DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Gerald P. Belle
President
Aventis Pharmaceuticals North America
300 Somerset Corporate Boulevard
Bridgewater, NJ 08807

RE: NDA # 20-449
Taxotere® (docetaxel) for Injection Concentrate
MACMIS ID # 11453

WARNING LETTER

Dear Mr. Belle:

This Warning Letter objects to dissemination by Aventis Pharmaceuticals (Aventis) of three violative direct-to-consumer (DTC) print advertisements (ads) for Taxotere (docetaxel) for Injection Concentrate. As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the DTC ads "Lung Cancer Cover Wrap" for *People* Magazine (TXT-AM-5138-1) and "Breast Cancer Cover Wrap" for *People* Magazine (TXT-AM-5140-1) and a patient advertisement (TXT-JA-7347-1) submitted on Form FDA 2253. DDMAC has concluded that these DTC ads are false or misleading because they make unsubstantiated effectiveness claims, and omit important risk information for Taxotere, in violation of Sections 502(n) and 201(n) of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 321(n) and 352(n)) and FDA implementing regulations (21 C.F.R 202.1(e)(5)(i), (e)(5)(iii), and (e)(6)(i)). These DTC ads misleadingly overstate the survival benefits of Taxotere and imply that survival depends on treatment with Taxotere, while also minimizing the serious and potentially life-threatening risks associated with the drug by omitting some risk information and presenting other risk information in an inconspicuous manner.

DDMAC had previously objected, in an untitled letter dated December 18, 2002, to your dissemination of physician-directed promotional materials for Taxotere that: (1) omitted material facts regarding limited approved indications for Taxotere; (2) made misleading effectiveness claims that overstated the drug's survival benefits; and (3) omitted important safety information on the life-threatening risks of the drug. We are concerned that you continued to promote Taxotere in a similar manner to consumers in popular consumer

magazines. The patient advertisement TXT-JA-7347-1 ran in publications up to and including July 2003, by your own admission.[1, 2]

Background

Product Information

According to the approved labeling (PI), Taxotere has limited indications in the treatment of certain kinds of breast and lung cancer. Specifically, on May 14, 1996, June 22, 1998, December 23, 1999, and November 27, 2002, respectively, Taxotere was approved for:

- locally advanced or metastatic breast cancer in patients who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy,
- locally advanced or metastatic breast cancer in patients who have failed prior chemotherapy,
- locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of prior platinum-based chemotherapy, and
- use in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic NSCLC who have not previously received chemotherapy for this condition.[3]

The PI for Taxotere contains a boxed warning highlighting the severe and potentially life-threatening adverse reactions that can occur with Taxotere and important information regarding patient selection and monitoring. In addition to describing which patients are not appropriate for Taxotere, the boxed warning describes the following risks associated with the drug:

- Increased incidence of treatment-related mortality associated with Taxotere therapy in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive Taxotere as a single agent at a dose of 100 mg/m^2.
- Increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death and the need to obtain bilirubin, SGOT or SGPT, and alkaline phosphatase values prior to each cycle of Taxotere therapy.
- Risk of neutropenia, which may be severe and result in infection, and the need for performing frequent blood cell counts on all patients receiving Taxotere.
- Risk of severe hypersensitivity reactions, characterized by hypotension and/or bronchospasm, or generalized rash/erythema.
- Risk of severe fluid retention, characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural

[1] Telephone conversation between Aventis and DDMAC on August 14, 2003.
[2] Written communication from Aventis to DDMAC dated August 21, 2003.
[3] This approval was based on demonstration of non-inferiority of the Taxotere/Cisplatin combination when compared with Vinorelbine/Cisplatin.

effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites).

Similarly, the Patient Information Leaflet (Patient PI) that is provided to patients being treated with Taxotere includes important risk information under the heading "**What is the most important information about Taxotere?**" The Patient PI states that routine blood tests are necessary and people with low blood counts can develop life-threatening infections; serious allergic reactions have occurred with Taxotere; patients who take Taxotere can develop severe fluid retention, which can be life-threatening; and, patients must tell their doctor if they are using any other medicines prior to receiving infusions of Taxotere.

Regulatory History

On December 18, 2002, DDMAC sent an untitled letter to Aventis stating that DDMAC had identified a sales aid and three billboards for Taxotere that were in violation of the Act and FDA implementing regulations. These promotional pieces were false or misleading because they omitted material facts with regard to the indication for Taxotere, made misleading effectiveness claims overstating the drug's survival benefits, and omitted safety information, including information from the boxed warning.

