PRESCRIBING INFORMATION

[Pr]NTP-Doxycycline Capsules

Doxycycline Hyclate Capsules, USP

100 mg doxycycline (as hyclate)

[Pr] NTP-Doxycycline Tablets

Doxycycline Hyclate Tablets, USP

100 mg doxycycline (as hyclate)

Antibiotic

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

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NAME OF DRUGS

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THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION

Doxycycline hyclate is a broad-spectrum antibiotic and is active against a wide range of Gram-negative and Gram-positive organisms. Doxycycline exerts its bacteriostatic effect by the inhibition of protein synthesis.

INDICATIONS AND CLINICAL USE

NTP-Doxycycline Capsules / NTP-Doxycycline Tablets may be indicated for the treatment of:

Pneumonia:	Single and multilobe pneumonia and bronchopneumonia due to susceptible strains of *Streptococcus pneunomiae* and other *Streptococcus* spp., *Staphylococcus* spp., *H. influenzae* and *Klebsiella pneumoniae*.
Other Respiratory Tract Infections:	Pharyngitis, tonsillitis, sinusitis, otitis media, bronchitis caused by susceptible strains of β-hemolytic *Streptococcus*, *Staphylococcus* spp., *Streptococcus pneumoniae* and *H. influenzae*.
Genitourinary Tract Infections:	Pyelonephritis, cystitis, urethritis, gonococcal urethritis caused by

susceptible strains of *Klebsiella* spp., *Enterobacter aerogenes, E. coli*, *Enterococcus* spp., *Staphylococcus* spp., *Streptococcus* spp. and *Neisseria gonorrhoeae.*

In adult patients with urethritis, cervicitis and vaginitis with a positive test for *Chlamydia trachomatis* and/or *Ureaplasma urealyticum*, clinical resolution and absence of detectable organisms have only been observed at completion of ORAL therapy with doxycycline hyclate. Relapses or reinfection can occur. In these cases, limited data suggest that some patients may derive clinical benefit from an alternative therapy. The effect on long term morbidity has not been established.

Skin and Soft Tissue Infections: Impetigo, furunculosis, cellulitis, abscess, wound sepsis, paronychia, caused by susceptible strains of *Staphylococcus aureus* and *epidermidis*, *Streptococcus* spp., *E. coli*, *Klebsiella* spp. and *Enterobacter aerogenes.*

Gastro-intestinal Infections: Caused by susceptible strains of *Shigella* spp., *Salmonella* spp. and *E.coli*.

Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs.

Appropriate culture and susceptibility studies should be carried out prior to initiation of therapy with doxycycline hyclate and if clinically indicated during treatment. Consideration may be given to the initiation of therapy before obtaining results of these tests, however modification of such treatment may be required once the results become available.

CONTRAINDICATIONS

Doxycycline hyclate is contraindicated in individuals who have shown hypersensitivity to tetracyclines, and in patients with myasthenia gravis.

WARNINGS

Doxycycline hyclate like other tetracyclines, may form a stable calcium complex in any bone-forming tissue, though *in vitro* it binds calcium less strongly than other tetracyclines. It should be anticipated that the use of doxycycline hyclate during tooth development (last trimester of pregnancy, during lactation, neonatal period and early

childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Though more commonly associated with long term use of tetracyclines, this effect has also been known to occur after short courses. Enamel hypoplasia has also been reported.

Doxycycline hyclate should, therefore, not be used in these age groups unless other drugs are unlikely to be effective or are contraindicated. Instances of esophageal lesions (esophagitis and ulcerations), sometimes severe, have been reported in patients receiving doxycycline. The patients must be instructed to take doxycycline hyclate with a full glass of water, to keep in orthostatic position after the administration and not to go to bed within 1-2 hours after the intake. If symptoms such as dysphagyia and retrosternal pain occur, doxycycline hyclate should be discontinued and an esophagic lesion must be investigated (see **PRECAUTIONS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION** and **INFORMATION FOR THE PATIENT**). Doxycycline hyclate should not be prescribed to patients with obstructive esophagic pathology, such as stenosis and achalasia.

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including doxycycline hyclate. 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 colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 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, as surgical intervention may be required in certain severe cases. (see **ADVERSE REACTIONS**)

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with Doxycycline hyclate**,** and treatment should be discontinued at the first evidence of skin erythema (see **PRECAUTIONS, ADVERSE REACTIONS** and **INFORMATION FOR THE PATIENT**). The use of sunscreen or sunblock prior to sun or UV light exposure should be considered in patients taking doxycycline hyclate.

Usage in Pregnancy

Doxycycline hyclate should not be administered to pregnant women, unless in the judgment of the physician the potential benefit to the mother outweighs the risk to the fetus (see above **WARNINGS** section about use during tooth development).
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). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Usage During Lactation

Tetracyclines are excreted in the milk of lactating women. Accordingly the use of doxycycline hyclate is not recommended in women while they are breast feeding (see above **WARNINGS** section about use during tooth development).

Use in Newborns, Infants and Children

The use of doxycycline hyclate in children under 8 years is not recommended because safe conditions for its use have not been established (see above **WARNINGS** section about use during tooth development).

Doxycycline hyclate like other tetracyclines forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

PRECAUTIONS

In clinical studies to date, administration of doxycycline hyclate did not lead to increased serum levels nor to an increase in the serum half-life of doxycycline in patients with impaired renal function. Modification of doxycycline hyclate dosage for these patients is not necessary. Although no evidence of increased toxicity has been observed in such patients, the potential for increased hepatic or other toxicity should be considered until further data on the metabolic fate of doxycycline under these conditions become available.

Concurrent administration of doxycycline hyclate with agents known to be hepatotoxic should be avoided.

The use of antibiotics may occasionally result in overgrowth of non-susceptible organisms including fungi; thus, observation of the patient is essential. Patients should be advised that the use of doxycycline might increase the incidence of vaginal candidiasis

(see **ADVERSE REACTIONS** and **INFORMATION FOR THE PATIENT**).
Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages. Although the mechanism of this phenomenon is unknown the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae (see **ADVERSE REACTIONS**).

Cases of esophageal injury consisting of esophagitis and esophageal ulceration have been reported in patients receiving doxycycline hyclate orally. Most of these patients took medication immediately before going to bed and/or without adequate amount of fluid (see **DOSAGE AND ADMINISTRATION**). If this should occur, doxycycline hyclate should be discontinued until healing occurs. Administration of antacids and/or cimetidine has provided relief in the treatment of such cases. TO REDUCE THE RISK OF ESOPHAGEAL INJURY, PATIENTS SHOULD BE ADVISED TO TAKE DOXYCYCLINE HYCLATE WITH AN ADEQUATE AMOUNT OF FLUID WHILE STANDING OR SITTING UPRIGHT. Doxycycline hyclate should not be given at bedtime.

In long term therapy with doxycycline hyclate**,** periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed. Liver function tests should be carried out at regular intervals on patients receiving high doses for prolonged periods of time.

Drug interactions

Doxycycline hyclate should be given with caution to patients receiving oral anticoagulants. Because the tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Antacids containing aluminum, calcium or magnesium impair absorption and should not be given to patients taking doxycycline hyclate.

The concurrent use of doxycycline hyclate with alcohol, barbiturates, phenytoin and carbamazepine (hepatic enzyme inducers) has been reported to result in a reduction of plasma half-life of doxycycline, thereby reducing the antimicrobial effectiveness of doxycycline hyclate**.** This effect may last for several days after discontinuation of therapy with the interacting agent. Therefore, consideration should be given to re-adjustment of the daily dose of doxycycline hyclate when administered concomitantly with alcohol and with drugs known to be enzyme inducers.

It has been reported that concurrent administration of ferrous sulphate (iron) lowered serum concentrations of doxycycline given orally and shortened the serum half-life after a single intravenous injection. In the event that iron and iron-containing products have to be given during treatment with doxycycline hyclate**,** the interval between administration of each drug should be as wide as possible.

It has been reported that when subsalicylate bismuth was given simultaneously and as a multiple-dose regimen before oral doxycycline hyclate there was a reduced bioavailability of doxycycline. Also peak serum concentrations of doxycycline were significantly decreased when subsalicylate bismuth was given 2 hours before oral doxycycline hyclate but not when given 2 hours after oral doxycycline hyclate**.** Therefore subsalicylate bismuth should not be taken during therapy with oral doxycycline hyclate**.**

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving doxycycline hyclate**,** or any other tetracycline, in conjunction with penicillin.

There have been anecdotal reports that concurrent use of tetracyclines may render oral contraceptives less effective.

ADVERSE REACTIONS

GASTROINTESTINAL:
As with other broad spectrum antibiotics administered orally and parenterally, gastro-intestinal disturbances such as anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, stomatitis, proctitis and enterocolitis, may occur, but have rarely been sufficiently troublesome to warrant discontinuation of therapy with doxycycline hyclate**.** Abdominal pain, dyspepsia, pseudomembranous colitis, *C. difficile* diarrhea and inflammatory lesions (with monilial overgrowth) in the anogenital region have also been reported.

Cases of esophagitis and esophageal ulcerations, sometimes severe, in patients receiving capsule and tablet form of doxycycline hyclate have been reported (see **WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION**, **INFORMATION FOR THE PATIENT**).

AUTONOMIC NERVOUS SYSTEM:
Flushing

BODY AS A WHOLE:
Hypersensitivity reactions consisting of urticaria, angioneurotic edema, anaphylaxis, anaphylactic shock, anaphylactoid reaction, anaphylactoid purpura, dyspnea, hypotension, pericarditis, peripheral edema, serum sickness, tachycardia and exacerbation of systemic lupus erythematosus have been reported.

