DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Robert B. Clark
Vice-President, US Regulatory Affairs
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

RE: NDA # 20-998, 21-341
Celebrex® (celecoxib) Tablets
Bextra® (valdecoxib) Tablets
MACMIS # 12560

Dear Mr. Clark:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed:

1) a 15-second direct-to-consumer (DTC) television advertisement for Celebrex® (celecoxib) Tablets entitled "With Celebrex, Guitar" (ID# CL151775A) (guitar TV ad);
2) a 30-second television DTC advertisement entitled "Celebrex Presents, Arthritis Tips" (arthritis tips TV ad);
3) a print advertisement directed to healthcare providers for Celebrex entitled "Strength They Can Stay With" (ID# CL170002B) (Celebrex print ad);
4) a direct mail patient brochure for Bextra® (valdecoxib) (VA142934A) (Bextra direct mail brochure); and
5) a 27-minute long format DTC television advertisement entitled "On The Road to Joint Pain Relief" (ID# VA167865A) (infomercial).

All of these promotional pieces were identified by DDMAC through routine monitoring and surveillance, and the guitar TV ad, Celebrex print ad, Bextra direct mail brochure, and infomercial were submitted by Pfizer Inc. (Pfizer) under cover of Form FDA 2253. These five promotional pieces variously: omit material facts, including the indication and risk information; fail to make adequate provision for the dissemination of the FDA-approved product labeling; and make misleading safety, unsubstantiated superiority, and unsubstantiated effectiveness claims. They are, therefore, in violation of the Federal Food, Drug, and Cosmetic Act (Act) and FDA implementing regulations. See 21 U.S.C. 321(n), 352(a) & (n); 21 CFR 202.1(e). Additionally, Pfizer failed to submit the arthritis tips TV ad accompanied by a completed transmittal Form FDA 2253 as required by 21 CFR 314.81(b)(3)(i).

The omission or minimization of risk information in these promotional materials is a public health concern because Celebrex and Bextra are contraindicated for several patient populations, both products contain warnings of serious gastrointestinal (GI) effects and anaphylactoid reactions and Bextra contains an additional warning regarding serious, possibly life-threatening skin reactions.

Background

According to the drugs' FDA-approved labeling (PI), Celebrex and Bextra are COX-2 non-steroidal inflammatory drugs (NSAIDs) that are indicated for relief of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA) in adults, and for the treatment of primary dysmenorrhea. Celebrex is also indicated for the management of acute pain in adults.

Celebrex and Bextra are associated with a number of serious risks, as stated in their respective PIs.

Both products are contraindicated for patients who have demonstrated allergic-type reactions to sulfonamides. Both products are also contraindicated for patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs, because of severe, rarely fatal, anaphylactic-like reactions to NSAIDs. Both products bear specific warnings related to: gastrointestinal (GI) effects, including risks of GI ulceration, bleeding and perforation; hypersensitivity reactions including anaphylactoid reactions and angioedema; use in patients with advanced renal disease, due to lack of controlled clinical studies regarding use of the products in this population; and use in patients with preexisting asthma. There is an additional warning in the Bextra PI labeled "Serious Skin Reactions" that states:

> Serious skin reactions, including exfoliative dermatatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported through post-market surveillance in patients receiving Bextra . . . . As these reactions can be life-threatening, Bextra should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

1. <u>Guitar TV Ad</u>

<u>Violative "Reminder Ad"/Omission of Risk Information</u>

Reminder ads are those which call attention to the name of the drug product, but do not include indications, dosage recommendations, or other written, printed, or graphic matter containing representations or suggestions relating to the advertised drug product. (see 21 CFR 202.1(e)(1)(i))

The Guitar TV ad does not qualify as a "reminder" ad because it makes various representations about Celebrex. The Guitar TV ad in its entirety makes a representation about the indication and benefits of Celebrex for osteoarthritis or rheumatoid arthritis. A woman playing an acoustic guitar is featured. The visuals focus on her hands/fingers and playing ability (i.e., she finger-picks the strings with one hand while executing chord changes with the other hand). These images are accompanied by a voice-over "With Celebrex, I will play the long version." Together, these images and claim suggest that because of using Celebrex, there is a direct benefit to this patient's wrist/hand/finger joints related to movement and flexibility such that she can now play the long version of the song whereas she previously could not.

