DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FOI

TRANSMITTED VIA FACSIMILE

APR - 2 1999

Carol A. Sever
Associate Director
Bayer Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516-4175

RE: NDA # 19-537
Cipro (ciprofloxacin) Tablets
MACMIS ID # 7451

Dear Ms. Sever:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has received information regarding promotional activity that occurred in Sidney, Ohio. Specifically, a Bayer Corporation (Bayer) hospital representative at the Wilson Memorial Hospital disseminated what appears to be a "home-made" promotional labeling piece. DDMAC has determined that this promotional labeling piece is misleading. As labeling, the dissemination of the "home-made" piece is in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and the applicable regulations.

Specifically, the piece contains numerous unsubstantiated statements that disparage the efficacy of a competitor's product (i.e., levofloxacin)[1], implies superiority for Cipro over levofloxacin without substantial evidence, and lacks fair balance. Additionally, the labeling piece fails to provide full prescribing information, and has not been submitted to FDA pursuant to the post-marketing reporting requirements.

Disparaging Statements

The labeling piece, "Levaquin a true qd drug?" contains statements that imply that Levaquin's once a day dosing regimen may not provide patients with therapeutic doses to treat their indicated conditions. Such statements include, for example, "Thus, there may be a potential for sub-optimal dosing if the drug is prescribed qd when a bid regimen is actually called for;" "Although at this time there are no studies that prove qd dosing of Levaquin is clinically inferior to bid dosing, sub-optimal dosing could theoretically

[1] Levofloxacin (Levaquin) is a product of Ortho-McNeil Pharmaceutical, Inc.

contribute to treatment failure, bacteriologic persistence, and possibly, bacterial selection and resistance;" and "As a result of its ambiguous dosing recommendation, levofloxacin is perceived to have a complicated treatment regimen ..."

However, the Food and Drug Administration (FDA) determined that Levaquin is safe and effective as a once daily dosing regimen, in patients with normal renal function, to treat indicated conditions. This determination was based on adequate and well controlled clinical studies. Thus, the referenced statements that call into question Levaquin's efficacy at the once daily dosing regimen are misleading without substantial evidence for support. A sponsor misbrands its own drug product by making false or misleading representations about another product in its labeling [21 C.F.R. § 201.6(a)].

Implied Superiority Claims

"The information continues.
Cipro is BID everywhere in the world.
Levaquin is BID in U.K., Germany not QD, Japan-TID.
Double their costs, double their CNS
Cipro is still more effective against gram-negatives."

The above statements that are handwritten across the top of the labeling piece are misleading because they imply superiority for Cipro over levofloxacin without substantial evidence for support. In clinical studies used as the basis of approval for levofloxacin's use in treating uncomplicated skin and skin-structure infections, complicated UTI and acute pyelonephritis, levofloxacin was compared to Cipro. In these studies, Cipro demonstrated comparable efficacy, rather than superior efficacy, to levofloxacin. In addition, the side effect profiles, as they relate to CNS effects, were comparable for both drugs. Therefore, statements that suggest that the bacteriologic activity, clinical efficacy, or safety profile of Cipro is superior to that of levofloxacin are misleading in the absence of substantial evidence for support and misbrand Cipro.

Failure to Provide Fair Balance

The labeling piece is lacking in fair balance or otherwise misleading because it fails to present any information relating to side effects and contraindications or other risks associated with the use of Cipro to balance promotional claims about the product. Such promotional claims include, e.g., "Cipro is BID everywhere in the world;" "Cipro is still more effective against gram-negatives; etc." Materials are generally considered to be misleading if they contain promotional claims about a drug but fail to adequately disclose information on risks such as the contraindications and serious or most common side effects of the drug.

Failure to Submit Post-Marketing Reports

DDMAC notes that the referenced labeling piece has not been submitted to FDA pursuant to the post-marketing reporting requirements. All labeling and advertisements used in promotion must be submitted to FDA at the time of its first use under the post-marketing reporting requirement [21 C.F.R. 314.81 (b)(3)(i)].

In order to address these violations, DDMAC recommends that Bayer take the following actions:

1. Immediately discontinue the use of the aforementioned materials and any other promotional materials for Cipro that contain the same or similar presentations;

2. Investigate the activities of Bayer's representatives and submit a written statement describing the extent of dissemination of this or similar pieces; and

3. Provide a written response to DDMAC of your intent to comply with the above requests, and a list of promotional materials containing the misleading presentations that will be discontinued.

Bayer's response should be received no later than 10 business days from the issue date of this letter. If Bayer has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

DDMAC reminds Bayer that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID # 7451 in addition to the NDA number.

Sincerely,

/S/

Jo Ann Spearmon, Pharm.D., M.P.A.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications