DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

OCT 23 1998

Dan Henry, R.Ph.
Manager, U.S. Drug Regulatory Affairs
Marketed Products
Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

RE: NDA 20-905
Arava (leflunomide) tablets
MACMIS ID #7192

Dear Mr. Henry:

Reference is made to Hoechst Marion Roussel, Inc.'s (HMR) September 16, 1998 submission of promotional materials for Arava (leflunomide) on Form FDA 2253. The Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed this submission and finds the following materials in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations:

- New Release (ID# 98190106/2934P8)
- Media Alert (ID# 98190105/2933P8)
- Dear Editor/Producer Letter (ID# 98190101/2930P8)
- Video with Script (ID# 98181101/2887P8)

DDMAC objects to these materials for the following reasons.

Fair Balance - Pregnancy/Risk to Fetus

The materials are misleading because they lack fair balance and/or minimize the importance of serious risk information included in the approved product labeling (PI) for Arava concerning pregnancy and the potential risks to the fetus. Specifically, the PI for this product includes a prominent boxed contraindication and warning stating that pregnancy must be excluded before the start of treatment with Arava. Arava is also contraindicated in pregnant women and women of childbearing potential who are not using reliable contraception. Before starting treatment with Arava, patients must be fully counseled on the potential for serious risk to the fetus. Pregnancy must be avoided during Arava treatment or prior to the completion of a

specific drug elimination procedure after Arava treatment. It is recommended that all women of childbearing potential undergo this elimination procedure upon discontinuing Arava. These warnings and contraindications are due to the fact that Arava may increase the risk of fetal death or teratogenic effects when administered to a pregnant woman. If this drug is 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. In addition, men wishing to father a child should consider discontinuing use of Arava and taking cholestyramine 8 grams 3 times daily for 11 days to minimize any possible risk to the fetus. The disclosure of this information should be preceded by a signal that both emphasizes the importance of this information and provides adequate prominence for disclosure of these risks and related material facts.

Fair Balance - Hepatotoxicity

The materials are misleading because they lack fair balance and/or minimize the importance of serious risk information included in PI for Arava regarding hepatotoxicity. The WARNINGS section of the PI indicates that Arava was associated with elevations of liver enzymes, primarily ALT and AST, in a significant number of patients enrolled in clinical trials. Although these effects were generally reversible with dose reduction or discontinuation of treatment, marked elevations (greater than three times the upper limit of normal) occurred as well. Therefore, at minimum, ALT measurements should be performed at baseline and monitored initially at monthly intervals, then, if stable, at intervals determined by the individual clinical situation. In addition, Arava should not be used in patients with significant hepatic impairment or positive hepatitis B or C serologies, given the risk of increased hepatotoxicity.

Superiority Claim

"The treatments we have now are good but many patients either have an incomplete response or don't have a response and need a choice such as Arava."

This claim is misleading because it suggests that Arava is more effective than current treatment options for rheumatoid arthritis (RA) when such has not been demonstrated by substantial supporting evidence. The PI for Arava states that Arava was statistically significantly superior to placebo in reducing the signs and symptoms of RA and reducing the progression of the disease. However, the PI also states that no consistent differences were demonstrated between Arava and methotrexate or between Arava and sulfasalazine in these efficacy parameters.

In order to address these objections, DDMAC recommends that HMR take the following corrective actions:

1. Immediately discontinue the use of this, and all other promotional materials for this product that contain the same or similar violations.

2. Provide to DDMAC, in writing, HMR's intent to comply with #1 above. Your response should be received by November 6, 1998.

3. This response should include a list of all similarly violative promotional materials and HMR's method for discontinuing their use.

If HMR 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 HMR that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #7192 in addition to the NDA number.

Sincerely,

Mark W. Askine, R.Ph.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications