DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

February 2, 2001

James McMillen, MD
Central Pennsylvania Clinical Research
3335 Market Street
Camp Hill, PA 12011

RE: NDA 20-998
Celebrex (celecoxib) capsules
MACMIS ID #9684

Dear Dr. McMillen:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC), has become aware of promotional audio conferences presented by you, on behalf of Pharmacia Corporation (Pharmacia)[1], that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. We refer specifically, to five promotional audio conferences held on March 7, 2000, March 23, 2000, May 2, 2000, May 4, 2000, and May 16, 2000, entitled, "COX-2 Technology in Clinical Practice: One Year Later," in which your promotion of Celebrex is false or misleading.

Based on information received from Pharmacia (at the time Searle), it is our understanding that you were retained by Pharmacia to conduct promotional audio conferences on their behalf and you were trained by Pharmacia prior to making these presentations. It is our understanding that you were specifically trained to adhere to content outlined in a Pharmacia approved slide kit, to not discuss unapproved uses, and to adhere to the regulations governing the content of prescription drug promotion. It is also our understanding that, at some point, Pharmacia became aware that you were not adhering to all of their instructions and brought you to their corporate headquarters for retraining on certain issues.

Despite this training, these presentations are false or misleading in that you minimize the potentially serious risk of using Celebrex and Coumadin (warfarin) concomitantly. Your minimization of this risk raises significant public health and safety concerns because it minimizes the risk of significant bleeding. Additionally, these presentations are false or misleading in that you omit important risk information, minimize Celebrex's contraindication in patients who have demonstrated allergic-type reactions to sulfonamides, make unsubstantiated comparative claims, and promote an unapproved new use and dosing regimen for Celebrex. Our specific objections follow.

[1] Pharmacia & Upjohn merged with Monsanto Company (parent company of G.D. Searle & Co.) on April 3, 2000

Minimizing Celebrex / Coumadin Interaction

Statements made by you during promotional audio conferences identified above minimized the risk of Celebrex therapy in patients who are also taking Coumadin. For example, in your March 23, 2000, audio conference you stated that there is no drug interaction between Celebrex and Coumadin. Specifically, you claimed that:

> Yes, Celebrex and Vioxx are different compounds. They have different reactions in the body. They are not interchangeable. Celebrex has shown drug interactions with lithium and Diflucan. Vioxx has not shown any drug interactions with lithium and Diflucan. Vioxx has shown drug interactions with Rifampin, Coumadin, and methotrexate. Celebrex, no drug interactions with those drugs.

Your direct statement that Celebrex does not interact with Coumadin directly contradicts the PI that clearly states, "...in post-marketing experience, bleeding events have been reported, predominately in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin." As previously stated, the PI for Celebrex was purposefully changed in response to these post-marketing bleeding events that have resulted from the concomitant use of Celebrex and Coumadin in order to warn of the very interaction that your promotion denied.

Your message that Celebrex does not interact with Coumadin is reinforced in the audio conferences by your selective presentation of Vioxx's (rofecoxib) labeling change regarding its risks in patients taking Coumadin. Your selective presentation of Vioxx's labeling change about its use with Coumadin, and failure to state that Celebrex's PI was also changed for the same reason, further implies that Celebrex and Coumadin can be used safely together with no risks. In addition, your failure to present Celebrex's labeling change suggests Celebrex is safer than Vioxx in patients taking Coumadin when such has not been demonstrated by substantial evidence. This misleading suggestion is further reinforced by your claim during the March 23, 2000, audio conference that, "Celebrex is the non-steroidal of choice if one is needed when a patient is on Coumadin."

We note that earlier in your promotional audio conferences before the discussion of Celebrex's drug interactions, you state, "Now after 16 million prescriptions were out there for Celebrex there has been a very rare increase in prothrombin time and bleed in the elderly. So prothrombin should be monitored...." However, your disclosure that "prothrombin should be monitored" does not adequately convey the extent to which anticoagulation monitoring is required after initiating or changing Celebrex therapy in patients who are taking Coumadin. Additionally, this disclosure does not correct your misleading message that Celebrex and Coumadin have no drug interaction.

