

Carcinogenesis, Mutagenesis, Impairment of Fertility: Doxycycline hyclate was assessed for potential to induce carcinogenesis in a study in which the compound was administered to Sprague-Dawley rats by gavage at dosages of 20, 75, and 200 mg/kg/day for two years. An increased incidence of uterine polyps was observed in female rats that received 200 mg/kg/day, a dosage that

resulted in a systemic exposure to doxycycline approximately nine times that observed in female humans that used Periostat (exposure comparison based upon AUC values). No impact upon tumor incidence was observed in male rats at 200 mg/kg/day, or in either gender at the other dosages studied. Evidence of oncogenic activity was obtained in studies with related compounds, i.e., oxytetracycline (adrenal and pituitary tumors), and minocycline (thyroid tumors).

Doxycycline hyclate demonstrated no potential to cause genetic toxicity in an *in vitro* point mutation study with mammalian cells (CHO/HGPRT forward mutation assay) or in an *in vivo* micronucleus assay conducted in CD-1 mice. However, data from an *in vitro* assay with CHO cells for potential to cause chromosomal aberrations suggest that doxycycline hyclate is a weak clastogen.

Oral administration of doxycycline hyclate to male and female Sprague-Dawley rats adversely affected fertility and reproductive performance, as evidenced by increased time for mating to occur, reduced sperm motility, velocity, and concentration, abnormal sperm morphology, and increased pre-and post-implantation losses. Doxycycline hyclate induced reproductive toxicity at all dosages that were examined in this study, as even the lowest dosage tested (50 mg/kg/day) induced a statistically significant reduction in sperm velocity. Note that 50 mg/kg/day is approximately 10 times the amount of doxycycline hyclate contained in the recommended daily dose of Periostat® for a 60 kg human when compared on the basis of body surface area estimates (mg/m²). Although doxycycline impairs the fertility of rats when administered at sufficient dosage, the effect of Periostat® on human fertility is unknown.

Pregnancy: *Teratogenic Effects:* Pregnancy Category D. (See **WARNINGS** Section). Results from animal studies indicate that doxycycline crosses the placenta and is found in fetal tissues.

Nonteratogenic effects: (See **WARNINGS** Section).

Labor and Delivery: The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers: Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from doxycycline, the use of Periostat® in nursing mothers is contraindicated. (See **WARNINGS** Section).

Pediatric Use: The use of Periostat® in infancy and childhood is contraindicated. (See **WARNINGS** section.)

ADVERSE REACTIONS

Adverse Reactions in Clinical Trials of a bioequivalent form of doxycycline hyclate capsules: In clinical trials of adult patients with periodontal disease 213 patients received 20 mg BID over a 9 - 12 month period. The most frequent adverse reactions occurring in studies involving treatment with a bioequivalent form of doxycycline hyclate capsules or placebo are listed below:

Incidence (%) of Adverse Reactions in Clinical Trials of Doxycycline Hyclate Capsules, 20mg (Bioequivalent to Doxycycline Hyclate Tablets, 20mg) vs. Placebo		
Adverse Reaction	Doxycycline Hyclate Capsules 20 mg BID (n=213)	Placebo (n=215)
Headache	55 (26%)	56 (26%)
Common Cold	47 (22%)	46 (21%)
Flu Symptoms	24 (11%)	40 (19%)
Tooth Ache	14 (7%)	28 (13%)
Periodontal Abscess	8 (4%)	21 (10%)
Tooth Disorder	13 (6%)	19 (9%)
Nausea	17 (8%)	12 (6%)
Sinusitis	7 (3%)	18 (8%)
Injury	11 (5%)	18 (8%)
Dyspepsia	13 (6%)	5 (2%)
Sore Throat	11 (5%)	13 (6%)
Joint Pain	12 (6%)	8 (4%)
Diarrhea	12 (6%)	8 (4%)
Sinus Congestion	11 (5%)	11 (5%)
Coughing	9 (4%)	11 (5%)
Sinus Headache	8 (4%)	8 (4%)
Rash	8 (4%)	6 (3%)
Back Pain	7 (3%)	8 (4%)
Back Ache	4 (2%)	9 (4%)
Menstrual Cramp	9 (4%)	5 (2%)
Acid Indigestion	8 (4%)	7 (3%)
Pain	8 (4%)	5 (2%)
Infection	4 (2%)	6 (3%)
Gum Pain	1 (<1%)	6 (3%)
Bronchitis	7 (3%)	5 (2%)
Muscle Pain	2 (1%)	6 (3%)

Note: Percentages are based on total number of study participants in each treatment group.

