DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Cary Rayment, President and Chief Executive Officer
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134-2099

Re: NDA 20-805
CIPRO® HC OTIC (ciprofloxacin hydrochloride and hydrocortisone otic suspension)
MACMIS # 13122

WARNING LETTER

Dear Mr. Rayment:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the Alcon website (URL: http://www.alconlabs.com/us/aj/products/RxTher/CiproHC_ProdPRO.jhtml) for CIPRO® HC OTIC (ciprofloxacin hydrochloride and hydrocortisone otic suspension) through routine monitoring and surveillance. The website is misleading because it makes unsubstantiated superiority claims, fails to reveal important risk information associated with the use of CIPRO® HC OTIC, and overstates the efficacy of the drug. Therefore, the website misbrands CIPRO® HC OTIC within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(a) & (n), 321(n), and FDA implementing regulations. See 21 CFR 202.1(e)(5)(i).

DDMAC has previously objected, in an untitled letter dated July 18, 2003, to your dissemination of CIPRO® HC OTIC promotional material that made unsubstantiated superiority claims, omitted important risk information, and overstated the efficacy of the drug. We are concerned that you are continuing to promote CIPRO® HC OTIC in a violative manner.

Background

The Indications and Usage section of the approved product labeling (PI) for CIPRO® HC OTIC states:

> **"CIPRO® HC OTIC is indicated for the treatment of acute otitis externa in adult and pediatric patients, one year and older, due to susceptible strains of *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Proteus mirabilis*."**

CIPRO® HC OTIC is associated with several important contraindications, warnings, and precautions. For example, the PI for CIPRO® HC OTIC contains the following important risk information:

CONTRAINDICATIONS

CIPRO® HC OTIC is contraindicated in persons with a history of hypersensitivity to hydrocortisone, ciprofloxacin or any member of the quinolone class of antimicrobial agents. This nonsterile product should not be used if the tympanic membrane is perforated. Use of this product is contraindicated in viral infections of the external canal including varicella and herpes simplex infections.

WARNINGS

NOT FOR OPHTHALMIC USE. NOT FOR INJECTION.
CIPRO® HC OTIC should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first does, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment.

PRECAUTIONS

GENERAL: If the infection is not improved after one week of therapy, cultures should be obtained to guide further treatment.

Unsubstantiated Superiority Claims -- Efficacy

Your website implies that CIPRO® HC OTIC provides faster relief of the pain associated with acute otitis externa than other available treatment options. For example, the following claims appear on the first page of your website:

- "What a difference a day makes."
- "YOU DON'T WANT 19 EXTRA HOURS OF THIS. OR OF OTITIS EXTERNA."
- "CIPRO® HC OTIC Ends The Pain 19 Hours Sooner"

These claims suggest that use of CIPRO® HC OTIC is superior to other products in the treatment of otitis externa in that it ends the pain 19 hours sooner. Your website does not specify what comparison products require 19 additional hours to "end pain." There is, however, a footnote that contains a reference for a clinical trial conducted by Pistorius et al.[1], the description of which indicates that the trial compared CIPRO® HC OTIC and an investigational otic preparation of ciprofloxacin alone to an otic suspension of polymyxin B-neomycin-hydrocortisone (Cortisporin). The website also contains the following reference at the end of the section entitled "Combination Strength Delivers Results" -- "**Clinical success defined as resolution and improvement in a controlled, nonblinded, multicenter U.S. trial comparing CIPRO® HC OTIC with a polymyxin B-neomycin-hydrocortisone combination [Cortisporin] in patients with acute otitis externa." The description of this reference fails to mention that the trial also compared CIPRO® HC OTIC to an investigational otic preparation of ciprofloxacin alone.

[1] Pistorius B, Westberry K, Drehobl M, et al. Prospective, randomized, comparative trial of ciprofloxacin otic drops, with or without hydrocortisone, vs. polymyxin B-neomycin-hydrocortisone otic suspension in the treatment of acute diffuse otitis externa. *Infect Dis in Clin Pract*. 1999;8:387-395.

The claims, together with the references, suggest that CIPRO® HC OTIC ends ear pain 19 hours sooner than Cortisporin (the referenced polymyxin B-neomycin-hydrocortisone combination) and ciprofloxacin alone. While it is true that CIPRO HC OTIC ends pain 19 hours sooner than ciprofloxacin alone, it does not end pain 19 hours sooner than Cortisporin. In fact, in the trial that is referenced, CIPRO® HC OTIC and Cortisporin were not statistically significantly different in their effect on ear pain. The difference in time to end ear pain in the trial of CIPRO HC OTIC® and Cortisporin was 7 hours. FDA is not aware of substantial evidence or substantial clinical experience to support the 19-hour claim. Therefore, these claims are false or misleading in that they suggest that CIPRO® HC OTIC ends pain 19 hours sooner than Cortisporin. It should be noted that FDA found this trial (Pistorius et al.) to be inadequate to support such claims in a previous untitled letter dated July 18, 2003.

Failure to Reveal Important Risk Information

Your website fails to reveal material facts in light of representations made and with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Specifically, the main part of the website presents numerous effectiveness claims for CIPRO® HC OTIC, such as:

1. "What a difference a day makes."
2. "YOU DON'T WANT 19 EXTRA HOURS OF THIS. OR OF OTITIS EXTERNA."
3. "CIPRO® HC OTIC Ends The Pain 19 Hours Sooner"

Your website fails to present <u>any</u> risk information within the body of the main CIPRO® HC OTIC page on the website. One must navigate to other pages titled "CIPRO HC Otic Comparative Information," "CIPRO HC Otic Prescribing Information," and "Frequently Asked Questions / Contact Us" to obtain risk information. Furthermore, once the viewer reaches the "CIPRO HC Otic Comparative Information" page, the risk information is listed at the end of the page without any headers or other signals to indicate to the reader that it is important risk information. The website therefore misleadingly fails to reveal important risk information necessary for context on the pages containing information about the efficacy of CIPRO® HC OTIC, including the following important Contraindication and Warning information:

> CIPRO® HC OTIC is contraindicated in persons with a history of hypersensitivity to hydrocortisone, ciprofloxacin or any member of the quinolone class of antimicrobial agents. This nonsterile product should not be used if the tympanic membrane is perforated. Use of this product is contraindicated in viral infections of the external canal including varicella and herpes simplex infections.
>
> **NOT FOR OPHTHALMIC USE. NOT FOR INJECTION.**
> CIPRO® HC OTIC should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first does, have been reported in patients receiving systemic quinolones.

> Serious acute hypersensitivity reactions may require immediate emergency treatment.

Furthermore, in the main body of the CIPRO HC Otic page on the website you fail to include important precautions such as "If the infection is not improved after one week of therapy, cultures should be obtained to guide further treatment." The failure to present this important risk information may lead to serious health risks because failure to improve may represent a fungal superinfection or a resistant bacterial infection.

Overstatement of Efficacy

Your website includes the claims "Fewer drops to total pain relief" and "Shorter course to total pain relief." These claims are misleading because they overstate the efficacy of CIPRO® HC OTIC. The phrase "total pain relief" suggests that patients have 100% pain relief when using the product. FDA is not aware of substantial evidence or substantial clinical experience demonstrating 100% pain relief. We note that in the Pistorius et al. study cited on the website, CIPRO® HC OTIC had a clinical response rate at the end of therapy (defined as resolution of infection or improvement) of 90%. Resolution of infection or improvement of 90% is not evidence of "total pain relief." Therefore, the phrase "total pain relief" is misleading because it overstates the efficacy of CIPRO® HC OTIC.

Conclusion and Requested Action

Your website makes unsubstantiated superiority claims, fails to reveal important risk information included in the labeling of CIPRO® HC OTIC, and overstates the efficacy of the drug in violation of 21 U.S.C. §§ 352(a) & (n), 321(n); 21 CFR 202.1(e)(5)(i).

DDMAC requests that Alcon immediately cease the dissemination of violative promotional materials for CIPRO® HC OTIC such as those described above. Please submit a written response to this letter on or before May 11, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for CIPRO® HC OTIC such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42 Room 8B-45, 5600 Fishers Lane, Rockville MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 13122 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for CIPRO® HC OTIC comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Elaine J. Hu
4/27/05 11:18:02 AM
Signed for Thomas W. Abrams