (yellow-grey-brown) has resulted from the use of tetracyclines, including minocycline, during tooth development (last half of pregnancy, infancy and childhood under the age of thirteen years). Although it has been observed following short-term courses, it is more common during long-term use. There have also been reports of enamel hypoplasia. A stable calcium complex is formed by all tetracyclines, including minocycline, in any bone forming tissue. The fibula growth rate has been observed to decrease in prematures given oral tetracycline in doses of 25 mg/kg every

6 hours. Upon discontinuation of the drug, this appeared to be reversible. Unless other drugs are ineffective or are contraindicated, minocycline should not be used in such patients.

Pregnancy and Lactation: Because of possible adverse effects on developing bones and teeth of the foetus and neonate, tetracyclines, including RIVA- minocycline hydrochloride capsules USP), are not recommended during pregnancy and lactation. Animal study results have indicated that tetracyclines cross the placenta, are found in foetal tissues and can have toxic effects on the developing foetus (often related to retardation of skeletal development).

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

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

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

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

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

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

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

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

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

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

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

PRECAUTIONS

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

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

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

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

RIVA-MINOCYCLINE therapy may result in overgrowth of non-susceptible organisms (including fungi), as with other antibiotics. RIVA-MINOCYCLINE should be discontinued if superinfection occurs, and appropriate therapy instituted.

Cross-resistance to many antibiotics can develop rapidly in several species of micro-organisms. The clinician should consider this if therapy with RIVA-MINOCYCLINE is not achieving the expected results.

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

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

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

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

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

Plasma prothrombin activity has been depressed with minocycline. Patients on anticoagulant therapy should, therefore, be monitored regularly. Their anticoagulant dosage may require

downward adjustment. The interference of vitamin K synthesis by micro-organisms in the gut has been reported.

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

Dairy products can delay absorption. However, studies to date have not indicated that food notably influences minocycline absorption.

ADVERSE REACTIONS

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

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

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

c) Teeth and Bone: There have been reports of dental staining (yellow-grey-brown) in children of mothers given tetracyclines, including minocycline, during the latter half of pregnancy and in children given the drug during the neonatal period, infancy and

childhood to the age of 13 years. Enamel hypoplasia has been reported also. Rarely, upon extended treatment with minocycline, discoloration of bones and teeth has been documented to occur. The mechanism of staining, although not completely elucidated at present, appears to be mediated by the formation of a stable iron complex. The effects may be irreversible.

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

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

f) Hypersensitivity Reactions: Urticaria, angioneurotic oedema, anaphylaxis, anaphylactoid purpura, pericarditis, polyarthralgia and exacerbation of systemic lupus erythematosus.

g) Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve soon after stoppage of the tetracycline, the possibility for permanent consequences exists.

h) Other: Elevated SGOT or SGPT values, hepatic cholestasis, haemolytic anaemia, neutropenia, thrombocytopenia and eosinophilia. Minocycline, like other tetracyclines, has been reported to produce brown-black microscopic discoloration of the thyroid gland when given over prolonged periods. Abnormal–ities of thyroid function in humans, however, have not been shown to date. The administration of RIVA-MINOCYCLINE should be discontinued and appropriate alternate therapy instituted if adverse reactions or idiosyncrasy occur.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms and Signs:

Dizziness, nausea, vomiting, abdominal pain, intestinal haemorrhage, hypotension, lethargy, coma, acidosis, azotemia without a concomitant rise in creatinine.

Treatment:

There is no specific antidote. Antacids (e.g., calcium carbonate or lactate, milk of magnesia, aluminium hydroxide) are general antidotes as they form relatively insoluble complexes with minocycline. (Calcium solution 5%: 50 g calcium carbonate or lactate dissolved in 1000 mL water yields a 5% solution.) Gastric lavage may be used, if necessary.

DOSAGE AND ADMINISTRATION

Children 13 Years of Age or Older:

RIVA-MINOCYCLINE (minocycline hydrochloride capsules USP) should usually be initiated at 4 mg/kg, followed by 2 mg/kg every 12 hours. The administration of tetracyclines to children less than 13 years of age is not recommended (see WARNINGS).

