

What's your PerioStatus



*A Guide to
Healthy Gums*

for health...



for well-being...



for life...



What's your PerioStatus?

A G U I D E T O H E A L T H Y G U M S



*Do you know your **PerioStatus**?
If you don't, count yourself among
the vast majority of adults in the U.S.
who do not know that "**PerioStatus**"
– the condition of your periodontal
tissues, including the gums and bone
that anchor your teeth in place – is
an important factor in your overall
health and well-being.*

CollaGenex Pharmaceuticals has created the "**What's Your PerioStatus?**" brochure to help you build a better understanding of:

- The important role of healthy gum tissues in helping you keep your teeth
- The factors that increase your chances of developing periodontal disease, including smoking, diabetes and a family history of gum disease
- The "silent" symptoms that, if left unchecked, can lead to tooth loss and even more serious medical conditions
- How critical it is to take charge of your oral health by forming a partnership with your dentist or periodontist that includes regular evaluation of your **PerioStatus!**

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*Oral health is
key to overall
health
and*



Despite great advances made during the last two decades in reducing tooth decay, an estimated 67 million people in the U.S. (nearly one in three adults) suffer from some type of periodontal, or gum, disease. In fact, periodontitis, the most serious form of this condition, is the leading cause of adult tooth loss in our country. In addition, this problem reaches far beyond the discomfort and harm to nutrition, self-image and lifestyle caused by losing one's teeth. Recently, scientific research has uncovered an apparent relationship between periodontal diseases and other serious health conditions such as heart disease, diabetes, stroke and possibly pre-term, low-birth-weight childbirth.

For these reasons, the *"What's Your PerioStatus?"* brochure has been developed to help educate the public about the importance of maintaining proper oral health and to help illustrate that good overall health should begin with your teeth and gums.

It is our hope that each of you who reads this brochure will better understand why it is so critical to work with your oral health care professional to maintain the pleasing appearance and good health of your teeth, as well as the strength and integrity of the gums and supporting tissues responsible for keeping your teeth where they belong.

The "What's Your PerioStatus?" Editorial Review Board



Though nearly one in every three adults in the U. S. – many of them between the ages of 35 and 45 years – has some form of periodontal disease, a recent national survey of 1,000 adults aged 35 and older found that a surprising majority of those polled knew little, if anything, about the disease, its symptoms, available treatments, and most concerning, its consequences.

In summary, *The PerioStatus Report*, conducted by national polling organization Harris Interactive, Inc., revealed that very few people know their **PerioStatus** — even those who are at high risk for developing the disease or who have actually experienced symptoms!

Could it be that our society's emphasis on straight, shiny, cavity-free teeth – depicted in the bright smiles beaming from magazines and television – has distracted us from protecting the structures that keep our teeth safely anchored in our mouths – the gums and bone that are destroyed by periodontitis?

Here are some of the eye-opening findings of The PerioStatus Report:

- 60% of adults surveyed are not familiar with periodontal disease
- More than 80% do not know it is the leading cause of adult tooth loss
- Four of ten (39%) adults surveyed do not visit a dentist regularly
- Of those who say they are familiar with periodontal disease, one-third could not identify any treatments
- Two-thirds of those interviewed did not know that periodontal disease may be linked with other serious medical conditions

The compelling results of *The PerioStatus Report* paint a dramatic picture of how far we must come in our understanding of periodontal disease and the importance of working with your oral health professional to maintain good periodontal health.

2/3^{RDS}

TWO-THIRDS OF THOSE INTERVIEWED DID NOT KNOW THAT PERIODONTAL DISEASE MAY BE LINKED WITH OTHER SERIOUS MEDICAL CONDITIONS





Periodontal disease approaches silently. It may progress painlessly, producing few obvious signs. Then one day, on a visit to your dentist, you are told that you have chronic gum disease and may be at increased risk of losing your teeth. Sound unlikely? This disturbing scenario may be more common than you think.

