

Food and Drug Administration
Rockville MD 20857**TRANSMITTED BY FACSIMILE**

OCT 17 2000

Christopher Powala
Sr. Director, Drug Development & Regulatory Affairs
Collagenex Pharmaceuticals, Inc.
301 South State Street
Newtown, PA 18940

RE: NDA 50-744
Periostat (doxycycline hyclate), 20 mg Capsules
MACMIS ID # 9427

Dear Mr. Powala,

This letter is in reference to Collagenex Pharmaceuticals, Inc.'s (Collagenex) dissemination of two television broadcast advertisements and a print advertisement for Periostat. We specifically refer to your direct-to-consumer (DTC) advertisements submitted via FDA Form 2253. You submitted a 15-second "reminder" and 60-second "full product" storyboard for television broadcast advertisements, and a print advertisement. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the promotional materials and has concluded that they are misleading under the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Our specific objections follow:

Reminder Advertisement

Reminder advertisements call attention to the name of the drug product, but may not contain written, printed, or graphic matter containing representations or suggestions relating to the drug product. This advertisement states that a dentist prescribed the drug for his patient. Further, the telephone number (1-877-894-GUMS) includes "GUMS." Both of these presentations imply that the drug is a dental product for aiding gums. Thus, this is a full product advertisement and must comply with all the requirements related to benefits and risk disclosure.

Failure to Provide Adequate Risk Information

The 60-second "full product" advertisement is misleading because it fails to present important risk information. The advertisement states that one shouldn't "take Periostat if you are pregnant or nursing or if you're hypersensitive to tetracyclines." Failure to give the reason for why pregnant and nursing women should not take Periostat minimizes the significance of the risk information. To appropriately understand the risk, women patients should know that this is because their children's teeth could be permanently discolored. Further, consumers generally would not understand the technical language of the contraindication regarding hypersensitivity to tetracycline. Neither "hypersensitivity"

Christopher Powala
Collagenex Pharmaceuticals, Inc.
NDA 50-744

Page 2

nor "tetracycline" are consumer friendly terms. These same objections apply to your print advertisement.

Requested Actions

In our telephone conference with you on October 16, 2000, we requested that you immediately cease the dissemination of these violative advertisements and all similar promotional materials that contain the same or similar claims or presentations. In a follow-up telephone call the same day, you agreed to cease the dissemination of the advertisements.

If you have any questions, please contact the undersigned by telephone at (301) 827-2831, facsimile (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds Collagenex that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 9427 and NDA 50-744.

Sincerely,

/s/

Warren F. Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications



Gum disease with tooth pockets?

If you have periodontitis—gum disease with tooth pockets 4mm deep or more—you don't have to give up your smile.

PerioStat is the first FDA-approved prescription pill that is proven to help shrink tooth pockets when used in combination with a deep-cleaning procedure known as scaling and root planing.

PerioStat is an entirely different approach to the treatment of periodontitis. It fights the deterioration of support tissue around the tooth. When PerioStat is prescribed in combination with deep-cleaning therapies (scaling and root planing), clinical trials have shown significant

reduction in tooth pocket depth and improved tooth attachment. The results are significantly better than those achieved by scaling and root planing alone.

In clinical trials, adverse reactions to PerioStat were similar to taking a placebo. Don't take PerioStat if you are pregnant, nursing, or if you're hypersensitive to tetracyclines.

So if you're one of the millions of adults with periodontitis, now there's another tool to help you and your dentist win the battle.

Take care of your teeth and gums. Brush, floss and see your dentist regularly. And ask about PerioStat. The first prescription pill that can help you keep your teeth.

PerioStat[®] (doxycycline hyclate) 20 mg capsules

It can help you keep your teeth.
1-888-945-GUMS www.periostat.com

Be aware that the information before you about taking PERIOSTAT[®] This site provides a summary of certain information about PERIOSTAT. Your dentist or pharmacist can give you more complete information that is written for health professionals. This does not replace the careful discussions you should have with your dentist before taking PERIOSTAT and during your regular checkups.

What is PERIOSTAT?
PERIOSTAT is a medicine used together with a deep cleaning of your teeth (known as scaling and root planing) by your dentist. PERIOSTAT plus scaling and root planing improve the stability and health of the gums and teeth in adults with periodontitis (gum disease). PERIOSTAT works by reducing the activity of certain enzymes produced in gum and bone tissues around teeth in individuals with adult periodontitis disease.