Adults:

Initially, the usual oral dosage of RIVA-MINOCYCLINE is 100 mg or 200 mg, followed by 100 mg every 12 hours. If more frequent doses are preferred, two or four 50 mg doses may be given initially, followed by one 50 mg dose every 6 hours. RIVA-MINOCYCLINE therapy should be continued for 1 or 2 days beyond the time when characteristic symptoms or fever have subsided.

RIVA-MINOCYCLINE should be administered over a period of 10 or 15 days for the treatment of syphilis. In these patients, close follow-up, including laboratory tests, is recommended.

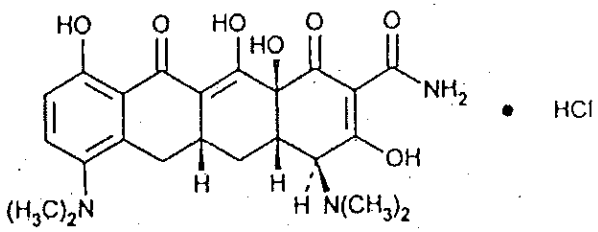
Concomitant therapy: Patients taking RIVA-MINOCYCLINE should not be given antacids containing aluminium, calcium or magnesium and/or iron preparations because they impair absorption.

PHARMACEUTICAL INFORMATION

Trade Name: RIVA-MINOCYCLINE

Proper Name: Minocycline hydrochloride

Structural Formula:



Molecular Formula: $C_{23}H_{27}N_3O_7.HCl$ Molecular Weight: 493.94

Chemical Name: 2-Naphthacenecarboxamide, 4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, monohydrochloride, [4S-(4α, 4aα, 5aα, 12aα)]–.

Description: Minocycline hydrochloride is a yellow crystalline powder that is slightly hygroscopic and slightly sensitive to light and oxidation. Soluble in water and in solutions of alkali hydroxides and carbonates; slightly soluble in alcohol; practically insoluble in chloroform and ether.

STABILITY AND STORAGE RECOMMENDATIONS

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

AVAILABILITY

RIVA-MINOCYCLINE (minocycline hydrochloride capsules USP) is available in orange, hard gelatine capsules containing 50 mg of minocycline base, and orange and purple, hard gelatine capsules containing 100 mg of minocycline base. Both strengths are packaged in bottles of 100, 250 and 500 and in unit dose strips of 100.

MICROBIOLOGY

The in vitro activity of minocycline against clinical isolates representing gram-positive, gram-negative, actinomyces, acid-fast and anaerobic bacteria and mycoplasma is presented in the following cumulative MIC tables.

Susceptibility Testing

Tube-Dilution Testing:

Depending on the minimum inhibitory concentration (MIC), micro-organisms may be considered susceptible (likely to respond to minocycline therapy), moderately susceptible (harbouring partial resistance), or resistant (not likely to respond to minocycline therapy):

Minocycline MIC Interpretative Standards (mg/L)

Susceptible	Moderately Susceptible	Resistant
≤4	8	≥16

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 haemolytic	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

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 gonorrhoea	1082	97	100		
Neisseria gonorrhoea – ß–lactamase positive	50	90	100		
Neisseria meningitidis 613	94	100			
Proteus indole positive species	102	1	30	47	61

BACTERIA	No. of Strains Tested	Cumulative % Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L) ≤1	≤4	≤8	≤16
GRAM-NEGATIVE					
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	85	99	99	99
Pseudomonas pseudomallei	157	10	77	89	92
Pseudomonas species	68	68	90	91	93
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			

BACTERIA	No. of Strains Tested	Cumulative % Strains Inhibited at the Indicated Concentrations of Minocycline (mg/L) ≤1	≤4	≤8	≤16
ANAEROBIC					
Bacteroides fragilis	673	44	80	97	99
Bacteroides species	431	58	77	90	92
Campylobacter foetus	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	

Acceptable Quality Control Ranges of MIC 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:

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

Zone Diameter Interpretative Standards (30 µg disc)

Susceptible	Moderately Susceptible	Resistant
≥ 19 mm	15 – 18 mm	≤ 14 mm

Minocycline powder may be used for additional susceptibility testing for Staphylococcal species.

Acceptable Quality Control Limits (Zone Diameter) for Disc Susceptibility Testing of Reference Strains:

Reference Strain	ATCC Number	Zone Diameter (mm)
Escherichia coli	25922	19 – 25
Staphylococcus aureus	25923	25 – 30

PHARMACOLOGY

Animal Pharmacology:

The oral administration of minocycline to various animal species produced the following blood levels: 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. There was extensive distribution to all tissues examined in ^{14}C-labelled minocycline studies in dogs.