Therefore, because the Guitar TV ad makes a representation or suggestion about Celebrex, it is a full product ad that is in violation of the Act and implementing regulations. While the Guitar TV ad suggests a direct benefit to this patient's wrist/hand/finger joints related to movement and flexibility, it fails to state the actual approved indication (e.g., relief of signs and symptoms of osteoarthritis). It also fails to include any risk information about Celebrex, thus omitting the major side effects and contraindications (including warnings and precautions) of Celebrex as required by 21 CFR 202.1(e)(1). Omission of this information implies that there are no risks to the patient who takes Celebrex, which overstates the drug's safety.

Failure to Meet Brief Summary Requirement or Make Adequate Provision for PI Dissemination

The Guitar TV ad also fails to present a brief summary of necessary information related to side effects and contraindications or make adequate provision for the dissemination of the approved product labeling in connection with the broadcast ad, as required by 21 CFR 202.1(e)(1). Specifically, the Guitar TV ad fails to offer options for persons who are uncomfortable with directly requesting additional prescription drug product information from their healthcare providers, persons without access to computers and the Internet, persons who are uncomfortable with actively requesting additional product information about a specific prescription drug by telephone, and persons concerned about providing phone numbers or other personal information in connection with their requests. Additional options could include having brochures containing the required information made available in a variety of public places such as libraries, pharmacies and grocery stores, or making a reference in the broadcast ad to concurrent print ads in publications reaching the exposed audience.

2. Arthritis Tips TV Ad

> *Announcer: "Celebrex presents, arthritis tips."*
> Woman dressed as doctor: "Arthritis is the most wide-spread crippling disability in the United States today. Arthritis is the predominant cause of activity limitations and is a major determinate of nursing home institutionalization for the elderly. One out of every 7 people and 1 in every 3 families is affected by arthritis. If you feel any pain or discomfort in your joints, contact your local doc."
> *Announcer: "These arthritis tips have been brought to you by Celebrex."*

The Arthritis Tips TV ad is a product-specific drug ad for Celebrex that is misleading because it omits important information about the drug's safety and effectiveness and makes unsubstantiated effectiveness claims. The ad promotes Celebrex by identifying the drug by name at the beginning and end of the ad. Moreover, stating that Celebrex is presenting/bringing you arthritis tips clearly suggests that Celebrex is an arthritis treatment. The Arthritis Tips TV ad purports to quantify the disease burden of "arthritis" ("the most wide-spread crippling disability in the United States today … the most predominant cause of activity limitations and … a major determinate of nursing home institutionalization for the elderly. One out of every 7 people and 1 in every 3 families is affected by arthritis.") Finally, the Arthritis Tips TV ad directs viewers to contact their local doctor "if you feel any pain or discomfort in your joints" and follows this statement with another reference to Celebrex.

Overstatement of Effectiveness

The Arthritis Tips TV ad is misleading because it overstates the proven effectiveness of Celebrex for the treatment of "arthritis." The Arthritis Tips TV ad discusses the serious progressive effects of arthritis, noting that it commonly can lead to "crippling disability" and "nursing home institutionalization of the elderly." The viewer is then instructed "If you feel any pain or discomfort in your joints, contact your local doc. These arthritis tips have been brought to you by Celebrex." The totality of this presentation therefore suggests that Celebrex is an effective treatment for preventing or modifying the progression of arthritis, such that crippling disability and nursing home institutionalization may be avoided.

Celebrex is indicated only for relief of the signs and symptoms of OA and RA. Celebrex is not indicated for disease modification (i.e., altering the course of the progression of arthritis). Moreover, we are not aware of substantial evidence or substantial clinical experience demonstrating that treatment with Celebrex will prevent crippling effects or disability due to arthritis or prevent nursing home institutionalization of elderly patients with arthritis. Therefore, your Arthritis Tips TV ad greatly overstates the proven benefits of Celebrex.

Omission of Risk Information

The Arthritis Tips TV ad fails to disclose any risk information about Celebrex and thus omits the major side effects and contraindications (including warnings and precautions) of Celebrex as required by 21 CFR 202.1(e)(1). Omission of this information implies that there are no risks to the patient who takes Celebrex, thus overstating its safety.

Failure to Meet Brief Summary Requirement or Make Adequate Provision for PI Dissemination

The Arthritis Tips TV ad also fails to present a brief summary of necessary information related to side effects and contraindications, or make adequate provision for the dissemination of the approved product labeling in connection with the broadcast ad, as required by 21 CFR 202.1(e)(1). Specifically, it fails to offer options for persons who are uncomfortable with directly requesting additional prescription drug product information from their healthcare providers. Additional options could include providing a toll-free number to call and arrange for the information to be sent, providing a website address where the information is available, and providing reference to a concurrent print advertisement containing the information in a publication reaching the exposed audience or having brochures containing the required information made available in a variety of public places such as libraries, pharmacies and grocery stores.

Failure to Submit Under Form FDA 2253

FDA has not received a submission of the "Arthritis tips brought to you by Celebrex" TV ad accompanied by a completed transmittal Form FDA 2253, as required by 21 CFR 314.81(b)(3)(i).

3. Celebrex Print Ad

Unsubstantiated Superiority Claims

The print ad features the prominent headline "Strength They Can Stay With" and shows a chart comparing Celebrex, Ibuprofen and Naproxen, titled "6-Month Patient Persistency Rate." Over the chart is the statement, "In a study of approximately 1 million patients, persistency rates of different OA/RA treatments were assessed at 6 months." The tagline below the Celebrex logo in the print ad is "Proven strength that lasts."

The above referenced claims imply that Celebrex is more effective (i.e., stronger) than ibuprofen and naproxen for treatment of osteoarthritis or rheumatoid arthritis and that patients "stay with" or are more compliant with Celebrex therapy than the compared products. We are not aware of substantial evidence or substantial clinical experience to support these claims. The cited retrospective retail pharmacy database analyses by NDC Health, "Persistency Analysis: Celebrex, Vioxx, and All Other NSAIDs," August 2002 and "Persistency Analysis: Celebrex, Vioxx, Ibuprofen, and Naproxen," from November 2002 (almost 2 years ago), do not contain any data or information demonstrating that patients found Celebrex to be more effective than the other products, or that patients will be more "persistent" or compliant with Celebrex therapy. Moreover, the database information did not note the indication for which the drug was prescribed, so the suggestion that these rates reflect specifically OA/RA patients is misleading. In addition, the analyses do not account for factors that affect persistence or compliance, such as cost, insurance coverage, side effects, dosage regimen, and ease of use. Therefore, the analyses do not constitute substantial evidence or substantial clinical experience demonstrating that OA/RA patients are more compliant with Celebrex or stay on Celebrex longer because it is more effective than other products for the treatment of OA or RA.

4. Bextra Direct Mail Brochure

The patient brochure, "How to Hit Arthritis Joint Pain Hard," features safety claims and presentations that are misleading because they minimize the serious GI risks associated with Bextra therapy. The brochure features a two-page headline "BEXTRA TARGETS A MAJOR SOURCE OF ARTHRITIS JOINT PAIN…WHILE THE STOMACH STAYS PROTECTED." Below the headline is a brief discussion about efficacy and safety. Demonstrating efficacy, a graphic of an untreated inflamed elbow joint from the targeting action of the COX-2 enzyme is presented next to a Bextra-treated elbow where the drug is blocking the COX-2 enzyme, thus showing relief of joint pain, stiffness, and swelling. Demonstrating safety, a graphic of an inflamed stomach from the blocking action of the COX-1 enzyme is presented next to a Bextra-protected stomach with the claim "If the action of the COX-1 is blocked, the body can't make what it needs to protect the stomach lining. When doctors prescribe Bextra, they know that COX-1 will not be targeted. That's how your stomach stays protected." The totality of the graphic and the "stomach stays protected" safety claim are misleading because they suggest that Bextra provides significant protection from serious GI side effects. However, these safety claims are inconsistent with the Warning in the Bextra PI regarding serious and life-threatening GI side effects, including bleeding in the stomach and intestines.