SKIN:
Maculopapular and erythernatous rashes, photosensitivity skin reactions, photo-onycholysis, erythema multiforme, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis have been reported. Exfoliative dermatitis has also been reported but is uncommon (see **WARNINGS**).

MUSCULO-SKELETAL:
Arthralgia and myalgia.

CENTRAL NERVOUS SYSTEM:
Headache, bulging fontanels in infants and benign intracranial hypertension in adults (see **PRECAUTIONS**).

LIVER/BILIARY:
There have been reports of hepatotoxicity (including hepatic failure, autoimmune hepatitis and cholestasis). As with other tetracyclines, hepatitis, elevation of SGOT or SGPT values have been reported, the significance of which is not known.

HAEMATOLOGIC:
Hemolytic anemia, thrombocytopenia, neutropenia, eosinophilia, leukopenia.

HEARING/VESTIBULAR:
Tinnitus.

INVESTIGATIONS (Renal Function Analyses)
Elevated BUN (apparently dose related) has been reported.

OTHERS:
When given over prolonged periods tetracyclines have been reported to produce brown-black microscopic discolouration of the thyroid gland. Abnormalities of thyroid function have not been shown to date (see **TOXICOLOGY**, Subacute Toxicity).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Specific information on symptoms or treatment of overdosage with doxycycline hyclate is not available. Treatment, therefore, should be symptomatic and gastric lavage may be considered for overdosage with the oral preparation. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

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

DOSAGE AND ADMINISTRATION

DOSAGE

EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults The recommended dosage of oral NTP-Doxycycline Capsules / NTP-Doxycycline Tablets for the majority of susceptible infections is a single loading dose of 200 mg on the first day of treatment followed by a maintenance dosage of 100 mg once daily at the same time each day thereafter.

In the management of more severe infections (particularly chronic infections of the urinary tract), 200 mg should be given daily throughout the treatment period.

Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 to 36 hours following discontinuance of doxycycline hyclate therapy.

When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

For treatment of uncomplicated acute gonococcal infections, the recommended dosage is 200 mg starting and 100 mg in the evening, the first day, followed by 100 mg b.i.d. for 3 days.

For treatment of uncomplicated urethral, endocervical, or vaginal infections in adults associated with *Chlamydia trachomatis* and *Ureaplasma urealyticum*: 100 mg, by mouth, twice a day for at least 10 days.

No alteration in recommended dosage schedule need be made when treating patients with impaired renal function.

ADMINISTRATION

NTP-Doxycycline Capsules / NTP-Doxycycline Tablets should be given with or after a meal in order to minimize the possibility of gastric upset. Antacids and iron preparations impair absorption and should not be given concomitantly to patients taking oral doxycycline hyclate.

Patients should be advised to take NTP-Doxycycline Capsules / NTP-Doxycycline Tablets with a full glass of water, to keep in orthostatic position after the administration and not to go to bed within 1-2 hours after the intake.

PHARMACEUTICAL INFORMATION

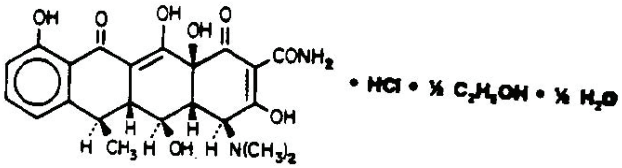
CHEMISTRY

Trade Name(s): NTP-Doxycycline Capsules / NTP-Doxycycline Tablets

Proper Name: Doxycycline hyclate

Chemical Name: 2-Naphthacenecarboxamide, 4-(dimethyIamino)-1,4,4a,5,5a,6,11,12aoctahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-monohydrochloride, compd. with ethanol (2:1), monohydrate, | 4S-(4α,4aα,5α,5aα,6α, 12α) | -or α-6-deoxy-5-oxytetracycline

Structural Formula:



Molecular Formula: $(C_{22}H_{24}N_2O_8 \bullet HCl)_2 \cdot C_2H_6O \cdot H_2O$

Molecular Weight: 1025.89

Description:
Doxycycline hyclate is a yellow crystalline powder with a slight ethanolic odour and a bitter taste. The melting point is about 200°C with decomposition. It is soluble in a 1 in 3 dilution with water, 1 in 60 with alcohol and 1 in 4 with methyl alcohol; slightly soluble in chloroform and ether; soluble in solutions of alkali hydroxides and carbonates.

Composition:
NTP-DOXYCYCLINE CAPSULES: each blue, hard gelatin capsule contains: doxycycline
hyclate equivalent to doxycycline 100 mg. Also contains FD&C Blue #1, gelatin, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, sodium starch glycolate and titanium dioxide.

NTP-DOXYCYCLINE TABLETS: each orange film coated tablet contains doxycycline hyclate equivalent to doxycycline 100 mg. Also contains carnauba wax, colloidal silicon dioxide, FD&C Blue #2, FD&C Red #40, FD&C Yellow #6, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and titanium dioxide.