Human Pharmacology:

Normal adults given a single 200 mg capsule produced serum concentrations averaging 2.24 (0.74 - 4.45) mg/L at one hour and 1.25 (0.34 - 2.36) mg/L at 12 hours. Minocycline had a serum half-life of about 16 hours after a single oral dose. Serum levels of a group of 5 healthy volunteers were maintained at 1.4 - 1.8 mg/L at 12 and 24 hours with doses of 100 mg every 12 hours for 3 days. The serum levels had fallen to approximately 1 mg/L at 24 hours when given 200 mg once daily for 3 days.

TOXICOLOGY

Minocycline was administered orally and parenterally in acute experiments in mice and rats, and in sub-chronic and chronic experiments in rats and dogs.

The i.v. and i.p. LD_{50}'s of minocycline in mice were 95 mg/kg and 280 mg/kg, respectively. In mice, the oral LD_{50} was 3100 mg/kg.

Dogs were administered minocycline orally each day at doses of 0, 4, 20 and 60 mg/kg/day (100 mg/kg/day for the first month) in equally divided doses. There were no apparent drug related findings at 20 mg/kg/day except yellow discoloration of the skeleton and teeth in some animals, occasional emesis and black discoloration of the thyroid gland.

Discoloration of the thyroid gland and possibly some yellowing of the bones were the only drug related findings during the six month period at a dose of 4 mg/kg/day. Peak serum concentrations obtained ranged from 8.5 to 100 mg/L 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.

A very similar dose range as that used in the oral study (5, 10, 20 and 40 mg/kg/day) was used in a one month intravenous study in dogs. Untoward findings associated primarily with the high dose (40 mg/kg/day) included body weight loss, reduced food consumption, erythema of the skin and visible mucous membranes of varying duration, intensity and incidence. After the same dose of tetracycline, similar findings were obtained except for erythema. The serum concentration of minocycline associated with these drug related findings was 95 mg/L, three times that found with tetracycline (31 mg/L). Serum concentrations of 4, 12 and 38 mg/L were obtained in dogs administered 5, 10 and 20 mg/kg/day intravenously, and were essentially without toxicity. These drug levels exceed considerably those necessary for therapeutic effectiveness in man. Minocycline appeared to be tolerated as well intravenously as it was orally in these experiments.

The chronic oral administration of minocycline to rats for one year obtained similar results. They were fed 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. 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 were attained with these doses. There were no significant drug related signs of toxicity at doses less than 1% drug diet, with the exception of discoloration of the teeth (dose 0.04% drug diet or greater), femur and thyroid gland.

Minocycline, like other tetracyclines, has been found to produce discoloration of the thyroid gland in the rat, dog, monkey and human but not in the mouse. These investigations provided
no evidence, however, that thyroid function of monkeys or bone growth of the other species was affected. Minocycline was not carcinogenic and the black pigment in the thyroid gland did not cause neoplastic changes in a 23 month carcinogenic study in the rat.

Following the administration of minocycline and tetracycline to man, biopsy specimens revealed an intraepithelial lipofuscin deposition of both drugs, considered to be within normal limits. A decrease within the normal range of thyroxine found in thyroid function studies in man indicated a tendency toward relative hypothyroidism.

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

Minocycline, like other tetracyclines, has been shown in reproduction studies performed in rats, rabbits and dogs to cross the placenta, appear in foetal tissues and produce toxic effects in the developing embryo, foetus or neonate when present in sufficient amounts.

At oral doses of 70 mg/kg/day in rats and 25 mg/kg/day in rabbits during pregnancy, the conceptus were seen to have a low incidence of slight retardation of ossification and slight

angulation of ribs. More extensive retardation of ossification and generalised morphologic changes and death were observed at doses of 150 mg/kg/day and higher in the rat foetus.

No deleterious effects were reported in rats or rabbits in other experiments with oral doses as high as 100 and 75 mg/kg/day, respectively. The new-born of 2 dogs given 20 mg/kg in 2 equally divided daily doses from days 35 to 62 of pregnancy did not experience adverse effects.

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