5. TV Infomercial

The 27-minute TV infomercial "On the Road to Joint Pain Relief" ad from Pfizer on arthritis and joint pain relief is a drug ad for Celebrex and Bextra that is misleading because it overstates its proven effectiveness and omits important information about the drugs' safety and effectiveness. The infomercial points to and describes benefits from taking a specific prescription drug therapy from Pfizer, though it does not mention Celebrex or Bextra by name. The infomercial features patient testimonials and statements from healthcare providers that promise complete pain-free relief, freedom of movement, and dramatic effects on "quality of life" in terms of personal activities and work-related activities for arthritis patients, linking these benefits to a specific drug therapy, and solicits patients to seek out that specific medicine. Pfizer's name is featured at the beginning, end, and throughout the infomercial. The infomercial also suggests that this drug is a breakthrough treatment (and the "right" treatment) offering superior effectiveness and safety over other arthritis treatments. The infomercial omits any risk information for Celebrex or Bextra. Therefore, the infomercial overstates the effectiveness of the drugs while minimizing, by complete omission, the risks.

Misleading Product Claim Ad

The infomercial clearly points to Pfizer's arthritis medicine(s) for joint pain. Pfizer's name is featured in sponsorship at the beginning and end of the infomercial ("The following is a paid advertisement for arthritis sufferers brought to you by Pfizer.") as well as throughout the infomercial (e.g., on the van that travels through the country to reach the patients giving testimonials). References are all made to a specific medicine. The patients speak in terms of "this prescription medicine" and tie their extraordinary benefits to taking the specific medicine. The drug is also referred to as a "breakthrough" and "a powerful prescription medicine that's giving people back their lives." After the dramatic testimonials, the announcers tie the benefits to a specific drug and encourage consumers to find out what the specific drug is (e.g., "Get information about the same prescription medicine that brought [the featured firefighter] relief" and "What did they take? Call to get..."). Therefore, the ad clearly promotes a specific arthritis drug from Pfizer. Moreover, a Pfizer van travels across the country to talk to arthritis/joint pain sufferers about the sometimes crippling limitations on their daily activities, quality of life, and ability to work at their jobs caused by their arthritis/joint pain, and the spectacular results of how a prescription drug took away their pain and limited movement and gave them their life back. These patient testimonials are interspersed with comments from healthcare providers, touting the benefits of this medicine. Then the audience is told that if they want to know what specific prescription medicine these people took, they should send away for Pfizer's information packet or visit their "leavepainbehind.com" website (where they can send away for the packet). The packet contains information on Celebrex and Bextra, and also features some of the same testimonials as the infomercial.

The mechanism of action and once-daily dosing of this medicine are also repeatedly discussed, further pointing to a specific medicine. For example, a graphic is shown of how this drug is different because it "targets the chemicals produced that cause pain, enabling smooth pain-free movement." The medicine is described as "a totally different kind of prescription pain reliever" and patients talk about taking one pill, once a day, and getting 24 hour (pain free) relief. Thus, it is clear that the infomercial is discussing a once-daily prescription drug from Pfizer that targets the chemicals producing joint pain

and gives you 24-hour relief from arthritis/joint pain, namely Celebrex and Bextra. Therefore, this infomercial is an advertisement for Celebrex and Bextra.

Overstatement of Effectiveness/Unsubstantiated Effectiveness Claims

The infomercial features statements from healthcare providers and patient testimonials, two highly credible sources of information for consumers that greatly overstate the demonstrated benefits of Celebrex and Bextra. In addition to the name of the website, testimonials promise that patients will "leave pain behind," and the infomercial features testimonials portraying dramatic efficacy results from the medicine regarding being completely pain-free (e.g., "the pain went down to zero," and "You can be free of the pain," and "I take one pill a day and that's all I need. I don't feel the pain anymore") and having complete freedom of movement again. For example, it shows a grandfather, who previously walked with a cane and had limited function, now actively playing with his grandson in a playground and stating (reinforced by superimposed text) that "I threw the cane away." One of the healthcare providers featured no longer uses her wheelchair. These testimonial claims showing complete pain relief and complete return of movement and functionality for all patients on the medicine are not representative of the results from the Celebrex and Bextra clinical trials and make promises of benefits that go well beyond the proven effectiveness of these drugs.