Periodontal disease begins with bacteria, which is often referred to as plaque or calculus, and is an inhabitant of every mouth. As bacteria make themselves at home on your gums and teeth, these unwelcome visitors can cause your gums to become inflamed. As a natural defense mechanism, your body attempts to oust the bacteria by sending infection-fighting white blood cells to the site of the inflammation. These white blood cells release enzymes, which in some people are overproduced. This overproduction of enzymes leads to advanced stages of gum disease and is responsible for the destruction of the tissues that surround and support the teeth, including the gums and bone.

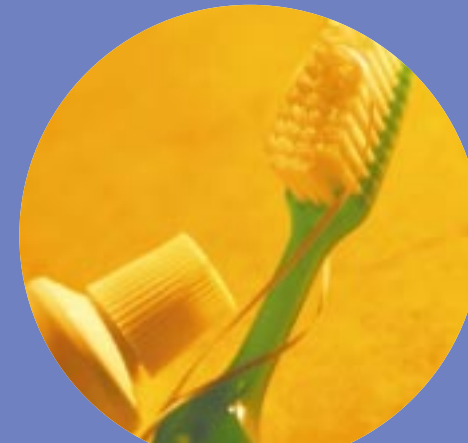
These symptoms may point to some form of periodontal disease, which usually is classified as gingivitis or periodontitis, depending on severity. Gingivitis is considered an early stage of the disease and is associated with inflamed, red and swollen gums. At this point, vigilant brushing and flossing, medicated mouthwashes and regular dental cleanings can put you back on the track to healthy gums.

Untreated gingivitis may lead to the advanced stage, periodontitis, which also is associated with gum inflammation, but even more serious, may permanently damage the tissues and bone surrounding and supporting the teeth. Unfortunately, this destruction is largely irreversible, and good dental hygiene alone cannot stop it. Periodontitis must be treated by dental professionals to halt the progression of the disease and prevent tooth loss.

a silent disease

Though the symptoms of periodontal disease are often subtle, the disease is not entirely without warning signs, which may include:

- *gums that bleed when you brush or floss*
- *red, swollen or tender gums*
- *persistent bad breath or bad taste*
- *receding gums*
- *formation of deep pockets between teeth and gums*
- *loose or shifting teeth*
- *changes in the way teeth fit together when you bite*



PERIODONTITIS
MUST BE TREATED
BY DENTAL PROFES-
SIONALS TO HALT THE
PROGRESSION OF THE
DISEASE AND PREVENT
TOOTH LOSS.

WHY DO I NEED TO CONTROL PERIODONTAL DISEASE?



... because it is the leading cause of adult tooth loss.

Missing teeth are often the subject of jokes and comedy sketches. You can certainly recall at least one humorous portrayal of a toothless, gum-smacking grandpa or granny. But, if you are like most people today, losing your teeth would be no laughing matter. We no longer accept tooth loss as an inevitable part of getting older — nor should we.

In fact, chances are that you value your teeth more than gold and are not willing to lose them unnecessarily, or without a fight. One reason is your appearance. Your teeth contribute to the way you look and to your self-image.

Tooth loss can spread to other parts of your life as well, affecting your overall health (loose or missing teeth may prevent you from eating crunchy, high fiber foods necessary for a nutritious diet), influencing your career and/or social life (tooth loss may affect your appearance and your ability to speak clearly) and even resulting in costly and time-consuming procedures to extract and cosmetically repair or replace teeth.

... because periodontal disease can affect the health of other parts of your body

Cardiovascular Disease. Preliminary studies show that people with periodontal disease are one and a half to two times more likely to suffer a fatal heart attack and nearly three times more likely to suffer a stroke.

Diabetes. It has long been known that people with diabetes are more susceptible to bacterial infections like periodontal disease. Recent studies reveal that moderate to advanced periodontal disease also makes it more difficult for people with diabetes to maintain proper blood sugar levels.

Premature Birth. There is some indication that periodontal disease may put pregnant women at an increased risk of giving birth to pre-term, low-weight babies.

PERIODONTAL DISEASE - ARE YOU AT RISK?