Aventis responded in a letter dated December 30, 2002, stating that Aventis wished "to assure you [DDMAC] that effective immediately, the use of this sales aid has been discontinued" and "all unused copies of these or similar sales aids will be destroyed." Aventis further stated that "we [Aventis] are discontinuing the use of these [billboards], and any similar materials." On January 10, 2003, DDMAC contacted Aventis by telephone and left a voice message requesting that Aventis send a comprehensive list of all promotional materials that contained the same or similar violations and were discontinued as a result of the untitled letter. In response, Aventis sent a letter dated January 17, 2003, containing a list of twelve promotional items that were "discontinued and ordered destroyed" by Aventis.

On January 27, 2003, DDMAC again contacted Aventis by telephone and requested that Aventis reexamine its inventory of promotional items that contained the same or similar violations and were discontinued as a result of the untitled letter and submit a revised comprehensive list as described above. DDMAC was particularly concerned that Aventis issued a "Dear Doctor" letter dated December 2002, with similar violations. DDMAC was also concerned that this letter was not submitted to DDMAC on Form FDA 2253, as required under the Act and FDA implementing regulations, and was not included in the January 17, 2003, list that Aventis sent to DDMAC. On February 6, 2003, Aventis sent a follow-up letter stating that "this piece [the 'Dear Doctor' letter] was intended for one-time use and has been destroyed." You also included a list containing one additional item that was discontinued as a result of the untitled letter.

Subsequently, DDMAC sent a letter to Aventis dated July 17, 2003, stating that DDMAC had identified two additional promotional pieces (DTC ads "Lung Cancer Cover Wrap" for *People* Magazine (TXT-AM-5138-1) and "Breast Cancer Cover Wrap" for *People* Magazine (TXT-AM-5140-1)) from 2002, that raised concerns similar to those that were highlighted in the December 18, 2002, untitled letter to Aventis. DDMAC stated that these two pieces were not included in either of the previous lists that Aventis submitted to DDMAC. DDMAC requested

that Aventis submit a letter stating the status (i.e., active or discontinued) of the items as well as yet another list of all promotional materials that contained the same or similar violations and have been discontinued as a result of the untitled letter.

Aventis replied on August 1, 2003, that:

> These pieces were not included in our list of pieces that had been discontinued and destroyed as a result of the Untitled Letter because we did not believe the Untitled Letter applied to these pieces. We have again reviewed these pieces in light of the December 18, 2002, Untitled Letter, and we continue to believe that the information presented in these ads is not inappropriate for the intended use as consumer communications.

Aventis further stated that, "Although these ads are not currently in use, another DTC piece identified as TXT-JA-7347-1 'Revised 2003 Patient Ad,' is very similar to the two referenced in your letter," and "We have identified no additional active pieces that we believe would be impacted by the Untitled Letter." DDMAC followed up on this communication with telephone calls to Aventis on August 7, 2003, and August 14, 2003, to ascertain whether or not the Aventis patient advertisement (TXT-JA-7347-1), cited in Aventis' August 1, 2003, response to DDMAC, was still in use. Aventis responded on August 21, 2003, in a letter stating:

1) The ad was disseminated in "Coping" Magazine (March & July 2003); "MAAM" Magazine (March, May, & July 2003); and "Cure" Magazine (April & June 2003); and
2) The ad is planned to be disseminated in "Coping" Magazine (September & November 2003); "MAAM" Magazine (September & November 2003); "Cure" Magazine (September & December 2003); and "Y-Me" Magazine (October 2003).

Aventis further stated that "…The ad has been discontinued and pulled from all scheduled runs." DDMAC remains concerned that Aventis continued to provide false or misleading information about Taxotere to patients as recently as July 2003, despite the multiple communications between DDMAC and Aventis following the December 18, 2002, untitled letter emphasizing the importance of discontinuing all pieces containing similar violations.

Description of the Materials in Question

Similar to the promotional pieces cited in the December 18, 2002, untitled letter, the three ads at issue feature a chess theme. Two of the ads at issue appeared on the back of a circulation wrap on the October 21, 2002, and November 4, 2002, issues of *People* magazine. The cover of the circulation wrap features the "People" logo, a cancer-awareness ribbon, and the prominent statement "Raising awareness of breast cancer across America" on the October issue and "Raising awareness of lung cancer across America" on the November issue, with the "Aventis Oncology" corporate logo featured underneath this statement. The ads feature the prominent headline "THE NEXT MOVE MAY BE THE KEY TO SURVIVAL." Below this headline is a picture portraying two people as pieces on a chessboard, with the queen chess piece in prominent view between them a few squares away. The logo for Taxotere is a prominent feature at the bottom of the ads with the tagline, "It's your move."

