DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FOI

JUN - 8 1998

TRANSMITTED BY FACSIMILE

Ms. Diane Mitrione
Director, Marketed Products I
Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

Re: **NDA 20-353**
Naprelan (naproxen sodium) Tablets
MACMIS ID #6457

Dear Ms. Mitrione:

This letter is in reference to Wyeth-Ayerst Laboratories' (Wyeth) submissions of promotional materials under cover of Form FDA 2253 for Naprelan (naproxen) Tablets. These submissions contained three promotional brochures (40145-00, 72653-00, and 72765-00), a give away item with accompanying placard (72810-00), and a videotape (45190-00). The Division of Drug Marketing, Advertising, and Communications (DDMAC) regards these promotional materials as false or misleading under the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder.

Misleading Comparisons to Relafen

In its promotional brochure (72765-00), Wyeth states that "Naprelan 1000mg compared favorably with Relafen 1,500 mg." To substantiate this promotional statement, Wyeth cites two references, "data on file" and a journal article by Fleischmann et al.[1] Upon request, Wyeth submitted the article by Fleischmann et al. summarizing a study comparing the efficacy and tolerability of Naprelan, Relafen, and placebo in the treatment of osteoarthritis of the knee. Wyeth also presented the results of the Fleischmann et al. study in its promotional videotape (45190-00).

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1 Fleischmann et al., *A Double-Masked Comparison of Naprelan and Nabumetone in Osteoarthritis of the Knee*, Clinical Therapeutics, 642-655.

However, based upon the Fleischmann et al. data, Wyeth cannot support a claim that Naprelan is equivalent to or superior to Relafen. The Fleischmann data only confirm that Naprelan is superior to placebo in the treatment of osteoarthritis. This was established in the clinical trials for approval. A review of the Fleischmann et al. data shows that these data do not support a claim that Naprelan was comparable to nabumetone in the treatment of osteoarthritis because this was not the result of the study. DDMAC noted that the reference to "data on file" consisted of pharmacological data that could not be used to support a claim of comparability for Naprelan to nabumetone.

In the promotional brochure identified as 72653-00, Wyeth presents the results of one study comparing the efficacy and safety of Naprelan and nabumetone. Based on the results of this study Wyeth claims that Naprelan has "GI tolerability comparable with Relafen (nabumetone)." The results of the study presented are the results from the Fleischmann et al. study discussed above. Wyeth also states that a second study confirms equal efficacy and safety of Naprelan and nabumetone. Wyeth cites "data on file" as the references for these promotional claims. The second study was identified as protocol 95-075 and was submitted by Elan (the manufacturer of Naprelan) to the new drug application for Naprelan. The single study 95-075 is insufficient support to substantiate Wyeth's claim of comparability between Naprelan and nabumetone in the treatment of osteoartritis. Comparative efficacy or safety advertising and promotional lableing must be based on substantial evidence. This generally means data from two adequate and well-controlled clinical trials. The need for substantial evidence applies to claims either of superiority or comparability. Thus, Wyeth's claim that Naprelan is comparable to nabumetone is false or misleading.

Onset of Action

In its promotional materials for Naprelan, Wyeth claims that Naprelan gets "arthritis patients off to a fast start," with a "30 minute onset of acute pain relief." The presentation in the brochures (40145-00 and 72765-00), the placard, and the video (45190-00) imply that the use of Naprelan provides a 30 minute onset of pain relief in arthritic conditions. The presentation of older arthritic patients and combining the claim of fast onset with the claim of 24-hour arthritis pain relief, does not accurately represent that the 30 minute onset of pain relief achieved by the use of Naprelan was in oral surgery and not in arthritic conditions. The approved product labeling for Naprelan states that in clinical trials designed to determine the efficacy of Naprelan in osteoarthritis and rheumatoid arthritis, clinical effectiveness was noted at one week. Therefore, implications that the use of Naprelan has a faster onset than one week in osteoarthritis or rheumatoid arthritis are false or misleading.

In comments contained in a letter dated June 18, 1998, concerning direct-to-consumer promotional materials for Naprelan, DDMAC stated its concerns with claims that Naprelan

works fast and begins to work within 30 minutes suggested that the onset of pain relief begins within 30 minutes. However, such a claim in patients with arthritis has not been supported by clinical trials and claims of a 30 minute onset of pain relief in the treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis would be false or misleading. The current misleading representations do not accurately reflect the onset of action as described in the approved product labeling for the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

Comparative Onset of Action Claims

Wyeth presents data in its promotional brochure (72765-00) and videotape (45190-00) comparing the alleged onset of action for Naprelan to Relafen and to Daypro suggesting that Naprelan has a faster onset of action. These data were not derived from head-to-head clinical trials. Wyeth's comparative presentation of this information from different studies is misleading in that it suggests that Naprelan has a superior onset of pain relief without substantial evidence.

Requested Actions

Wyeth should immediately discontinue the use of all promotional activities that convey or contain the allegedly violative claims or information identified in this letter until these allegations are resolved. Wyeth should submit a written response to DDMAC on or before June 22, 1998, describing the steps that it has taken to ensure that the use of these materials have been suspended and to ensure that such violations will not occur again.

If Wyeth 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 Wyeth that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID #6457 in addition to the NDA number.

Sincerely, /S/

Stephen W. Sherman, JD, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications