DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 13 1999

TRANSMITTED VIA FACSIMILE

Peter F. East
Associate Director
Regulatory Affairs
G.D. Searle & Co.
4901 Searle Parkway
Skokie, Illinois 60077

RE: NDA 20-607
Arthrotec (diclofenac Na/misoprostol) tablets
MACMIS ID # 8376

Dear Mr. East:

This letter is in reference to G.D. Searle & Co.'s (Searle) submission, dated August 6, 1999, of promotional materials under cover of Form FDA 2253 for Arthrotec. This submission included two sales aids, identified as A99AR17504Q and A99AR17503Q. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these promotional materials and has concluded that they are in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Our specific objections follow:

Efficacy Claims

- The sales aid (A99AR17503Q) presents the claims "Arthrotec: The unselfish NSAID therapy," "The only NSAID therapy that gives something back instead of just taking," and "Are you ready for an unselfish NSAID therapy?" DDMAC objects to these claims for the following three reasons:

    - First, Arthrotec is a combination product containing diclofenac (an NSAID) and misoprostol. However, referring to Arthrotec as "NSAID therapy" does not accurately convey that Arthrotec is a combination product with misoprostol as a component. More importantly, the misoprostol component is responsible for specific risks associated solely with Arthrotec, which are not common to the class of NSAIDs as a whole. Therefore, describing Arthrotec as "NSAID therapy" or any implication that Arthrotec is something other than a combination of an NSAID and misoprostol is misleading.

    - Secondly, the statements that Arthrotec is "The unselfish NSAID therapy," and "The only NSAID therapy that gives something back instead of just taking," make

comparative claims to the entire class of traditional NSAIDs. These claims suggest that Arthrotec is safer, or has fewer side effects, than the NSAIDs that are currently available when such has not been demonstrated by substantial evidence. Therefore, DDMAC considers these comparative claims to be false or misleading.

- Lastly, the approved product labeling (PI) for Arthrotec contains a box warning and several serious contraindications, warnings, and precautions. Therefore, the claim that Arthrotec is "unselfish" minimizes the importance of the risks associated with this drug, and is thus, misleading.

- The sales aids (A99AR17504Q and A99AR17503Q) both present the claim "Significantly reduces the risk of ulceration vs. diclofenac alone." This statement suggests that Arthrotec's ability to reduce the risk of ulceration has been demonstrated in a broad range of patients. However, the study offered in support of this claim was limited to or only included patients over the age of 65 with symptomatic osteoarthritis of the knee and/or hip, and a documented history of significant upper GI mucosal damage (i.e. gastric, pyloric channel, or duodenal ulcer, or more than 10 endoscopically confirmed erosions in the stomach or duodenum). Therefore, without prominently disclosing this qualifying contextual information, the above claim is misleading. Furthermore, the data from this clinical study demonstrated that there was a statistically significant difference between Arthrotec and diclofenac only in the incidence rate of endoscopically diagnosed gastric ulcers and not duodenal ulcers. Accordingly, the PI for Arthrotec states, "...patients receiving ARTHROTEC have a lower incidence of endoscopically defined gastric ulcers compared to patients receiving diclofenac." (emphasis added). Therefore, DDMAC considers the claim "Significantly reduces the risk of ulceration vs. diclofenac alone" (emphasis added), to be misleading.

- The sales aid (A99R17504Q) also states, "Misoprostol...Enables Arthrotec to reduce the risk of GI ulceration vs. diclofenac alone." For the same reasons cited in the paragraph above, DDMAC considers this claim to be misleading.

- The sales aid (A99R17504Q) states, "At 6 weeks, the mean improvement in patients' assessment of arthritis pain was 48% for Arthrotec 75 mg BID vs. 43% for diclofenac 75 mg BID (P=NS between active treatments)." This presentation is misleading because it is a selective presentation of Data. Specifically, the PI states that for osteoarthritis, the recommended dosage for maximal GI mucosal protection is 50 mg given three times a day. In addition, the PI states, "For patients who experience intolerance, ARTHROTEC 75 bid or ARTHROTEC 50 bid can be used, but are less effective in preventing ulcers." Therefore, the above claim pertaining to twice daily dosing of Arthrotec is misleading, due to omission of the material fact that Arthrotec, taken as a twice daily regimen, is less effective in preventing ulcers.

Mechanism of Action

- Page 2 of the sales aid (A99AR17503Q) presents the hypothetical mechanisms of action of Arthrotec and the NSAIDs. This page also presents claims concerning the role of prostaglandins in pain relief and the inverse relationship between the risk of ulcer complications and the amount of prostaglandins in the GI tract. This presentation implies that the hypothetical mechanisms of action and claims are accepted as fact. In addition, this presentation implies that Arthrotec is superior to NSAIDs because of these hypotheses. However, the PI for Arthrotec states, "The mechanism of action of diclofenac sodium, like other NSAIDs, is not completely understood...." Therefore, DDMAC considers this presentation to be misleading. DDMAC notes Searle includes a small disclaimer on the bottom of the page that states, "The mechanism of action of NSAIDs is not completely understood." However, this disclaimer is not sufficient to correct the misleading messages presented on this page.

In order to address these violations, Searle should immediately cease distribution of this and other similar promotional materials for Arthrotec that contain the same or similar messages. Searle should submit a written response to DDMAC on or before October 27, 1999, describing its intent to comply with the above.

Searle should direct its response to the undersigned by facsimile at (301) 594-6771, or by written communication 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 Searle that only written communications are considered official.

Sincerely,

/S/

Spencer Salis, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications