Food and Drug Administration
Rockville MD 20857

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TRANSMITTED VIA FACSIMILE

Jerome M. Prahl
Associate Director
Regulatory Affairs
G.D. Searle & Co.
4901 Searle Parkway
Skokie, Illinois 60077

RE: NDA 20-998
Celebrex (celecoxib) capsules
MACMIS ID #8237

Dear Mr. Prahl:

Reference is made to G.D. Searle & Co.'s (Searle) letter, dated September 24, 1999, in response to a letter from the Division of Drug Marketing, Advertising, and Communications (DDMAC), dated, September 10, 1999. DDMAC's letter concerned the alleged dissemination of two "homemade" promotional pieces, entitled "Top 10 Reasons To Choose Celebrex Over the Other Branded COX 2 product," by or on behalf of Searle, that promoted Celebrex (celecoxib) capsules in violation of the Federal Food, Drug and Cosmetic Act (Act) and its regulations. DDMAC requested that Searle investigate the extent to which these "homemade" pieces were used to promote Celebrex, and the number of health care professionals who received these pieces.

In your letter, you described that one sales representative in southern Oregon and one sales representative in eastern Pennsylvania distributed these "homemade" pieces. Your letter also described Searle's policy for prohibiting dissemination of homemade materials by your sales force, and specified the corrective actions taken to ensure that this activity will not continue.

DDMAC has reviewed these promotional pieces and has determined that they are false or misleading because they contain unsubstantiated comparative claims, misrepresentations of Celebrex's safety profile, and are lacking in fair balance.

Unsubstantiated Comparative Claims

Promotional materials are false or misleading if they contain representations or suggestions that a drug's safety or effectiveness is comparable or superior to another drug when such has not been demonstrated by substantial evidence. Some examples of misleading comparative claims in Searle's "homemade" promotional pieces include:

- Searle claims that, "With more than 5 million patients on Celebrex, physicians know what to expect when they prescribe Celebrex – the new standard of care for analgesic and anti-inflammatory therapy in the management of pain for OA and RA." This statement makes a broad superiority claim comparing Celebrex to not only the class of NSAIDs, of which Celebrex is a member, but to all analgesic and anti-inflammatory therapies available for the management of osteoarthritis (OA) and rheumatoid arthritis (RA). However, this global superiority claim has not been demonstrated by substantial evidence. Therefore, this claim is false or misleading.

- Searle also presents several unsubstantiated comparative claims to Vioxx (rofecoxib), including but not limited to, "Why should I use Celebrex over Vioxx? My first response to your question leads me to ask, 'With all the experience that you and thousands of other physicians just like you have with the proven efficacy and benefit of superior safety of Celebrex, why wouldn't you want to prescribe Celebrex?'" (emphasis added). This claim suggests Celebrex has a "superior safety" profile compared to Vioxx, when such has not been demonstrated by substantial evidence. Therefore, DDMAC considers this unsubstantiated comparative claim to be false or misleading.

Misrepresentation of Safety Information

- Searle presents claims that misrepresent the safety profile for Celebrex, including but not limited to,

  > Celebrex has been studied for use in patients taking low dose aspirin. Approximately 440 patients in 4 of the 5 initial endoscopy trails. Patients taking an aspirin a day were excluded from the other product's clinical trials, so there's no information regarding the safety in combination use.

  These statements make an unsubstantiated comparative claim by implying that Celebrex used in combination with low dose aspirin, is safer than Vioxx's use with aspirin when such has not been demonstrated by substantial evidence. In addition, the claim fails to disclose material facts concerning Celebrex's concomitant use with aspirin. Specifically, the approved product labeling states, "...concomitant administration of aspirin with CELEBREX may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX alone." Therefore, failure to disclose this material fact misrepresents the safety profile for Celebrex and is thus misleading. Furthermore, the statement, "Patients taking an aspirin a day were excluded from the other product's clinical trials, so there's no information regarding the safety in combination use," is not accurate.

- Searle claims, "Celebrex can confidently be prescribed for patients taking coumadin / warfarin as long as prothrombin time is monitored, unlike the other COX 2 agent which has a potential for significant drug interactions with warfarin, as stated in their package insert." This claim suggests Celebrex has no potential for significant drug interactions with warfarin. However, this message is in direct contrast to information in the approved product labeling for Celebrex concerning post marketing experience with bleeding events in patients receiving

Celebrex concurrently with warfarin. Moreover, this claim does not convey that, "Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing CELEBREX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications," stated in the approved product labeling. Furthermore, this message is contradictory to the Dear Healthcare Professional letter regarding the concomitant use of Celebrex and warfarin, issued by Searle, during the week of May 24, 1999. Therefore, the claim, "Celebrex can confidently be prescribed for patients taking coumadin / warfarin..." is misleading.

Fair Balance

Overall, Searle's "homemade" promotional pieces are lacking in fair balance with respect to the content and presentation of risk information related to the use of Celebrex. In general, promotional materials must present information about the risks associated with the use of a drug with a prominence and readability reasonably comparable to that of claims for the drug.

- Although these pieces contain numerous claims for the efficacy and safety of Celebrex, Searle has not presented any risk information concerning the contraindications, warnings, precautions, or adverse events associated with Celebrex's use. (emphasis added) Therefore, DDMAC considers these promotional pieces to be lacking in fair balance. In addition, promotional materials must be submitted to the FDA under Form FDA 2253 at the time of initial dissemination. However, our records indicate these promotional materials were not submitted at the time of initial use. This failure to submit promotional materials at the time of initial dissemination is in violation of the Act. Finally, these promotional pieces are in violation of the Act because the approved product labeling for Celebrex did not accompany them.

DDMAC has reviewed your response and actions taken in response to the dissemination of this violative promotional piece. DDMAC does not wish to comment on the internal processes of Searle, however we do acknowledge Searle's investigation and the corrective actions taken to prevent reoccurrence of this type of violative promotional activity. At this time, DDMAC has no further questions and considers this matter closed.

If you have any further questions or comments, please contact 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.

In all future correspondence regarding this matter, please refer to the MACMIS # 8237 and NDA 20-998.

Sincerely,

/S/

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