DEPARTMENT OF HEALTH & HUMAN SERVICES

FOI

Food and Drug Administration
Rockville MD 20857

**TRANSMITTED VIA FACSIMILE**

MAY 21 1999

Douglas N. Dobak
Quality Liaison Leader
Astra Pharmaceuticals
725 Chesterbrook Blvd.
Wayne, PA 19087-1000

**RE: NDA # 20-916**
**Prilosec (omeprazole) plus Biaxin (clarithromycin) and amoxicillin**
**MACMIS ID # 7342**

Dear Mr. Dobak:

The Division of Drug Marketing, Advertising, and Communications (DDMAC), as part of its routine monitoring and surveillance program, has reviewed materials that are used to promote Astra Pharmacetuicals' (Astra) product, Prilosec plus Biaxin and amoxicillin (triple therapy with Prilosec). This material included a patient information pak box 158274, a patient information pak 158174, a file card 158032, and a dosing magnet 158174, submitted under cover of Form FDA 2253. DDMAC finds the dissemination of the referenced promotional materials to be in violation of the Federal, Food, Drug, and Cosmetic Act (the Act) and its implementing regulations.

Specifically, DDMAC objects to the following:

**Failure to Provide Fair Balance**

Patient Information Pak box 158274 (Pak box) is lacking in fair balance or otherwise misleading because it fails to include an adequate presentation of the important risks associated with the use of tripe therapy with Prilosec. Although Astra presents the most frequently reported adverse events, it fails to present important information regarding the contraindications associated with the use of this therapy. Specifically, the pak box fails to include the information that Biaxin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, or any of the macrolide antibiotics; that Biaxin is contraindicated in patients receiving cisapride, or pimozide who have pre-existing cardiac abnormalities or electrolyte disturbances; that Biaxin should not be used in pregnant women except in circumstances where no alternative therapy is

appropriate; and that amoxicillin is contraindicated in patients with a history of allergic reaction to any of the penicillins. This is important information that addresses the limitations of this drug in certain patient populations.

Further, Astra's presentation of the most common adverse effects is not given prominence reasonably comparable to that of promotional claims about the therapy. Specifically, the risk information regarding the most frequently occurring adverse effects is stated as text, in very small size font at the bottom of the pak box, that minimizes the emphasis given to this information. In contrast, promotional statements, e.g., "Relief beyond belief for more acid suffers," and "10-day Triple Therapy with Prilosec (omeprazole) plus Biaxin (clarithromycin) and amoxicillin" are presented in much larger white print on a purple background, that enhances the readability of the statements. Promotional materials must present risk information reasonably comparable with the presentation of information relating to the efficacy of the drug.

Patient Information Pak 158174 is lacking in fair balance or otherwise misleading because it fails to provide adequate information regarding the risks associated with the use of triple therapy with Prilosec. Specifically, the patient information pak contains the most common adverse events and the statement "Tell your doctor or health care professional the names of all the prescription and nonprescription medicines you are taking," under the sub-header "What should I tell my doctor or health care professional." However, the presentation fails to include the names of the specific medications for which the coadministration with one of the drugs of the triple therapy, clarithromycin, is contraindicated. These medications include cisapride and pimozide. Additionally, the patient information pak states that patients should tell their practitioner if they are pregnant, breast-feeding, or are less than 18 years old. However, this presentation fails to adequately disclose the pregnancy warnings for use of triple therapy with Prilosec. Specifically, the presentation fails to state that one of the medications in the triple therapy, clarithromycin, should only be taken where no alternative therapy is appropriate because of its potential hazard to the fetus. This is important information needed by patients to prevent serious problems from occurring.

Additionally, the patient information pak fails to include the information that patients who fail therapy should have susceptibility testing. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. This is important information that addresses the limitation of triple therapy with Prilosec.

**Prominence and Readability**

Flash card 158032 is lacking in fair balance because the risk information is not presented in a manner that is reasonably comparable to the presentation of promotional messages for triple therapy with Prilosec. The flash card depicts promotional claims for triple therapy with Prilosec in large white letters on a purple background. In contrast, Prilosec

plus Biaxin and amoxicillin's risk information regarding patients who fail therapy with clarithromycin and patients in whom Prilosec is contraindicated is presented in a much smaller size font, in black lettering on a white background. This presentation minimizes the importance of the information that addresses the limitation of this triple therapy.

**Efficacy Presentation**

Flash card 158032 is misleading because it selectively presents the more favorable efficacy rates for triple therapy with Prilosec. Specifically, the flash card contains the statements: "Now just 10 days to treat *Helicobacter pylori*-associated duodenal ulcer disease"... "In 3 well-controlled multicenter clinical studies, eradication rates with Prilosec/clarithromycin/amoxicillin ranged from 77% to 90%." However, it fails to mention the lower efficacy rates demonstrated in the intent-to-treat (ITT) population. In the clinical studies used as the basis of approval for triple therapy with Prilosec's indication for *H pylori* eradication to reduce the risk of duodenal ulcer recurrence, clinical response rates included the ITT and the per-protocol population. These rates were 69%, 73%, 83% vs 77%, 78%, 90% for the ITT and per-protocol populations, respectively. Consequently, by omitting the efficacy rates for the ITT population and by only stating the clinical efficacy rates for the per-protocol population, Astra is selectively presenting its efficacy information.

**Misleading Statements**

- **"If you stop taking your medicines too soon and don't eliminate all the *H pylori*, your ulcer is likely to return."**

  The above statement that appears in the patient information pak is misleading because it overstates the effectiveness of triple therapy with Prilosec. Specifically, the statement implies that if patients take all of their medications, the *H pylori* organism will be eliminated and their ulcer will not return. In the clinical studies used as the basis of approval, the duodenal ulcer recurrence rates for patients in whom the *H pylori* organism was eradicated ranged from 5% to 35%. These recurrence rates indicate that patients in whom the *H pylori* organism has been eradicated may still experience a recurrence of their duodenal ulcer.

- **"How do I take my Triple Therapy with Prilosec (omeprazole)?"**

  The above header and accompanying presentation that states the directions for taking triple therapy with Prilosec are misleading because the dosing information presented is incomplete. The presentation states the dosing regimen for the referenced indication, but fails to include the information that Prilosec capsules should be taken before eating, and should not be opened, chewed or crushed, and should be swallowed whole.

Additionally, dosing magnet 158174 states the dosing regimen of triple therapy with Prilosec. However, the magnet also fails to include the information that, "Prilosec should be taken before eating, and that Prilosec capsules should not be opened, chewed or crushed, but swallowed whole. This is important information regarding the appropriate use of triple therapy with Prilosec.

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

1. Immediately discontinue the use of the aforementioned materials and any other promotional materials for triple therapy with Prilosec that contain the same or similar violations; and

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

Astra's response should be received no later than 10 business days from the issue date of this letter. If Astra 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 Astra that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID # 7342 in addition to the NDA number.

Sincerely,

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