



**TRANSMITTED BY FACSIMILE**

Marcus Herzig  
Executive Director, Regulatory Affairs and Quality Assurance  
OraPharma, Inc.  
732 Louis Drive  
Warminster, PA 18974

RE: **NDA 50-781**  
minocycline hydrochloride microspheres  
MACMIS # 9717

Dear Mr. Herzig:

This letter notifies OraPharma, Inc. (OraPharma) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional material and activities for minocycline hydrochloride microspheres, an unapproved new drug, that are in violation of the Federal Food, Drug, and Cosmetic Act (act) and its implementing regulations. The material in question was distributed at OraPharma's promotional exhibit at the Yankee Dental Convention meeting in Boston, Massachusetts, January 27-30, 2001. We also have information that these materials were distributed to dentist's offices. Our specific objections follow:

**Promotion of an Unapproved New Drug**

Sponsors may not represent in a promotional context that an investigational new drug is safe or effective for the uses that are under investigation (see 21 CFR 312.7(a)). Your promotional material titled, "What you think about LAAs is about to change," however, includes several claims and representations concerning the safety and efficacy of minocycline hydrochloride microspheres, an investigational new drug. For example, you state that "OraPharma will be soon introducing a revolutionary drug delivery system for a potent anti-infective against periodontal pathogens, minocycline."

You further claim that the product has an "ideal delivery system" that gives 14 days of therapeutic drug concentrations, it is safe, easily administered, efficient, and that the microspheres bioresorb so there is nothing to remove.

Further, your representatives detailed visitors at your promotional exhibit booth that minocycline hydrochloride microspheres has similar therapeutic outcomes as Atridox (doxycycline hyclate, 10%) and Periochip (chlorhexadine gluconate, 2.5 mg). Your representatives also claimed that minocycline hydrochloride microspheres is priced comparably to Atridox, and the product has no limit on the number of sites that can be treated. We are concerned that you have made numerous and extensive claims about your unapproved new drug.

**Requested Action**

You should immediately discontinue the use of the above promotional material, and any other promotional materials that promote the unapproved drug as safe or effective. You should respond to me regarding this violation by letter no later than February 27, 2001. In your response, you should state how OraPharma has addressed this violation.

If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-40; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds OraPharma that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 9717 and NDA 50-781.

Sincerely,

*{See appended electronic signature page}*

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

/s/

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Warren Rumble  
2/13/01 12:23:51 PM

# What you think about LAAs is about to change

## The problem with current, locally administered anti-infectives (LAAs)

The introduction of LAAs into the dental market was greeted with much enthusiasm. LAAs utilized well-known and effective anti-infective agents to treat periodontal disease in a locally administered form.

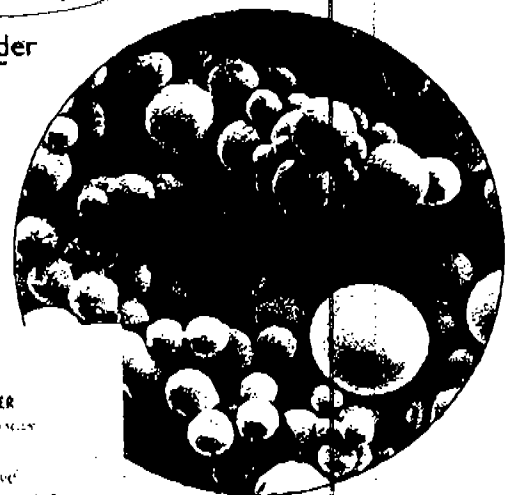
Although these LAA advances made significant improvements in oral health care their administration is often cumbersome and uncomfortable. This problem greatly limits their widespread acceptance and overall efficacy.

The next generation of LAAs is currently being developed by OraPharma. Soon you will be able to have consistent drug delivery in a product that is also easy to administer (without the mixing, refrigeration, and technique-sensitive administration often associated with current LAA treatments). Your patients will appreciate its effectiveness and simplicity, and we are confident that you will too.

## Introducing microspheres

OraPharma will soon be introducing a revolutionary drug delivery system for a potent anti-infective against periodontal pathogens, minocycline.

The delivery system, known as microspheres, is a powder that immediately begins to adhere in periodontal pockets. Microspheres then slowly release the anti-infective to maintain drug concentrations in crevicular fluid well above the minimal inhibitory concentration (MIC) for at least 14 days.



  
ORAPHARMA, INC.

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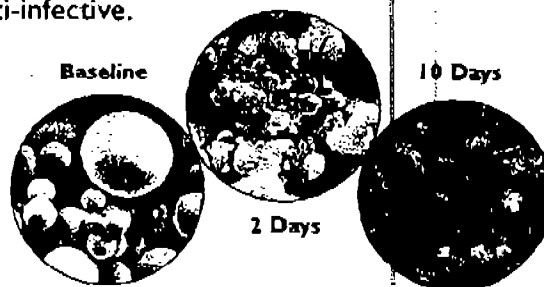
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## The technology behind microsphere delivery

The microspheres that comprise the OraPharma delivery system consist of an anti-infective encapsulated in a bioresorbable polymer.

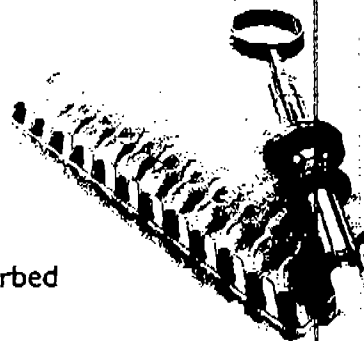
As soon as the microspheres are deposited in periodontal pockets, body fluids hydrolyze the polymer causing water-filled channels to form inside the microspheres. These holes provide "escape routes" for the encapsulated anti-infective.

The active drug dissolves and diffuses out of the microspheres through the channels into the surrounding tissues. Eventually, the microspheres themselves are fragmented through polymer hydrolysis and are completely bioresorbed.



## Microspheres, the ideal delivery system for LAAs, give you...

- Maintenance of therapeutic drug concentrations for at least 14 days
- The safety of localized delivery provides drug concentration at site of infection
- Easy setup—no mixing, no refrigeration
- Easy, local administration—adheres on contact with moisture; no slippage, no dressing or dental adhesives required
- Nothing to remove—microspheres are completely bioresorbed
- More efficient use of chair time



For more information go to [www.orapharma.com](http://www.orapharma.com).

ORAPHARMA, INC.