The infomercial also promotes numerous dramatic claims tied to the drug regarding quality of life, in terms of being able to do personal activities and work-related activities. The infomercial shows people returning to their work and activities. These patients go from not being able to work or do anything they want to do, to being able to work and do everything they want to do, pain-free. Patients talk about being able to "do anything," "do as much as I want to do," being "back to doing what I do," and such. They talk about "enjoying life" again, how the drug improved their "quality of life," and how the drug "gave them back their lives" (a theme repeated over and over in the ad and in the background music). One person states that "you can be free." Another states that the medicine "brought new vitality in life." Everyone portrayed has 100% efficacy in all of these outcomes. We are not aware of substantial evidence or substantial clinical experience with Celebrex or Bextra demonstrating such effectiveness in these outcomes measures.

Unsubstantiated Superiority Claims

The infomercial represents the promoted prescription drug as superior to other therapies or as effective when other drugs fail. The medicine is referred to as a "different kind" of medicine and several of the patients refer to the medicine as a "breakthrough." The patients talk about not getting relief with other treatments (e.g., OTCs) and now getting relief with this drug.

We are not aware of any evidence showing that Celebrex or Bextra has superior effectiveness to non-selective NSAIDs. Indeed, none of the comparative studies with naproxen, ibuprofen, and diclofenac to-date has been designed to demonstrate superiority or a specified degree of similarity in a rigorous way. We are also not aware of any adequate and well-controlled studies evaluating whether Celebrex or Bextra is effective in patients who have previously failed non-selective NSAID therapies.

Omission of Risk

As noted above, the infomercial makes numerous effectiveness claims for Celebrex and Bextra, but fails to include any risk information, thus omitting the major side effects and contraindications (including warnings and precautions) of Celebrex and Bextra as required by 21 CFR 202.1(e)(1). Omission of this information implies that there are no risks to patients who take these drugs. This complete omission of risk information is especially concerning in light of the dramatic portrayals of patients who have been completely restored to health by taking these drugs.

Furthermore, the infomercial portrays OTC therapies as posing safety risks, while there is no discussion of any risks for the treatment being promoted. For example, one of the patients states that she took OTC medicines and they "didn't work and had some pretty bad side effects." The infomercial features headings from the information packet such as "Getting Pain Relief Safely" and "OTCs - Know the Risks", giving the clear implication that the OTC arthritis medicines have risks, and do not work well, but that the prescription medicine being discussed is “safe,” does not have risks, and is more effective, which has not been established.

Failure to Provide Brief Summary or Make Adequate Provision for PI Dissemination

The infomercial also fails to present a brief summary of necessary information related to side effects and contraindications or make adequate provision for the dissemination of approved product labeling in connection with the broadcast ad, as required by 21 CFR 202.1(e)(1). Specifically, it fails to offer options to persons without access to computers and the Internet, persons who are uncomfortable with actively requesting additional product information about a specific prescription drug by telephone, and persons concerned about providing phone numbers or other personal information in connection with their requests. Additional options could include encouraging consumers to seek additional prescription drug product information directly from their healthcare provider, and making reference to a concurrent print ad containing the information in publications reaching the exposed audience or having brochures containing the required information made available in a variety of public places such as libraries, pharmacies and grocery stores.

Conclusion and Requested Action

For the reasons discussed above, the TV ads and print ad misbrand Celebrex and Bextra under section 502(n) of the Act, 21 U.S.C. 352 (n), and FDA implementing regulations, 21 CFR 202.1(e). In addition, the arthritis tips TV ad was not submitted to FDA under cover of Form 2253, as required by 21 CFR 314.81(b)(3)(i). The Bextra patient brochure misbrands Bextra under 21 U.S.C. 352 (a).

DDMAC requests that Pfizer immediately cease the dissemination of promotional materials for Celebrex and Bextra that contain claims and presentations the same as or similar to those described above. Please submit a written response to this letter on or before January 26, 2005, describing your intent to comply with this request, listing all promotional materials for Celebrex and Bextra that contain claims or presentations the same as or similar to those described above, and explaining your plan for discontinuing use of such materials.

The seriousness of the violations concerning your promotion of Celebrex described above would generally have warranted a Warning Letter; however, in light of your recent agreement to a voluntary suspension on all consumer promotion for Celebrex, we do not feel that is appropriate at this time. You should be aware, however, of the serious nature of the violations described above and act to avoid disseminating similarly misleading promotion for your products in the future.

Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID# 12560 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Celebrex and Bextra comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Joan Hankin
Consumer Promotion Analyst
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joan Hankin

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