PERIOSTAT is available as a capsule that you take twice a day, by mouth. Each PERIOSTAT capsule contains 20 mg of the active ingredient doxycycline hyclate.

Who should not take PERIOSTAT?
Do not take PERIOSTAT if you:
• have had an allergic reaction to any of the tetracycline antibiotics, including doxycycline and minocycline. If you are unsure about any of these medications, talk to your dentist or pharmacist.
• are pregnant or plan to become pregnant, because it may harm the unborn. If you suspect or learn that you are pregnant while taking PERIOSTAT, immediately stop taking it and contact your dentist or medical doctor.
• are nursing an infant, because this medication is passed through breast milk and may cause harm to the infant. PERIOSTAT should not be given to infants or children, because it may cause permanent discoloration of the teeth or problems with tooth development.

What should I tell my dentist before and during treatment with PERIOSTAT?
Tell your dentist if you:
• have a history of allergic reactions to doxycycline or other tetracyclines.
• are pregnant or plan to become pregnant, because PERIOSTAT may harm the unborn.
• have kidney or liver disease.
• have a history of or are currently experiencing an oral or vaginal yeast or fungal infection.
• often expose your skin to sunlight or artificial sunlight, because more severe sunburns may occur in some people taking doxycyclines.
• are taking any other medications, including those that you can get without a prescription (over-the-counter products).

Tell your dentist if you develop:

- any skin rash and redness, and swelling or sores in your mouth.
- any allergic reactions, which may include skin swelling and difficulty breathing or a feeling of tightness in your throat. If any of these symptoms occur, you should contact your dentist or medical doctor immediately.
- any other possible side effects you are having or possible side effects below.

How should I take PERIOSTAT?
PERIOSTAT should be taken twice a day, by mouth, at least one hour before your morning or evening meal. PERIOSTAT should be taken with 1/2 cup of water in a sitting or standing position to avoid any irritation to your throat. You should not take more or less than the recommended daily dose of PERIOSTAT. Taking more than the recommended dose may increase the occurrence of side effects. You should continue to take PERIOSTAT until your dentist tells you to stop.

How long should I take PERIOSTAT?
PERIOSTAT has been shown to be effective for up to nine months of continuous use. In addition, PERIOSTAT has been shown to last for up to 12 months. The amount of time that you will take PERIOSTAT will depend on your dentist and depends on the severity of your gum disease and the time needed for your body's healing process to take place. During your checkups, your dentist will determine if you should stop or continue to take PERIOSTAT based on your response to treatment and the level of improvement of your gum disease.

Can I take PERIOSTAT with other medications?
PERIOSTAT and certain other medications may not work properly when taken together. So tell your dentist about medications that you are taking or plan to take while you are taking PERIOSTAT. Your dentist may need to talk to or refer you to your medical doctor.

• There is a possibility that PERIOSTAT may interfere with the effectiveness of oral contraception, resulting in pregnancy.
• If you take antacids or vitamins that contain calcium, aluminum, magnesium, iron, or zinc with PERIOSTAT, the effectiveness of PERIOSTAT may be reduced.
• If you are taking blood thinners such as Coumadin[®], your medical doctor may need to make changes to the dose of your blood thinner.
• PERIOSTAT may make certain antibiotics, including oxacillin, less effective.
• Taking tetracyclines (such as phenoxymethyl penicillin (Pen-Vee) and phenoxymethyl penicillin (Dianthyl)) may reduce the time that PERIOSTAT stays active in your system.
• Taking PERIOSTAT with the general anesthetic Propofol[®] (propofol) may cause serious harm to the kidneys.

What are the possible side effects of PERIOSTAT?

In studies, the side effects reported by individuals taking PERIOSTAT or placebo (sugar pill) were largely similar. Headache, the commonest side effect, was reported by the most commonly reported side effect in individuals receiving PERIOSTAT and PERIOSTAT with a 1/2 glass of water.

The other side effects reported by individuals taking PERIOSTAT or placebo included toothache, periodontal (gum) abscess, tooth abscess, abscess, throat sore, oral pain, diarrhea, oral congestion, coughing, nasal irritation, flat, back pain, headache, menstrual cramps, acid indigestion, pain, infection, gum pain, toothache, and flu-like pain.