Adverse Reactions for Tetracyclines: The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with vaginal candidiasis) in the anogenital region. Hepatotoxicity has been reported rarely. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving the capsule forms of the drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (See **DOSAGE AND ADMINISTRATION** Section).

Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See **WARNINGS** Section).

Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See **WARNINGS** Section).

Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdose.

DOSAGE AND ADMINISTRATION

THE DOSAGE OF PERIOSTAT® DIFFERS FROM THAT OF DOXYCYCLINE USED TO TREAT INFECTIONS. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN

INCREASED INCIDENCE OF SIDE EFFECTS INCLUDING THE DEVELOPMENT OF RESISTANT MICROORGANISMS.

Periostat® 20 mg twice daily as an adjunct following scaling and root planing may be administered for up to 9 months. Periostat® should be taken twice daily at 12 hour intervals, usually in the morning and evening. It is recommended that if Periostat® is taken close to meal times, allow at least one hour prior to or two hours after meals. Safety beyond 12 months and efficacy beyond 9 months have not been established.

Administration of adequate amounts of fluid along with the tablets is recommended to wash down the drug and reduce the risk of esophageal irritation and ulceration. (See **ADVERSE REACTIONS** Section).

HOW SUPPLIED

Periostat® (white tablet imprinted with a PS20) containing doxycycline hyclate equivalent to 20 mg doxycycline. Bottle of 60 (NDC 64682-008-01), Bottle of 100 (NDC 64682-008-02) and Bottle of 1000 (NDC 64682-008-03).

Storage: All products are to be stored at controlled room temperatures of 15°C - 30°C (59°F - 86°F) and dispensed in tight, light-resistant containers (USP).

Rx Only

PERIOSTAT® is a trademark of CollaGenex Pharmaceuticals, Inc., Newtown, PA, 18940

Manufactured by: Pharmaceutical Manufacturing Research Services, Inc. Horsham, PA 19044

Marketed by: CollaGenex Pharmaceuticals, Inc. Newtown, PA, 18940

REFERENCES

- Golub L.M., Sorsa T., Lee H-M, Ciano S., Sorbi D., Ramamurthy N.S., Gruber B., Salo T., Kontinen Y.T.: Doxycycline Inhibits Neutrophil (PMN)-type Matrix Metalloproteinases in Human Adult Periodontitis Gingiva. J. Clin. Periodontol 1995; 22: 100-109.
- Golub L.M., Ciano S., Ramamurthy N.S., Leung M., McNamara T.F.: Low-dose Doxycycline Therapy: Effect on Gingival and Crevicular Fluid Collagenase Activity in Humans. J. Periodont Res 1990; 25: 321-330.
- Golub L.M., Lee H.M., Greenwald R.A., Ryan M.E., Salo T., Giannobile W.V.: A Matrix Metalloproteinase Inhibitor Reduces Bone-type Collagen Degradation Fragments and Specific Collagenases in Gingival Crevicular Fluid During Adult Periodontitis. Inflammation Research 1997; 46: 310-319.
- Saivain S., Houin G.: Clinical Pharmacokinetics of Doxycycline and Minocycline. Clin. Pharmacokinetics 1988; 15: 355-366.
- Schach von Wittenau M., Twomey T.: The Disposition of Doxycycline by Man and Dog. Chemotherapy 1971; 16: 217-228.
- Campistron G., Coulais Y., Caillard C., Mosser J., Pontagnier H., Houin G.: Pharmacokinetics and Bioavailability of Doxycycline in Humans. Arzneimittel Forschung 1986; 36: 1705-1707.

(doxycycline hyclate tablets) 20mg

PERIOSTAT®



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