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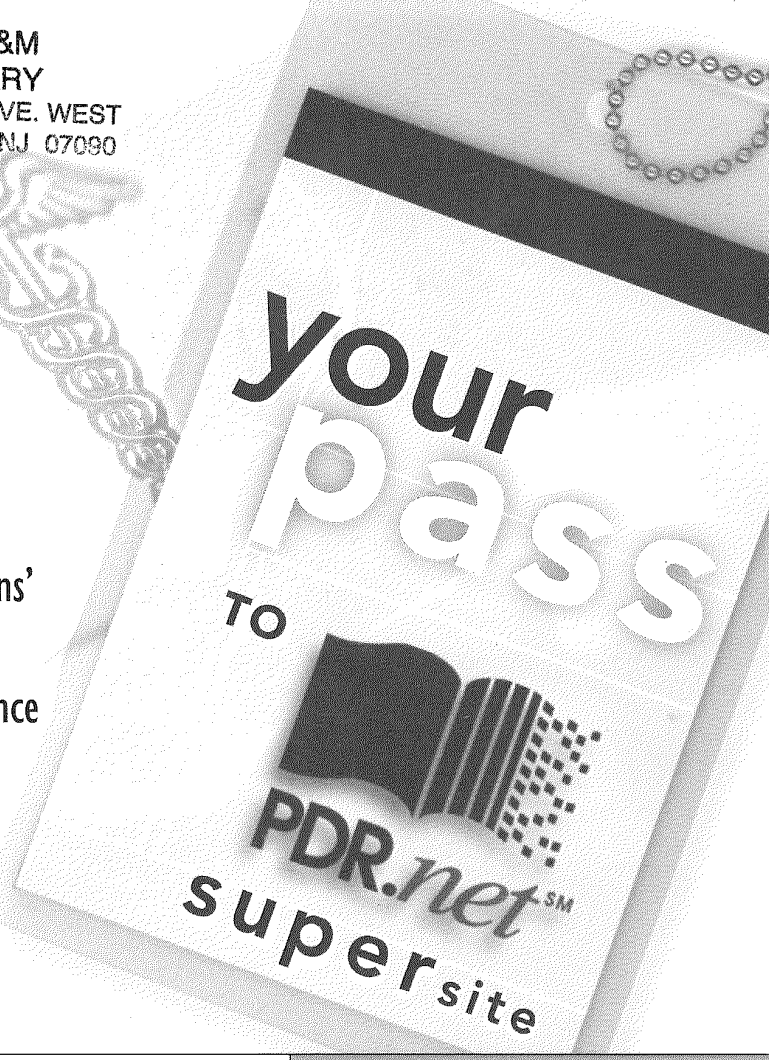

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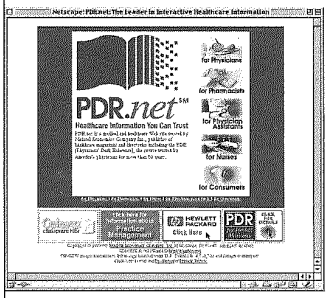

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years and, if the titer is less than complete neutralization at a 1:5 serum dilution by RFFIT, should have a booster dose of vaccine. Alternatively, a booster can be administered in the absence of a titer determination.

Veterinarians and animal-control and wildlife officers working in areas of low rabies enzooticity (infrequent-exposure group) do not require routine pre-exposure booster doses of RabAvert after completion of a full primary pre-exposure immunization scheme (Table 1).

B. Post-exposure Dosage

Immunization should begin as soon as possible after exposure. A complete course of immunization consists of a total of 5 injections of 1 mL each: one injection on each of days 0, 3, 7, 14 and 28 in conjunction with the administration of HRIG on day 0. For children, see *Pediatric Use* section, above.

Begin with the administration of HRIG. Give 20 IU/kg body weight.

This formula is applicable to all age groups, including children. The recommended dosage of HRIG should not exceed 20 IU/kg body weight because it may otherwise interfere with active antibody production. Since vaccine-induced antibody appears within 1 week, HRIG is not indicated more than 7 days after initiating post-exposure immunization with RabAvert. If possible, up to one-half the dose of HRIG should be thoroughly infiltrated in the area around the wound and the rest should be administered IM, in a different site from the rabies vaccine, preferably in the gluteal area.

Because the antibody response following the recommended immunization regimen with RabAvert has been satisfactory, routine post-immunization serologic testing is not recommended. Serologic testing is indicated in unusual circumstances, as when the patient is known to be immunosuppressed. Contact state health department or CDC for recommendations.

C. Post-exposure Therapy of Previously Immunized Persons

When rabies exposure occurs in an immunized person who was vaccinated according to the recommended regimen with RabAvert or other tissue culture vaccines or who had previously demonstrated rabies antibody, that person should receive two IM doses (1.0 mL each) of RabAvert: one immediately and one 3 days later. HRIG should not be given in these cases. Persons should be considered to have been immunized previously if they received pre- or post-exposure prophylaxis with RabAvert or other tissue culture vaccines or have been documented to have had an adequate antibody response to duck embryo rabies vaccine. If the immune status of a previously vaccinated person is not known, full primary post-exposure antirabies treatment (HRIG plus 5 doses of vaccine) may be necessary. In such cases, if antibodies can be demonstrated in a serum sample collected before vaccine is given, treatment can be discontinued after at least two doses of vaccine.

HOW SUPPLIED

Package with:
1 vial of freeze-dried vaccine containing a single dose
1 disposable syringe
1 longer needle for reconstitution, 21 gauge × 1.5″
1 vial of sterile Water For Injection, USP (1 mL)
1 smaller needle for injection, 25 gauge × 1″
N.D.C.# 53905-501-01 CAUTION: Federal law prohibits dispensing without a prescription

Storage

RabAvert should be stored protected from light at 2°C to 8°C (36°F to 46°F). After reconstitution the vaccine is to be used immediately. The vaccine may not be used after the expiration date given on package and container.

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Manufactured by:
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Shown in Product Identification Guide, page 310

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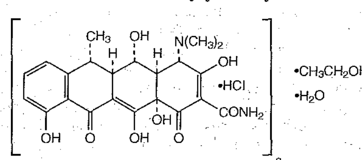
PERIOSTAT® ℞
[pĕrĭo-stat]
(doxycycline hyclate capsules)

DESCRIPTION

Periostat® is available as a 20 mg capsule formulation of doxycycline hyclate for oral administration.

Doxycycline is synthetically derived from oxytetracycline. The structural formula of doxycycline hyclate is:



with an empirical formula of $(C_{22}H_{24}N_2O_8{\cdot}HCl)_2{\cdot}C_2H_6O{\cdot}H_2O$ and a molecular weight of 1025.89. The chemical designation for doxycycline is 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-

mide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate.
Doxycycline hyclate is a light-yellow crystalline powder which is soluble in water.
Inert ingredients in the formulation are: hard gelatin capsules; magnesium stearate; and microcrystalline cellulose. Each capsule contains doxycycline hyclate equivalent to 20 mg of doxycycline.

CLINICAL PHARMACOLOGY

After oral administration, doxycycline hyclate is rapidly and nearly completely absorbed from the gastrointestinal tract. Doxycycline is eliminated with a half-life of approximately 18 hours by renal and fecal excretion of unchanged drug.
Mechanism of Action: Doxycycline has been shown to inhibit collagenase activity in vitro.[1] Additional studies have shown that doxycycline reduces the elevated collagenase activity in the gingival crevicular fluid of patients with adult periodontitis.[2,3] The clinical significance of these findings is not known.
Microbiology: Doxycycline is a member of the tetracycline class of antibiotics. The dosage of doxycycline achieved with this product during administration is well below the concentration required to inhibit microorganisms commonly associated with adult periodontitis. Clinical studies with this product demonstrated no effect on total anaerobic and facultative bacteria in plaque samples from patients administered this dose regimen for 9 to 18 months. This product **should not** be used for reducing the numbers of or eliminating those microorganisms associated with periodontitis.
Pharmacokinetics
The pharmacokinetics of doxycycline following oral administration of Periostat® were investigated in 3 volunteer studies involving 87 adults. Additionally, doxycycline pharmacokinetics have been characterized in numerous scientific publications.[4] Pharmacokinetic parameters for Periostat® following single oral doses and at steady-state in healthy subjects are presented as follows:
[See first table above]
Absorption: Doxycycline is virtually completely absorbed after oral administration. Following 20 mg doxycycline, twice a day, in healthy volunteers, the mean peak concentration in plasma was 790 ng/mL and the average steady-state concentration was 482 ng/mL. The effect of food on the absorption of doxycycline from Periostat® has not been studied.
Distribution: Doxycycline is greater than 90% bound to plasma proteins. Its apparent volume of distribution is variously reported as between 52.6 and 134 L.[4,6]
Metabolism: Major metabolites of doxycycline have not been identified. However, enzyme inducers such as barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.
Excretion: Doxycycline is excreted in the urine and feces as unchanged drug. It is variously reported that between 29% and 55.4% of an administered dose can be accounted for in the urine by 72 hours.[5,6] Half-life averaged 18 hours in subjects receiving a single 20 mg doxycycline dose.
Special Populations
Geriatric: Doxycycline pharmacokinetics have not been evaluated in geriatric patients.
Pediatric: Doxycycline pharmacokinetics have not been evaluated in pediatric patients. (See **WARNINGS**.)
Gender: A study was conducted in 42 subjects where doxycycline pharmacokinetics were compared in men and women. It was observed that C_{max} was approximately 1.7-fold higher in women than in men. There were no apparent differences in other pharmacokinetic parameters.
Race: Differences in doxycycline pharmacokinetics among racial groups have not been evaluated.
Renal Insufficiency: Studies have shown no significant difference in serum half-life of doxycycline in patients with normal and severely impaired renal function. Hemodialysis does not alter the half-life of doxycycline.
Hepatic Insufficiency: Doxycycline pharmacokinetics have not been evaluated in patients with hepatic insufficiency.
Drug Interactions: See "Precautions"