The following side effects were not reported in the PERIOSTAT studies but have been reported by individuals taking tetracyclines, including doxycycline:
• Gastrointestinal symptoms, including glossitis (inflamed tongue), dysphagia (difficulty swallowing), and inflamed throat with vaginal yeast infection in the axillary area. Liver toxicity has also been reported. Discoloration or ulceration of the mucous membranes that have been reported with capsule forms of these medications. These side effects can be avoided by taking PERIOSTAT with a 1/2 glass of water.
• Skin-related rash, severe rash with skin peeling (symptoms), photosensitivity (severe sunburn).
• Other: increased blood urea nitrogen (BUN) – an indicator of kidney function; hypersensitivity (allergic) reactions that can be life threatening; exacerbation of systemic lupus erythematosus (in people with this disease); anemia, and blood-related abnormalities.

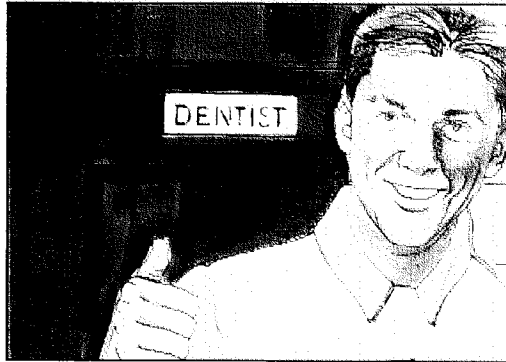
If you develop any of the side effects listed above or have a medical problem that you think may be related to PERIOSTAT talk to your dentist or medical doctor.

What else should I know about PERIOSTAT?
This provides a summary of certain information about PERIOSTAT. If you have any questions or concerns about PERIOSTAT, you should talk to your dentist. The pharmacist can give you an additional leaflet that is written for health professionals.
• Keep PERIOSTAT out of the reach of children.

Active ingredients include: two pain killers, naproxen sodium, and microcrystalline cellulose.



PROFESSIONAL TYPE MAN
IN MID 40's LEAVING
DENTIST'S OFFICE, TALKS
TO CAMERA



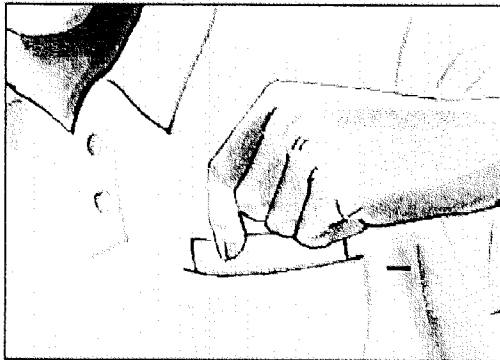
MAN TALKING TO CAMERA:
I've just seen my dentist and I
have good news.

DISSOLVE TO CU OF MAN



....my dentist prescribed

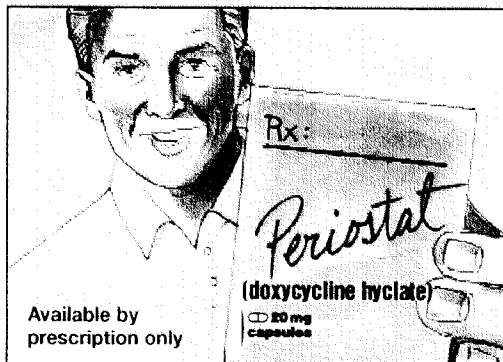
CUT TO MAN'S HAND
TAKING PRESCRIPTION
OUT



MAN'S (VO): this...

PULL BACK TO SHOW MAN
HOLDING PRESCRIPTION

SUPER: AVAILABLE BY
PRESCRIPTION ONLY



It's called Periostat.

DISSOLVE TO MAN NOW
FURTHER DOWN THE
ROAD

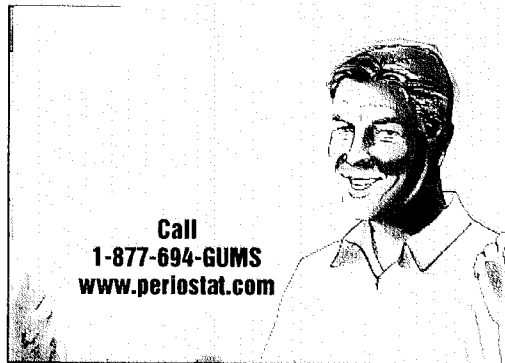
SUPER:
Call 1-877-694-GUMS
www.periostat.com



...it was news to me

MOVE IN ON MAN AS HE
CONTINUES WALKING

SUPER:
Call 1-877-694-GUMS
www.periostat.com



....but my dentist thinks that
adding Periostat is right for me.

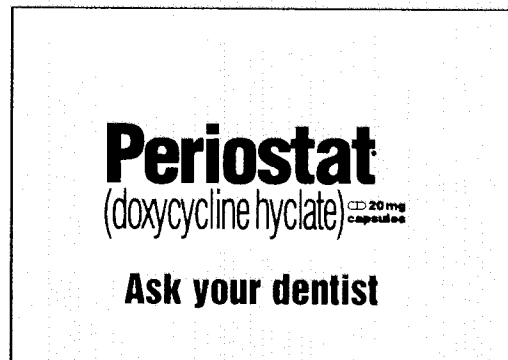
DISSOLVE TO CU OF MAN



Ask your dentist if Periostat is
right for you.

CUT TO LOGO

SUPER: Ask your dentist

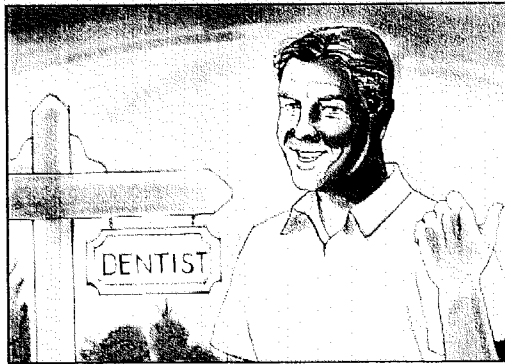


CLIENT/PRODUCT
10/3/00
DATE

TITLE
60
LENGTH

JOB NO.
1
PAGE

PROFESSIONAL TYPE MAN
IN MID 40's LEAVING
DENTIST'S OFFICE, TALKS
TO CAMERA



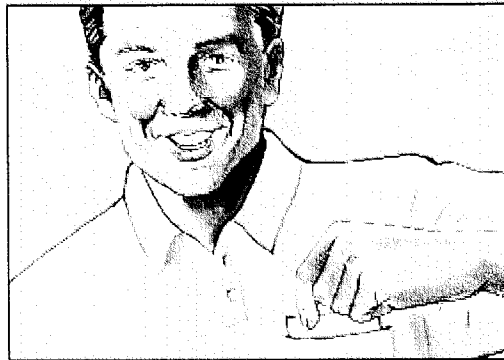
MAN TO CAMERA SMILING:
I'm one of millions of
Americans with
periodontitis...you know,
gum disease with
tooth pockets...4mm deep
or more. But guess what!

CU OF SAME MAN TALKING



I'm encouraged!
I've just started deep cleaning
treatments with my dentist...
scaling and root planing,

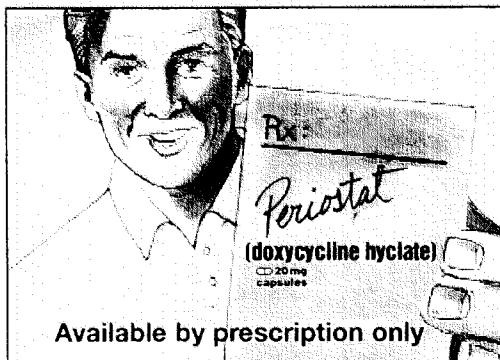
HE TAKES A DOCTOR'S
PRESCRIPTION OUT OF HIS
POCKET



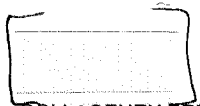
and my dentist prescribed
Periostat.