Minimizing Contraindication

Your promotional audio conferences minimize Celebrex's contraindication in patients who have demonstrated allergic-type reactions to sulfonamides. For example, you state that, "...many other drugs such as Diuril, Hydrodiuril, Hyzaar, Vasoretic are contraindicated in those allergic to sulfonamides," and "...if you have used these drugs without worrying about a sulfonamide

reaction, then Celebrex can be no different." Your suggestion that Celebrex can be safely used in patients who are allergic to sulfonamides if they have not had allergic reactions to other drugs that are contraindicated in those allergic to sulfonamides is inconsistent with Celebrex's labeled contraindication that states, "CELEBREX should not be given to patients who have demonstrated allergic-type reactions to sulfonamides." Therefore, your promotional audio conferences are misleading because they undermine the risks of Celebrex therapy in patients who have demonstrated allergic-type reactions to sulfonamides and are inconsistent with the PI for Celebrex.

Omission of Important Risk Information

Your promotional audio conferences fail to present other serious and important risks associated with Celebrex therapy. For example, your promotional audio conferences fail to present Celebrex's contraindication in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. You also fail to present the gastrointestinal (GI) warning for Celebrex about the possibility of serious GI toxicity such as bleeding, ulceration, or perforation. Moreover, you fail to present Celebrex's precautions in patients who have liver and kidney disease, patient populations in which Celebrex's use is not recommended such as late pregnancy, as well as Celebrex's most common adverse events.

Unsubstantiated Comparative Claims

You make several unsubstantiated comparative claims throughout your presentations. For example, you claim that Celebrex is safer, or has fewer side effects, than all available NSAIDs when used in patients that are on Coumadin. Specifically, in your March 23, 2000 audio conference, you claim that, "...Celebrex is the non-steroidal of choice if one is needed when a patient is on Coumadin." However, Celebrex has not been studied in head-to-head trials prospectively designed to assess its safety compared to other NSAIDs in patients who are taking Coumadin. Therefore, your superiority claim that Celebrex is " the non-steroidal of choice" when compared to the entire class of NSAIDs is misleading because such has not been demonstrated by substantial evidence.

In your audio conferences, you claim that, "...going from a dose of 100 mg of Celebrex a day to an increase of 8 times that dose to 800 mg a day, there was no increase in endoscopic ulcers, no increase in edema, no increase in blood pressure. This information becomes extremely important to all of us if you compare this to the Vioxx research data." Your suggestion that Celebrex is safer, or has fewer side effects than Vioxx is false or misleading because such conclusions have not been demonstrated by substantial evidence. Celebrex has not been compared to Vioxx in trials prospectively designed to assess these endpoints.

Another example of your unsubstantiated comparative claims, is your claim that, "...in rheumatoid arthritic patients taking Celebrex at 200 mg twice a day, this was more efficacious than 1000 mg of Naprosyn in rheumatoid arthritics." The study that you cited to support this superiority claim actually concludes that Celebrex produced improvement in the signs and symptoms of RA comparable to the improvements produced by Naprosyn. Therefore, your claim of Celebrex's superior efficacy to Naprosyn is false or misleading.

Promotion of Unapproved New Use and Dosing Regimen

Your audio conferences are misleading because they suggest that Celebrex is safe and effective in the treatment of acute pain. For example, you discuss a 400 patient, 5 day post-orthopedic surgical pain study comparing Celebrex to hydrocodone plus acetaminophen. You state that the results of the surgical pain study were that, "...over the first eight hours 200 mg of Celebrex had a similar onset of action and efficacy to 10 mg of hydrocodone plus 1000 mg of acetaminophen single dose. Now over the next five days, the Celebrex was as effective as the narcotic with less drop-offs for lack of efficacy and less drop-offs for adverse events." Celebrex was not approved for an acute pain indication after review of six studies that were submitted to the Agency prior to Celebrex's approval. Therefore, your audio conferences promote an unapproved new use for Celebrex.

You also promote an unapproved dosing regimen for Celebrex. For example, you state, " In this [RA] study the dose of Celebrex could go up to 800 mg a day and this accomplished with no increase in adverse events. Yes, this was one of our hopes for COX-2 technology that you could double the dose a few times without increasing toxicity." The approved dosing regimen for Celebrex for RA however, is 100 to 200 mg twice daily. Therefore, your suggestion that Celebrex can be safely dosed at 800 mg per day (double the approved dose) promotes an unapproved dosing regimen and is misleading.

Conclusions and Requested Actions

We are seriously concerned that your promotional activities described above raise significant health and safety concerns because they minimize crucial risk information and promote Celebrex for unapproved new uses. You should immediately discontinue any promotional activities for Celebrex that contain the same or similar claims or presentations described above.

Sincerely,

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Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising and Communications