Clinical Study

In a randomized, multi-centered, double-blind, 9-month Phase 3 study involving 190 adult patients with periodontal disease [at least two probing sites per quadrant of between 5 and 9 mm pocket depth (PD) and attachment level (ALv)], the effects of oral administration of 20 mg twice a day of doxycycline hyclate plus scaling and root planing (SRP) were compared to placebo control plus SRP. Both treatment groups were administered a course of scaling and root planing in 2 quadrants at Baseline. Measurements of ALv, PD and bleeding-on-probing (BOP) were obtained at Baseline, 3, 6, and 9 months from each site about each tooth in the two quadrants that received SRP using the UNC-15 manual probe. Each tooth site was categorized into one of three strata based on Baseline PD: 0–3 mm (no disease), 4–6 mm (mild/moderate disease), ≥ 7 mm (severe disease). For each stratum and treatment group, the following were calculated at month 3, 6, and 9: mean change in ALv from baseline, mean change in PD from baseline, mean percentage of tooth sites per patient exhibiting attachment loss of ≥ 2 mm from baseline, and percentage of tooth sites with bleeding on probing. The results are summarized in the following table.
[See second table above]

INDICATIONS AND USAGE

Periostat® is indicated for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce

	n	Cmax (ng/mL)	Tmax (hr)	Cl/F (L/hr)	$t_{1/2}$ (hr)
Single dose 20 mg	42	400 ± 142	1.5 (0.5–4.0)	3.80 ± 0.85	18.4 ± 5.38
Steady-State 20 mg BID	30	790 ± 285	2 (0.98–12.0)	3.76 ± 1.06	Not Determined

Clinical Results at Nine Months as an Adjunct to SRP

Parameter	Baseline Pocket Depth 0–3 mm	4–6 mm	≥ 7 mm
Number of Patients	90	90	79
Mean Gain in ALv			
Periostat® 20 mg BID	0.25 mm	1.03 mm*	1.55 mm*
Placebo	0.20 mm	0.86 mm	1.17 mm
Mean Decrease in PD			
Periostat® 20 mg BID	0.16 mm**	0.95 mm**	1.68 mm**
Placebo	0.05 mm	0.69 mm	1.20 mm
% of Sites with loss of ALv ≥2 mm			
Periostat® 20 mg BID	1.9%	1.3%	0.3%*
Placebo	2.2%	2.4%	3.6%
% of Sites with BOP			
Periostat® 20 mg BID	39%**	64%*	75%
Placebo	46%	70%	80%

*p<0.050 vs. the placebo control group.
**p<0.010 vs. the placebo control group.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP AND IN PREGNANT OR NURSING MOTHERS UNLESS THE POTENTIAL BENEFITS MAY BE ACCEPTABLE DESPITE THE POTENTIAL RISKS.
All tetracyclines form a stable calcium complex in any bone forming tissue. A decrease in fibula growth rate has been observed in premature infants given oral tetracyclines in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.
Doxycycline can cause fetal harm when administered to a pregnant woman. 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. If any tetracyclines are 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.
The catabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.
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 tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

PRECAUTIONS

While no overgrowth by opportunistic microorganisms such as yeast were noted during clinical studies, as with other antimicrobials, Periostat® therapy may result in overgrowth of nonsusceptible microorganisms including fungi.
The use of tetracyclines may increase the incidence of vaginal candidiasis.
Periostat® should be used with caution in patients with a history or predisposition to oral candidiasis. The safety and effectiveness of Periostat® has not been established for the treatment of periodontitis in patients with coexistant oral candidiasis.
If superinfection is suspected, appropriate measures should be taken.
Laboratory Tests: In long term therapy, periodic laboratory evaluations of organ systems, including hematopoietic, renal, and hepatic studies should be performed.
Drug Interactions: Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
Since bacteriostatic antibiotics, such as the tetracycline

tion of members of the b-lactam (e.g. penicillin) class of antibiotics, it is not advisable to administer these antibiotics concomitantly.
Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, and by iron-containing preparations. Absorption is also impaired by bismuth subsalicylate.
Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.
The concurrent use of tetracycline and Penthrane (methoxyfluorane) has been reported to result in fatal renal toxicity.
Concurrent use of tetracycline may render oral contraceptives less effective.
Drug/Laboratory Test Interactions: False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Doxycycline hyclate has not been evaluated for carcinogenic potential in long-term animal studies. 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/m^2). 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.) Results from animal studies indicate that doxycycline crosses the placenta and is found in fetal tissues.
Nonteratogenic effects: (See WARNINGS.)
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.)
Pediatric Use: The use of Periostat® in infancy and childhood is contraindicated. (See WARNINGS.)

ADVERSE REACTIONS

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

Continued on next page

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