The third ad, which was disseminated up to and including July 2003, features the same prominent headline, “THE NEXT MOVE MAY BE THE KEY TO SURVIVAL.” Below this headline is a picture of a hand moving the queen chess piece in prominent view. The ad also includes the logo for Taxotere and the tagline, “It’s your move.”

Misleading Effectiveness Claims

The DTC ads are misleading because they suggest that Taxotere is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The most prominent claim in your ads, the headline “THE NEXT MOVE MAY BE THE KEY TO SURVIVAL,” suggests to cancer patients that if they want to survive breast or lung cancer, the next course of cancer treatment (or "next move") should include Taxotere. The tagline “It’s your move” presented with the prominently featured logo for Taxotere at the bottom of the ads reinforces the message that treatment with Taxotere will result in significant survival advantages, when the survival differences observed in clinical trials with Taxotere were at best several months, were observed in specific populations as described in the indications above, and did not necessarily represent long-term survival or a cure. Your claim also implies to patients that if they do not add Taxotere to their treatment, they **will not** survive. This is misleading, given that there are other treatments available for breast cancer and lung cancer with **proven** survival benefits.

As stated in DDMAC’s December 18, 2002, untitled letter to Aventis, patients with newly-diagnosed advanced NSCLC have available to them approved therapies with a demonstrated survival benefit. These therapies, such as combination chemotherapy regimens including a platinum agent, offer improved survival over Taxotere when used in the first-line treatment of advanced NSCLC. As you know, Aventis submitted a June 30, 1999, supplemental new drug application (SNDA) to the FDA proposing that the indication for Taxotere be changed to “…the treatment of patients with chemotherapy-naïve locally advanced or metastatic NSCLC.” On April 26, 2000, Aventis withdrew this SNDA. FDA concluded that the data in this SNDA did not establish the safety or effectiveness of Taxotere for first-line treatment of NSCLC. Clinical trials with Taxotere in patients with advanced NSCLC failed to demonstrate improved survival benefits as compared to currently approved combination chemotherapy regimens. Cisplatin-based chemotherapy improves the median survival of patients with advanced NSCLC by 6-8 weeks and is associated with an increase of the rate of 1-year survival from 15% to 25%. Furthermore, the rate of deaths within 30 days and toxicity-related deaths on the Taxotere arm of your study TAX 308 was higher than that reported in the randomized, controlled trials that were the basis of approval for other first-line agents, based on the FDA’s revised toxicity-related death rate.

You also claim that, “Because Taxotere is generally safe and tolerable, you can stay involved in important aspects of your life.” We are not aware of substantial evidence or substantial clinical experience demonstrating such a benefit with Taxotere. Moreover, this claim ignores the risks associated with the drug that may prevent or interfere with the patient’s ability to stay involved in important aspects of his or her life, many of which are not discussed in your ads, as discussed below.

Omission and Minimization of Important Risk Information

The DTC ads omit risk information about Taxotere. The ads describe Taxotere as "generally safe and tolerable," but fail to present the information from the boxed warning on the risk of life-threatening infections, severe allergic reactions, and severe fluid retention, as described above. They also do not discuss common side effects associated with Taxotere, such as hair loss, muscle pain, rash, odd sensations (i.e., numbness, tingling, burning sensations or weakness in the hands and feet), nail changes, nausea, vomiting, and severe diarrhea.

Moreover, the risk information that is presented lacks prominence. It is placed at the bottom of the ads, in much smaller type size than the claims promoting the benefits of the drug. The presentation of risk information begins with the statement: "Like all anticancer agents, there are side effects associated with Taxotere that may affect some patients more than others." Framing the risks in this manner minimizes the risks of using this product.

Conclusions and Requested Actions

You have disseminated DTC ads that make misleading effectiveness claims, and omit and minimize risk information for Taxotere. Due to the significant public health and safety concerns raised by these ads, we request that you provide a detailed response to the issues raised in this Warning Letter. This response should contain an action plan that includes:

1) Immediately ceasing the dissemination of these materials, and all promotional materials that contain the same or similar violations outlined in this letter.

2) Providing a plan of action to disseminate accurate and complete information to the audience(s) that received the violative promotional materials.

3) Providing a written statement of your intent to comply with "1" and "2" above.

Please provide a written response to DDMAC by November 25, 2003, describing your intent and plans to comply with DDMAC's request. If you have any questions or comments, please contact Joseph A. Grillo, Pharm.D., Carol H. Barstow, J.D., or Lesley R. Frank, Ph.D., J.D. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 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 #11453 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 Taxotere, and may determine that additional measures will be necessary to fully correct the false and 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,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
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/

Thomas Abrams
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