AND SHOWS IT TO CAMERA

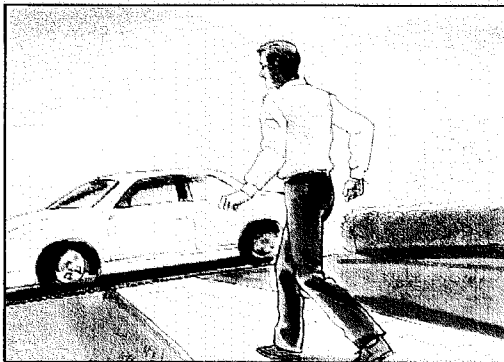
SUPER: Available by
prescription only



Periostat is an
FDA approved prescription
pill to help keep my
gum disease



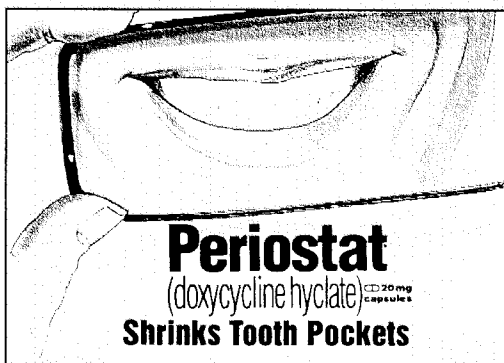
HE GOES TO HIS CAR,



from getting worse.

SMILING, CHECKING OUT HIS TEETH AND GUMS IN THE REARVIEW MIRROR.

SUPER: Periostat (doxycycline hyclate) 20mg capsules
Shrinks Tooth Pockets



AVO:
Periostat is proven to help shrink tooth pockets and improve tooth attachment.

MATCH CUT TO MAN



MAN: My dentist tells me that

MAN TAKES RX CONTAINER



Periostat, along with professional treatments, and

MAN AT BATHROOM
MIRROR PREPARING TO
TAKE PILL.
NOT PICTURED:
CU OF PILL IN HAND



regular brushing
and flossing can

MAN TALKING TO CAMERA

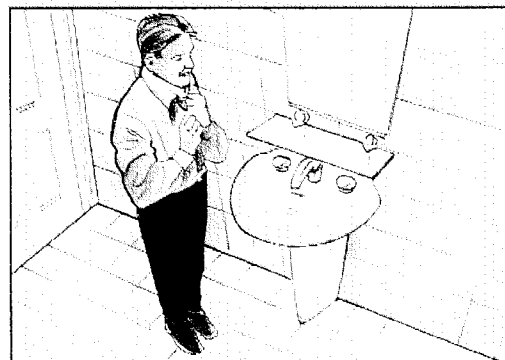


help me keep my teeth.



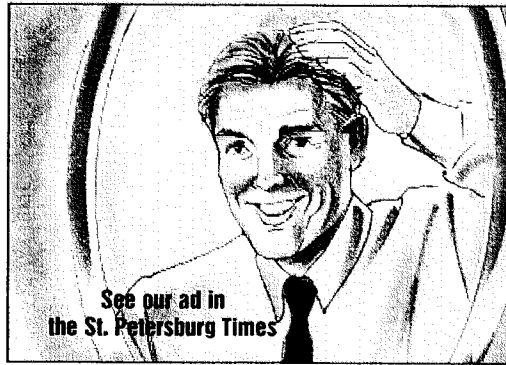
MAN:
Hey, that works for me.

MAN FINISHES HIS
TOILETTE, LOOKS AT HIS
HANDSOME SELF IN
MIRROR AND PLACES
OTHER ORAL HYGIENE
ITEMS ON SHELF.



AVO: In clinical trials, adverse
reactions to Periostat were
similar to taking a placebo.
Don't take Periostat if you are
pregnant, nursing

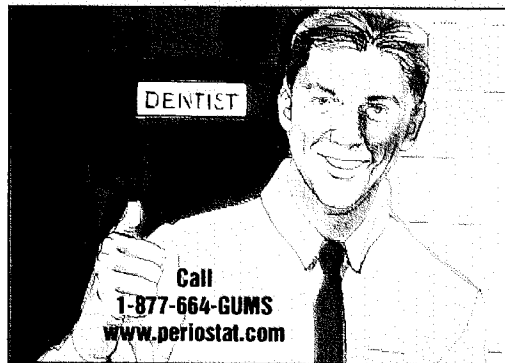
HE PASSES WALL MIRROR
ON HIS WAY OUT AND
SMOOTHES HIS HAIR



or if you're hypersensitive
to tetracyclines.

SUPER: See our ad in
the St. Petersburg Times

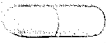
DISSOLVE TO THE SAME
MAN IN FRONT OF
DENTIST'S DOOR AT A
LATER DATE



MAN: Don't just take my
word for it. Ask your dentist
about Periostat

SUPER:
Call 1-877-664-GUMS
www.periostat.com

Periostat
(doxycycline hyclate) 20 mg capsules



**It can help you
keep your teeth**

AVO: Periostat. The first
prescription pill that can help
you keep your teeth.