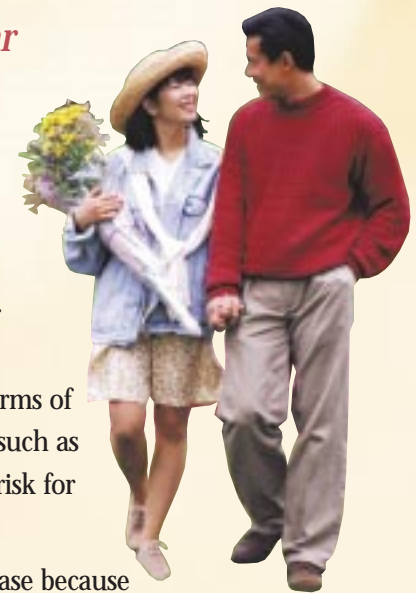


A number of factors can increase your chances of developing periodontal disease. The good news is that you may be able to reduce your risk simply by changing your behavior. Smoking, poor oral hygiene, infrequent dental visits, inadequate nutrition and stress all negatively impact your oral health and promote gum disease. To help prevent gum disease:

- *If you smoke, quit* — smoking increases your risk of periodontal disease between two-to-seven-fold
- *Brush your teeth well at least twice a day*
- *Floss/clean between your teeth daily*
- *Eat a balanced diet*
- *Visit your dentist on a regular basis for professional care*

Unfortunately, periodontal disease is not “fair” and can invade the mouth of even the most devout brusher and flosser. In some cases, this injustice may be attributed to genetic makeup. Studies show that your genes, passed along to you by your parents, may make you more susceptible to some forms of periodontitis. In addition, certain diseases, such as diabetes or osteoporosis, can increase your risk for periodontal disease.

If you are predisposed to periodontal disease because it runs in your family or if you have diabetes, don't give up your fight to keep your teeth. While good oral hygiene, regular professional care and a healthy lifestyle may not prevent periodontal disease, they can help you



To get a better idea of your PerioStatus, ask yourself these questions:

1. Do my gums bleed easily when I brush or floss?
2. Are my gums red, swollen or tender?
3. Do I have bad breath or a bad taste in my mouth that does not seem to go away?
4. Do I have diabetes or osteoporosis?
5. Am I a smoker?
6. Does anyone in my family have periodontal disease?
7. Do I brush and floss my teeth infrequently?
8. Was my last dental visit more than six months ago?
9. Do I have teeth that feel loose or are there gaps appearing between my teeth?
10. When I bite, are there changes in the way my teeth fit together?

ask yourself



IF YOU ANSWERED "YES" TO ANY OF THESE QUESTIONS, YOU SHOULD CONSIDER MAKING AN APPOINTMENT WITH YOUR DENTIST OR WITH A SPECIALIST CALLED A PERIODONTIST TO ASSESS YOUR PERIOSTATUS AND TO DISCUSS WAYS OF

FIGHTING THE BATTLE AGAINST PERIODONTAL DISEASE



Once you have been diagnosed by a dental professional with *adult periodontitis* or any form of progressive periodontal disease, you should receive appropriate treatment as soon as possible to control or prevent further destruction of tooth-supporting tissues.

As mentioned earlier, periodontitis has two components: *bacterial infection* followed by the body's production of *tissue-destroying enzymes* as part of the body's attempt to fight the infection. Scientists now have determined that the best way to control periodontal disease is through a two-step process that treats both components, including:

1. Reducing the amount of bacteria in the gum pockets, the spaces formed between the gum and tooth
2. Blocking or suppressing the action of the tissue-destroying enzymes released in the gum tissues

The most common procedure used to eliminate bacteria is an intensive professional cleaning method called scaling and root planing (SRP), during which soft (plaque) and hard (calculus) deposits are removed from the tooth surface above and below the gumline; this includes shaving off a layer of the root surface, which encourages the gum to re-attach to the tooth.

In addition, you may be given a prescription for antibiotics or antimicrobials to help kill bacteria. They can be given in pill-form, as a mouth rinse or implanted directly into your gum pocket as an antibiotic-laden thread, gel, or antimicrobial chip. Most of these treatments are given with or following SRP.