DOSAGE FORMS

AVAILABILITY

NTP-DOXYCYCLINE CAPSULES: 100 mg are available as blue hard gelatin capsules containing doxycycline hyclate equivalent to 100 mg of doxycycline, supplied in bottles of 100 and 250.

NTP-DOXYCYCLINE TABLETS: 100 mg are available as orange film coated tablets containing doxycycline hyclate equivalent to 100 mg of doxycycline, supplied in bottles of 100.

STABILITY AND STORAGE RECOMMENDATIONS:

Store bottles between 15°C and 30°C and protect from light.

MICROBIOLOGY

Doxycycline is a broad spectrum antibiotic and has been shown to be active *in vitro* against the following Gram-negative, Gram-positive and other micro-organisms:

Staphylococcus aureus
Staphylococcus epidermidis (albus)
Streptococcus pyogenes
Streptococcus faecalis
Streptococcus pneumoniae
Streptococcus viridans
Listeria monocytogenes

Klebsiella pneumoniae

Salmonella typhi
Salmonella typhimurium
Salmonella enteriditis
Shigella sonnei
Shigella flexneri

Corynebacterium diphtheriae
Bacillus anthracis
Bacillus subtilis
Neisseria gonorrhoeae
Neisseria catarrhalis
Escherichia coli
Enterobacter aerogenes
Pseudomonas aeruginosa
Haemophilus influenzae
Serratia spp.
Brucella spp.
Proteus spp.
Pasteurella spp.

Mycoplasma pneumoniae
Chlamydia trachomatis
Ureaplasma urealyticum

There is evidence to suggest that oral doxycycline because of its rapid and almost complete absorption, may have less effect on the gut flora than other tetracyclines. Hinton (1968) has reported that the normal dosage regime of tetracycline HCI administered to 17 volunteers was associated with important effects on the intestinal flora in terms of both changes in total population and the emergence of resistant strains. Large doses of oral doxycycline (double the maximum recommended dosage) had to be administered to produce an equivalent effect.

In a similar number of volunteers, however, administration of the normal dosage regime of oral doxycycline was associated with substantially less effect on gut flora. Barteaux (1968) noted that the gut flora of patients on various dosages of oral doxycycline for 10-80 days showed no significant deviation from the normal flora or from the flora of a control group of patients. These data suggest that microbiological intestinal complications (e.g., diarrhoea) associated with tetracycline therapy may be less frequent when ordinary therapeutic doses of doxycycline are used.

The drugs in the tetracycline class have closely similar antimicrobial spectra, and cross-resistance among them is common.

SUSCEPTIBILITY TESTING

The Kirby-Bauer method of disc susceptibility testing (using the 30 µg doxycycline disc) and dilution susceptibility should be interpreted according to the criteria in **TABLE 1**.

TABLE 1

SUSCEPTIBILITY TEST

	ZONE DIAMETER (30 µ doxycycline disc) mm	M.I.C. mg/L
Susceptible	≥ 16	≤ 4
Intermediate	13-15	8
Resistant	≤ 12	≥16

PHARMACOLOGY

A comparative two-way, single-dose bioavailability study was carried out in twelve adult volunteers on two 100 mg doxycycline hyclate tablet products, NTP-Doxycycline 100 mg Tablets and Vibra-Tabs 100 mg Tablets. The pharmacokinetic data calculated for the NTP-Doxycycline and Vibra-Tabs formulations is tabulated below:

TABLE 2

Pharmacokinetic Indices for Doxycycline Hyclate Tablets:

Geometric Mean

Arithmetic Mean (C.V.)

Doxycycline Hyclate (2 x 100 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	NTP-Doxycycline * (2 x 100 mg)	Vibra-Tabs † (2 x 100 mg)	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_t (ng*h/mL)	57.78 60.21 (30)	58.68 60.41 (24)	99	88.95-109.60%
AUC_I (ng*h/mL)	63.03 65.32 (27)	63.73 65.38 (22)	99	89.79-109.55%
C_{max} (ng/mL)	3.22 3.30 (22)	3.28 3.37 (23)	98	91.58-105.04%
T_{max} § (h)	2.38 (0.88)	2.88 (0.99)		
$T_{½}$ § (h)	19.3 (5)	19.0 (3)		

* NTP-Doxycycline 100 mg tablets (Teva Canada Limited, Canada)
† Vibra-Tabs 100 mg tablets (Pfizer Canada Inc.) was purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only

A comparative two-way, single-dose bioavailability study was carried out in twelve adult volunteers on two 100 mg doxycycline capsule products, NTP-Doxycycline 100 mg Capsules and Vibramycin 100 mg Capsules. The pharmacokinetic data (mean ± standard deviation) calculated for the NTP-Doxycycline and Vibramycin Capsule formulations is tabulated below:

TABLE 3

Pharmacokinetic Indices for Doxycycline Capsules:

