



**TRANSMITTED VIA FACSIMILE**

February 1, 2001

Fred Hassan  
President and CEO  
Pharmacia Corporation  
100 Route 206 North  
Peapack, New Jersey 07977

**RE: NDA 20-998**  
**Celebrex (celecoxib) capsules**  
MACMIS ID # 8432

## **WARNING LETTER**

Dear Mr. Hassan:

This Warning Letter concerns Pharmacia Corporation's (Pharmacia) promotional activities and materials for the marketing of Celebrex (celecoxib) capsules. Specifically, we refer to promotional audio conferences given on behalf of Pharmacia<sup>1</sup> by James McMillen, MD, and certain materials used to promote Celebrex. As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed your promotional activities and materials and has concluded that they are false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and applicable regulations. See 21 U.S.C. §§ 331(a) and (b), 352(a), (f), and (n).

You have engaged in repeated promotional activities that 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. Your promotional activities that minimize this risk are particularly troublesome because we have previously objected in two untitled letters to your promotional materials for Celebrex that, among other violations, minimized the Celebrex / Coumadin drug interaction. Based upon your assurances that corrective steps had been taken in order to prevent future violative promotional activities of this type, we considered these matters closed. Despite your assurances, however, your violative promotion of Celebrex has continued.

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<sup>1</sup> Pharmacia & Upjohn merged with Monsanto Company (parent company of G.D. Searle & Co.) on April 3, 2000

## **Background**

Since Celebrex's approval on December 31, 1998, post-marketing bleeding events have occurred in patients receiving Celebrex concurrently with warfarin. In fact, these post-marketing bleeding events ultimately led to the June 10, 1999, "Special Supplement—Changes Being Effected" labeling supplement. This supplement included a change in the Precautions Section of the approved product labeling (PI) for Celebrex to inform healthcare professionals about the need to monitor anticoagulant therapy closely when Celebrex and warfarin are used in combination. Specifically, the Precautions section of the PI for Celebrex includes risk information that states:

[a]nticoagulant 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. . . . 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 a result of this important new risk information being added to the PI, we requested that you revise your promotional materials for Celebrex to include this new risk information. Specifically, our letter dated June 24, 1999, requested that promotional materials for Celebrex that include presentations about the use of Celebrex with warfarin, or drug interaction information in general, be revised to include prominent disclosure of the new risk information related to post-marketing bleeding events. We also informed you that your revised materials should alert healthcare providers about the need to monitor anticoagulant activity, particularly in the first few days, after initiating or changing Celebrex therapy in patients receiving warfarin. We requested that these revisions be completed no later than thirty days from the date of our letter.

In your letter dated July 23, 1999, you stated that revisions were made to your promotional materials for Celebrex, including the master sales aid. Furthermore, you stated that future professional journal advertisements for Celebrex would include the new risk information regarding the interaction between Celebrex and warfarin.

### **Promotional Audio Conferences**

We have become aware of five promotional audio conferences presented on behalf of Pharmacia by Dr. James McMillen that are in violation of the Act and its implementing regulations. These audio conferences were held on March 7, 2000, March 23, 2000, May 2, 2000, May 4, 2000, and May 16, 2000.

On May 5, 2000, we sent you a written inquiry concerning your involvement with and influence on the initiation, preparation, development, and publication of audio conferences given by Dr. McMillen. We also asked you to describe the nature of the relationship between you and Dr. McMillen. In your response dated May 19, 2000, you stated:

[o]ur company policy and operational basis is to require that our speakers follow the content of our approved slide kit, to not discuss off-label uses in their

presentations, to adhere to the promotional regulations, and to provide disclosure of the funding of the program. We did have a report that Dr. McMillen was not adhering to all of our instructions, and in fact, brought him in to corporate headquarters in November, 1999, for retraining on these issues. Subsequent to our meeting with Dr. McMillen, we monitored his speeches and were reassured that he understood his obligations and was following our company policy.

Despite your assurances about retraining and monitoring of Dr. McMillen, subsequent programs by him on your behalf are false or misleading. Our specific objections follow.

#### Minimizing Celebrex / Coumadin Interaction

The statements made during promotional audio conferences identified above minimized the risk of Celebrex therapy in patients who are also taking Coumadin (warfarin). 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. Additionally, [ ] and were also deemed insufficient to support Celebrex's effectiveness for the treatment of acute pain. 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.

#### **Violative Celebrex Promotional Labeling Pieces**

We have identified a sales aid (CE18586Q), a four-sided card (CE18528W · YCE18528W), and a wall chart entitled, "Commonly Available Sulfur-Containing Drugs" (YCE18591W) that are false or misleading in violation of the Act for similar reasons as stated above.

Specifically, these materials minimize the importance of Celebrex's contraindication in patients who have demonstrated allergic-type reactions to sulfonamides. For example, they indicate that sulfonamides can generally be grouped into two categories, "antimicrobials" and "others." They further state that the antimicrobial sulfonamides have metabolites that may be more likely to cause primary allergic reactions than the metabolites of the "other" sulfonamide classes, thereby suggesting Celebrex is less likely to cause primary allergic reactions. However, your claims and representations that Celebrex is less likely to cause allergic reactions than other sulfur-containing compounds is inconsistent with Celebrex's labeled contraindications. Specifically, the PI states,

“Celebrex should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.” Therefore, your promotional materials are false or misleading because they suggest that Celebrex may be used safely in patients who have demonstrated allergic-type reactions to sulfonamides when, in fact, such is not the case.

## **Conclusions and Requested Actions**

Your promotional activities described above raise significant health and safety concerns in that they minimize crucial risk information and promote Celebrex for unapproved new uses. In two previous untitled letters dated October 6, 1999, and April 6, 2000, we objected to your dissemination of promotional materials for Celebrex that misrepresented Celebrex’s safety profile by minimizing the updated Celebrex / warfarin risk information and other risks, contained unsubstantiated comparative claims, and lacked fair balance. Based upon your written assurances that this violative promotion of Celebrex had been stopped, we considered these matters closed. Despite our prior written notification, and notwithstanding your assurances, Pharmacia has continued to engage in false or misleading promotion of Celebrex.

It is our understanding that you have decided to terminate this audio conference series with Dr. McMillen. Due to the seriousness of your violations and the fact that this behavior has continued despite your written assurances to the contrary, we request that you provide a detailed response to the issues raised in this Warning Letter on or before February 15, 2001. This response should contain an action plan that includes a comprehensive plan to disseminate corrective messages about the issues discussed in this letter to the audiences that received these misleading messages. This corrective action plan should also include:

1. Immediately ceasing the dissemination of all promotional activities and materials for Celebrex that contain violations like those outlined in this letter.
2. Issuing a “Dear Healthcare provider” letter to correct false or misleading impressions and information. This proposed letter should be submitted to us for review. After agreement is reached on the content and audience, the letter should be disseminated by direct mail to all healthcare providers who were, or may have been exposed to the violative promotion.
3. A written statement of your intent to comply with “1” and “2” above.

Your written response should be received no later than February 15, 2001. If you have any questions or comments, please contact the undersigned, Spencer Salis, Pharm. D., or Mark Askine R.Ph., by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #8432 in addition to the NDA number.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Celebrex, and may

determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

**/S/**

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