In addition to reducing bacteria in the mouth, another important treatment step is preventing enzymes from destroying gum and bone tissue. To date, the only available medication aimed specifically at halting these enzymes is **Periostat**[®] (doxycycline hyclate) 20 mg capsules. This prescription capsule was approved by the U. S. Food and Drug

Administration for the treatment of adult periodontitis in conjunction with SRP. Research studies have shown that when used after SRP, **Periostat**[®] significantly improved on the results of this standard treatment and helped to stop progression of the disease *better* than SRP alone.

In the research studies, patients who took **Periostat**[®] had side effects similar to those of patients who received the placebo, or sugar pill. **Periostat**[®] should be taken twice a day for a minimum of three months, or as recommended by your dentist.

In addition to these treatments, more involved procedures, such as periodontal surgery, may be necessary. That is why it is so important to talk with your dentist or periodontist about your **PerioStatus** and the options that are available to ensure you receive the most effective treatment possible.

Take a few minutes during your check-up to ask your dentist the following questions. Let him or her know that you care about the condition of your gums, as well as your teeth. After all, your total oral health affects your overall health!

1. Do my gums look healthy?
2. Did my gums bleed during this exam?
3. Have any spaces formed between my gums and my teeth?
4. Are any of my permanent teeth loose or separating?
5. Have there been any changes in the way my teeth fit together when I bite?
6. What steps can I take to achieve healthy gums?
7. Do you suggest that I schedule an appointment with a periodontist?

Engaging in a conversation with your dentist could help you feel more comfortable during the check-up. If you tend to feel anxious or intimidated just thinking about sitting in the dentist's chair, remember that a thorough exam today could save you from a more complicated one in the future.



IN ADDITION TO REDUCING BACTERIA IN THE MOUTH, ANOTHER IMPORTANT TREATMENT STEP IS PREVENTING ENZYMES FROM DESTROYING GUM AND BONE TISSUE.

working with

YOUR DENTIST TO MAINTAIN GOOD PERIODONTAL HEALTH



*Do you usually leave the dentist's office with sparkling teeth, a new toothbrush and a reminder to floss? Though clean, cavity-free teeth are very important, your dental check-up should include something else as well — an assessment of your **PerioStatus**.*

If your dentist advises you that your gums and teeth are healthy, pat yourself on the back and continue with your good habits. Regular dental cleaning at home and at a dentist's office is the best way to prevent gum disease.

By making your total oral health a priority, you will leave the dentist's office with a smile and the reassurance that you are on your way to the best possible **PerioStatus**.

Here's to your excellent oral health!

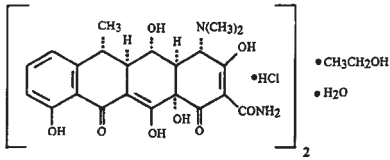


PERIOSTAT®
(doxycycline hyclate capsules)

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 $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_5O \cdot H_2O$ 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-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide 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:

Pharmacokinetic Parameters for Periostat®					
	n	C _{max} (ng/mL)	T _{max} (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 (0.98 - 12.0)	2	3.76 ± 1.06	Not Determined

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.

Clinical Results at Nine Months as an Adjunct to SRP				
Parameter	Baseline Pocket Depth			≥ 7 mm
	0-3 mm	4-6 mm	90	
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.

INDICATIONS AND USAGE

Periostat® is indicated for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

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

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 coexistent 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 class of antibiotics, may interfere with the bactericidal action of members of the β-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 (methoxy-fluorane) 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/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.) 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:

Adverse Reaction	Incidence (%) of Adverse Reactions in Periostat Clinical Trials	
	Periostat 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 (%)	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.)

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

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

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 MICRO-ORGANISMS.

Periostat® 20 mg twice daily as an adjunct following scaling and root planing may be administered for up to 9 months. Safety beyond 12 months and efficacy beyond 9 months have not been established.

Periostat® should be administered at least one hour prior to morning and evening meals.

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

HOW SUPPLIED

Periostat® (white capsule imprinted with "Periostat™") containing doxycycline hyclate equivalent to 20 mg doxycycline. Bottle of 100 (NDC 27280-007-01).

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

Rx Only

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

Manufactured by Applied Analytical Inc. Wilmington, NC 28403

Marketed by CollaGenex Pharmaceuticals, Inc. Newtown, PA 18940

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