Vibramycin	**NTP-Doxycycline**	
	2 x l00 mg	**2 x l00 mg**
Area Under the Curve: (μg—hours/mL); 0—96 hours	80.57 ± 20.46	71.05 ± 18.94
Peak Plasma Concentration: Cmax (μg/mL)	4.70 ± 1.45	4.30 ± 1.15
Time to Peak Plasma Level: Tmax (hours)	2.58 ± 0.51	2.42 ± 0.90
Plasma Half—Life: t—1/2 (hours)	13.95 ± 1.83	13.24 ± 2.02
Elimination Rate Constant: Kel ($hours^{-1}$)	0.05 ± 0.01	0.05 ± 0.01

Serum levels of doxycycline administered orally follow a similar pattern to those obtained with equivalent dosages administered intravenously as shown in **TABLE 4**. Peak serum levels were slightly higher and occurred earlier following intravenous administration than for oral administration (see **TABLE 4**).

TABLE 4

Serum levels (mg/L) after oral and I.V. infusion over 60 minutes (0.5 mg/Ml) of a total daily dose of 200 mg of doxycycline hyclate on the first day (100 mg every 12 hours) and a dose of 100 mg on the second and third day of administration (22 Male Volunteers/Group).

Time (hr:min)	Mean Serum Level I.V.	Mean Serum Level Capsules	p
0:05	2.455	0.000	<.001
1:00	1.608	1.206	< .01
2:00	1.551	1.643	
3:00	1.421	1.482	
16:00	1.131	1.124	
11:00	0.800	0.815	
13:00	2.397	1.107	<.001
15:00	2.130	2.000	
24:00	1.468	1.663	.088
35:00	1.734	1.725	
48:00	1.159	1.078	
48:05	3.658	1.124	<.001
49:00	2.945	2.147	<.001

50:00	2.848	2.406	.056
51:00	2.760	2.436	
54:00	2.150	1.989	
59:00	1.665	1.516	
72:00	1.021	0.945	
83:00	0.700	0.709	
96:00	0.426	0.399	
107:00	0.247	0.234	
	mean area I.V.	mean area capsules	
AUC (mg•h/L) 0-107 hr	138	128	

Where no p is stated, p>.10

_____ time of dosing

Doxycycline was rapidly and almost completely absorbed following oral administration. The absorption of doxycycline was not significantly influenced by ingestion of food or milk (see **TABLE 5**).

TABLE 5

Effect of Food or Milk on Absorption of a Single Oral Dose of Doxycycline 100 mg as Hyclate (5 Male Volunteers/Group).

AVERAGE SERUM LEVELS (mg/L)			
Hours	Breakfast	Fasting	6 oz. milk
0	0	0	0
1	0.966	1.004	1.081
2	1.188	1.377	1.325
3	1.269	1.296	1.244
5	1.036	1.133	1.046
8	0.973	0.936	0.885
12	0.738	0.801	0.686
24	0.498	0.528	0.475

Doxycyline is approximately 93% protein bound. The serum half-life of doxycycline is 18 hours. Doxycycline is excreted in the urine (approximately 35-40% of the administered dose) and in the bile. The volume of distribution is approximately 0.7 L/kg. Hemodialysis does not alter the serum half-live.

Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal renal function (creatinine clearance about 75 mL/min.). This percentage excretion may fall to a range as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min.). The serum half-life of doxycycline is not increased, nor does it accumulate in the blood of patients with impaired renal function.

TOXICOLOGY

Doxycycline Hyclate

a) Acute Toxicity

The acute oral and parenteral toxicity of doxycycline in mice, rats and dogs are as follows:

TABLE 6

	LD_{50} (95% Confidence Limits) mg/kg	
	ORAL	I.V.
Mice	1,900 (1696-2128)	241 (230-253)
Rats	>2,000	228 (202-258)
Dogs	> 500	>100

The intraperitoneal LD_{50}' s of doxycycline in weanling and newborn rats are 262 (222-309) and 300 (275-327) mg/kg, respectively.

b) Subacute Toxicity

One to 2 1/2-month subacute toxicity studies were conducted in rats, hamsters, dogs and monkeys. Doxycycline induced a yellow fluorescence (under ultraviolet light) of bone, teeth, kidney and/or liver, in all animal species tested. In rats, doxycycline produced no toxic effects in doses of up to 500 mg/kg/day for 30 days. In hamsters, doxycycline in dosages of 500 or 250 mg/kg/day produced weight loss and early death, but the 50 mg/kg level (for 30 days) was nontoxic. In dogs, doxycycline in dosages of 250 mg/kg/day for one month produced discoloration of the thyroid gland with the presence of intracytoplasmic granules in follicular acini and occasional amorphous body formation within follicular colloid.

Certain biochemical, functional and histological changes of the liver occurred in the dogs (but not in the rats, hamsters, or monkeys) receiving doxycycline for 30 days at dosage levels of 250 and 50 mg/kg/day, but not at the 25 mg/kg/day level. The biochemical changes in the blood were elevations of alkaline phosphatase, SGPT

and/or BSP retention. Histologic changes were confined to bile ductular proliferation and hepatocellular intracytoplasmic inclusion bodies and Kupffer cells swollen with PAS-positive granular material. These changes in the dog were reversible upon drug withdrawal.

Monkeys which received doxycycline at dosages of 25 and 50 mg/kg/day for 1 1/2 to 2 1/2 months showed mild yellow ultraviolet fluorescence of liver, kidney and bone, and the presence of small amounts of intracytoplasmic granular material in the thyroid gland.

c) Chronic Toxicity

In an 18-month chronic toxicity study, rats were fed diets containing doxycycline at levels to provide daily drug intake of 500, 250, 50 and 0 mg/kg. Slight depression of weight gains in some rats receiving the 500 mg/kg/day dose occurred during the middle third of the study. The usual yellow ultraviolet fluorescence of bone, teeth and/or kidneys was seen in rats receiving all levels of doxycycline for 6, 12 or 18 months. Dark to light brown discoloration of the thyroid gland was also noted in rats receiving doxycycline for 12 months at levels of 500 and 250 mg/kg/day, and at 18 months at all levels. The only other change noted was depletion of hepatic glycogen in four rats receiving the highest dose level for 12 months.

Beagle dogs received doxycycline at levels of 10 and 100 mg/kg, six days per week. Moderate to marked elevations of alkaline phosphatase and SGPT (occasionally SGOT) were observed in animals receiving doxycycline, 100 mg/kg/day. One of two dogs receiving doxycycline, 100 mg/kg/day, displayed mild bile ductular proliferation and hepatocellular inclusion bodies after 5 months (biopsy sample) and 12 months (necropsy sample). Administration of doxycycline for 5 and 12 months at a level of 100 mg/kg/day and for 12 months at a level of 10 mg/kg caused black and brownish discoloration of the thyroid gland, respectively, with intracyloplasmic granules. Other changes included vasodilatation and focal areas of necrosis of the mucosa of the pyloric and fundic stomach of dogs, and yellow ultraviolet fluorescence of teeth and bones of animals at 100 mg/kg/day dose levels of doxycycline.

Additional groups of 4 beagles each received doxycycline in dosages of 5, 1 and 0 mg/kg/day for 6 months. The only abnormal findings were slight elevations of SGPT values in 3 dogs at the 5 mg/kg level at 180 days.

In a one year chronic toxicity study, groups of four rhesus monkeys each received doxycycline in oral doses of 0, 5, 25 and 50 mg/kg/day, respectively. Oral dosage of 100 mg/kg produced severe gastrointestinal symptoms, e.g., vomiting and diarrhea. In one out of 4 monkeys receiving the 50 mg/kg/day dose, occasional anorexia and diarrhea were observed during the first six months.

Significant pathologic changes noted in monkeys sacrificed after receiving

doxycycline for 1 year at dose levels of 50 mg/kg/day were: 1) grossly, very light brown discoloration of the thyroid gland in one of the four monkeys, and 2) microscopically, brownish intracytoplasmic inclusions in the acinar cells of thyroid follicles of three out of four monkeys. Bone and dentin exhibited slight to moderate ultraviolet fluorescence.

Two monkeys, in another study, receiving the 25 mg/kg/day dosage, were sacrificed after 6 and 8 months on test, respectively. Significant gross and histopathologic findings were slight yellow ultraviolet fluorescence of the endosteum and periosteum of bone, and microscopic appearance of small amounts of granular intracytoplasmic material in the acinar cells of thyroid follicles.

The highlights of the chronic toxicity studies can be summarized as follows:

1) Discoloration of the thyroid gland, with deposition of intracytoplasmic granules in the acinar cells of the follicle. Thyroid function, however, did not seem to be affected. This phenomenon appears to be a result of the interaction of the antibiotic with the active iodinating system of the gland.

2) Yellow staining of bones and teeth, which is thought to be due to formation of a tetracycline-calcium-phosphate complex.

Otherwise doxycycline was well tolerated by the rat and monkey at doses up to and including 500 and 50 mg/kg/day for 18 and 12 months, respectively. In dogs, however, repeated daily oral administration of large doses of doxycycline resulted in certain hepatic functional and histopathologic changes which are reversible after drug withdrawal. No adverse hepatic effects were noted in the hamster (1 month), rats (18 months) or monkeys (12 months) for doses up to and including 500, 500 and 50 mg/kg/day, respectively. In view of this and in view of the lack of notable toxicity in our wide human clinical program, it is our opinion that this is a species specific phenomenon, for the dog only.

d) <u>Reproduction and Teratogenic Studies</u>

Doxycycline has no teratologic effects in rats, rabbits or monkeys.

Breeding rats received doxycycline by gavage in doses of 50 and 250 mg/kg/day prior to and throughout two consecutive litters. There was no evidence that doxycycline interfered with the reproductive process in rats.

Pregnant female white New Zealand rabbits received doxycycline orally in doses of 8 and 40 mg/kg/day, respectively, from day 8 to day 16 of pregnancy. Spina bifida and partial anencephaly in one pup each in the control and the 8 mg/kg group, respectively, are believed to be spontaneous and drug-induced.

In teratogenic studies using a limited number of monkeys, doxycycline, in doses

ranging from 1 to 50 mg/kg/day, did not produce any teratologic effects.

Doxycycline Monohydrate

With bulk doxycycline monohydrate administered in a 10% aqueous suspension, the oral LD_{50} for albino male mice was greater than 5000 mg/kg.

Doxycycline Hyclate with Ascorbic Acid

Studies in mice and rats showed the LD_{50} of Doxycycline I.V. to be 75 mg/kg in mice and 88 mg/kg in rats of doxycycline (using a preparation of doxycycline hyclate equivalent to 100 mg of doxycycline with 480 mg of ascorbic acid as a sterile powder).

No signs of drug toxicity were seen in dogs receiving 20 to 21 daily doses of Doxycycline I.V. at a dose level of 5 mg/kg when administered as a 0.5% solution at a rate of 1 mg/kg/min. Dogs receiving 14, 16 or 17 daily intravenous doses of 10 mg Doxycycline I.V. per kg of bodyweight, or 4 daily 60 minute infusions of 300 mg Doxycycline I.V., or 300 mg degraded Doxycycline I.V. evidenced serum alkaline phosphatase and serum glutamic pyruvic transaminase elevations. No morphological basis for these enzyme elevations was established although moderate bile ductular proliferation was seen in 1 of 2 dogs receiving 4 daily intravenous infusions of degraded Doxycycline I.V.

In 8 dogs receiving daily intravenous doses of 10 mg Doxycycline I.V./kg/day (0.5% solution), 5 of 24 vessels used for injections evidenced degrees of thrombosis with recanalization.

Thrombosis in 3 of 6 sites occurred in 2 dogs receiving infusions of degraded Doxycycline I.V. (30 mg/kg-0.5% solution). Injection site thrombosis did not occur in 6 dogs (18 sites) receiving daily doses of 5 mg Doxycycline I.V./kg bodyweight administered as a 0.5% solution at a rate of 1 mg/kg/min (approximately 1 mL/min).

Studies to date indicate that the maximum tolerated intravenous daily dose of Doxycycline I.V. in dogs for 21 consecutive days is 5 mg/kg/day when administered as a 0.5% solution at a rate of 1 mg/kg/min.

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INFORMATION FOR THE PATIENT

Please read this leaflet carefully before you use this medication. This leaflet provides some useful information for you on NTP-Doxycycline Capsules / NTP-Doxycycline Tablets If you have any questions about this medication or your condition, please ask your doctor or pharmacist.

REMEMBER: This medication is for YOU. Never give it to others. It may harm them even if their symptoms are the same as yours.

What is NTP-Doxycycline Capsules / NTP-Doxycycline Tablets?

The name of this medication is NTP-Doxycycline. Each tablet contains 100 mg of the active ingredient doxycycline (as hyclate). Each tablet also contains the inactive ingredients: carnauba wax, colloidal silicon dioxide, FD&C Blue #2, FD&C Red #40, FD&C Yellow #6, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and titanium dioxide.

Each capsule contains 100 mg of the active ingredient doxycycline (as hyclate). Each capsule also contains the inactive ingredients: FD&C Blue #1, gelatin, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, sodium starch glycolate and titanium dioxide.

NTP-Doxycycline tablets are round, orange film coated tablets. NTP-Doxycycline capsules are blue and capsule-shaped.

What is NTP-Doxycycline Capsules / NTP-Doxycycline Tablets used for?

NTP-Doxycycline Capsules / NTP-Doxycycline Tablets may be prescribed by your doctor to treat bacterial infections.

When should NTP-Doxycycline Capsules / NTP-Doxycycline Tablets not be used?

Do not take NTP-Doxycycline Capsules / NTP-Doxycycline Tablets if:

- you are allergic to any of the ingredients listed at the beginning of this leaflet
- you have myasthenia gravis (a chronic autoimmune neuromuscular disease which cause muscle weakness)

Before taking NTP-Doxycycline Capsules / NTP-Doxycycline Tablets:

You should tell your doctor if:

- you are pregnant, or planning to become pregnant
- you are breastfeeding your child. NTP-Doxycycline Capsules / NTP-Doxycycline Tablets is not recommended in women who are breastfeeding. Tetracycline is

excreted in human breastmilk.

- NTP-Doxycycline Capsules / NTP-Doxycycline Tablets is prescribed for a child, and your child is under 8 years old.
  NTP-Doxycycline Capsules / NTP-Doxycycline Tablets is not recommended for children under 8 years of age.

- you have or have had any other health problems especially:

- you have difficulty swallowing, or medical conditions such as the narrowing or obstruction of your esophagus (passage from your mouth to stomach)

- you are taking any other medicines, including medicines you buy without a prescription from a pharmacy, supermarket, or health food store.

Taking NTP-Doxycycline Capsules / NTP-Doxycycline Tablets with other medicines:

- NTP-Doxycycline Capsules / NTP-Doxycycline Tablets should not be taken with alcohol, barbiturates, phenytoin and carbamazepine

Some medicines and NTP-Doxycycline Capsules / NTP-Doxycycline Tablets may interfere with each other and your doctor may wish to change dosage or directions for the following medications or may recommend other medications:

- oral anticoagulants
- penicillin
- bismuth subsalicylate
- antacids containing aluminum, calcium or magnesium reduce NTP-Doxycycline absorption and should not be given to patients taking NTP-Doxycycline
- iron-containing products should be taken at a different time than NTP-Doxycycline
- use of NTP-Doxycycline may reduce the effectiveness of oral contraceptives

How should you take NTP-Doxycycline Capsules / NTP-Doxycycline Tablets?

Antibacterial drugs including NTP-Doxycycline Capsules / NTP-Doxycycline Tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). Although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by NTP-Doxycycline Capsules / NTP-Doxycycline Tablets or other antibacterial drugs in the future.

Follow your doctor's instructions carefully about how much NTP-Doxycycline Capsules / NTP-Doxycycline Tablets to take and when to take it.

NTP-Doxycycline Capsules / NTP-Doxycycline Tablets should be swallowed, preferably with food.

How long should you take NTP-Doxycycline Capsules / NTP-Doxycycline Tablets?

NTP-Doxycycline Capsules / NTP-Doxycycline Tablets should be taken with or after a meal. This should be swallowed with a full glass of water to avoid potential irritation or ulceration of the esophagus (passage from mouth to stomach). Remain in an upright position for a time and do not go to bed right away (at least 1-2 hours), to avoid direct irritation of the esophagus.

What should you do if you forget to take your medication?

If you should forget to take your tablet at the usual time, take it as soon as you remember unless it is time to take the next one. Continue with the remaining doses as before. Do not take more than one dose at a time.

What if you take too many tablets?

Do not take more tablets than your doctor has told you to. If you take too many tablets by accident, call your doctor, pharmacist, **local poison control centre or hospital emergency department** immediately.

While taking NTP-Doxycycline Capsules / NTP-Doxycycline Tablets:

- Follow your doctor's instructions carefully.
- Stop taking NTP-Doxycycline Capsules / NTP-Doxycycline Tablets immediately if you become pregnant and consult your doctor.
- Tell your doctor and pharmacist that you are taking NTP-Doxycycline Capsules / NTP-Doxycycline Tablets if you are about to start taking any new medicines.
- Do not stop taking your medicine until your doctor tells you to, even if you are feeling better.
- Do not use NTP-Doxycycline Capsules / NTP-Doxycycline Tablets to treat any other medical complaints unless your doctor tells you to.

Are there any side effects with NTP-Doxycycline Capsules / NTP-Doxycycline Tablets?

NTP-Doxycycline Capsules / NTP-Doxycycline Tablets may cause side effects. If they occur, they are likely to be minor and temporary. However, some may be serious and need medical attention. NTP-Doxycycline Capsules / NTP-Doxycycline Tablets may cause side effects such as nausea, vomiting, diarrhea, loss of appetite, abdominal pain,

pain or difficulty in swallowing, tooth discolouration and rash.

Use of NTP-Doxycycline Capsules / NTP-Doxycycline Tablets may increase the incidence of vaginal candidiasis (infection) and benign intercranial hypertension (high blood pressure in the brain).

Sensitivity to sunlight and development of a sunburn reaction have occurred with some individuals taking tetracyclines. If you plan to be exposed to direct sunlight, preventative use of a sunscreen or other physical measures are recommended. Avoid excessive sunlight or artificial ultraviolet exposure. Discontinue use if photoxicity develops (e.g. skin eruption...).

Tell your doctor or pharmacist right away if you suffer from any of the following side effects while taking this medication:

- if you develop diarrhea, watery diarrhea, bloody stools, with or without stomach cramps and fever, contact your doctor as soon as possible.

Check with your doctor or pharmacist right away if you have ***any*** problems while taking NTP-Doxycycline Capsules / NTP-Doxycycline Tablets, even if you do not think the problems are connected with the medicine or are not listed in this leaflet.

You can report any suspected adverse reactions associated with the use of health products to the 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 0701C
    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.

How to store NTP-Doxycycline Capsules / NTP-Doxycycline Tablets:

Store bottles between 15°C and 30°C and protect from light.

You should not use your medication after the expiration date printed on the carton and label.

Keep all medications out of the reach of children. This medication could harm them.
This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited at:
1-800-268-4127 ext. 5005 (English Canada);
1-877-777-9117 (French Canada)
or druginfo@tevacanada.com

This leaflet was prepared by:

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

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