DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

MaryRose Salvacion
Director, US Regulatory Affairs Marketed Products
sanofi-aventis
P.O. Box 5925, 55 Corporate Drive
Bridgewater, NJ 08807

RE: NDA #20-449
Taxotere® (docetaxel) Injection Concentrate, Intravenous Infusion (IV)
MACMIS ID #17379

Dear Ms. Salvacion:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional reprint carrier [US.DOC.07.04.078] for Taxotere (docetaxel) Injection Concentrate, Intravenous Infusion (Taxotere) submitted under cover of Form FDA 2253 by sanofi-aventis (SA) and obtained at the American Society of Clinical Oncology annual meeting in June 2008. The reprint carrier includes a reprint[1] from the Journal of Clinical Oncology, which describes the TAX 311 study. This reprint carrier is false or misleading because it presents unsubstantiated superiority claims and overstates the efficacy of Taxotere. Therefore, this material misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) and 321(n). *Cf*. 21 CFR 202.1(e)(6)(i), (ii) & (e)(7)(ii).

Background

According to its FDA-approved product labeling (PI), Taxotere is indicated, among other things, for the following:

> TAXOTERE is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

The CLINICAL STUDIES section of the PI presents efficacy results from two randomized comparator trials that evaluated Taxotere in the treatment of locally advanced or metastatic breast cancer after failure of previous chemotherapy (alkylating agent-containing regimens or anthracycline-containing regimens). The primary endpoint in both studies was time to progression. In one randomized trial, patients with a history of prior treatment with an anthracycline-containing regimen were assigned to treatment with Taxotere (100 mg/m^2 every 3 weeks) or the combination of mitomycin (12 mg/m^2 every 6 weeks) and vinblastine (6 mg/m^2 every 3 weeks). The median time to progression was 4.3 months for Taxotere versus

[1]Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol*. 2005;23(24):5542-51.

2.5 months for the mitomycin/vinblastine combination (Risk Ratio = 0.75, 95% CI = 0.61-0.94, p=0.01). In a second randomized trial, patients previously treated with an alkylating-containing regimen were assigned to treatment with Taxotere (100 mg/m^2 every three weeks) or doxorubicin (75 mg/m^2 every 3 weeks). The median time to progression was 6.5 months for Taxotere versus 5.3 months for doxorubicin (Risk Ratio = 0.93, 95% CI = 0.71-1.16, p=0.45). The PI also includes data from an open-label, randomized dose ranging study of Taxotere and numerous single arm studies.

Unsubstantiated Superiority Claims / Overstatement of Efficacy

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. Furthermore, promotional materials are misleading if they contain representations that the drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The professional reprint carrier presents the following claims, which compare the efficacy of Taxotere to paclitaxel (emphasis in original):

- **This phase III study demonstrated that docetaxel is superior to paclitaxel in TTP, response duration, and OS**.
- **Phase III trial demonstrates improved survival for Taxotere vs paclitaxel in metastatic breast cancer**
- **TAX 311: Taxotere demonstrated efficacy benefits vs paclitaxel**
- "Significantly higher response rates with Taxotere in evaluable patients (P=.02)" in conjunction with:
    - A bar graph titled "**Overall response rates**" depicting overall response rates of 32% for Taxotere (n=225) and 25% for paclitaxel (n=224) in the intent-to-treat population (p=.10), and 37% for Taxotere (n=189) and 26% for paclitaxel (n=205) in the evaluable population (P=.02)
- "Significantly longer duration of response with Taxotere (P=.01)" in conjunction with:
    - A bar graph titled "**Duration of response**" depicting a duration of response of 7.5 months for Taxotere (n=225) and 4.6 months for paclitaxel (n=224) in the intent-to-treat population (P=0.01), and 7.5 months for Taxotere (n=189) and 4.6 months for paclitaxel (n=205) in the evaluable population (P=.01)
- "Significantly longer median overall survival with Taxotere (P=.03)" in conjunction with the following:
    - A graph titled "**Overall survival (intent-to-treat population)**" depicting median overall survival of 15.4 months for Taxotere and 12.7 months for paclitaxel in the intent to treat population
    - A graphic claiming a "**29% reduction in the risk of mortality with Taxotere (HR: 1.41, 95% CI, 1.15-1.73, P=.03)**"
    - "Median overall survival, evaluable population: Taxotere 16.1 months vs. paclitaxel 12.7 months (P=.02)"
- "Significantly longer median time to progression with Taxotere (P<.0001)" in conjunction with the following:
    - A graph titled "**Median time to progression (intent-to-treat population)**" depicting median time to progression of 5.7 months for Taxotere and 3.6 months for paclitaxel in the intent-to-treat population

- A graphic claiming a "**39% reduction in the risk of progression with Taxotere (HR: 1.64, 95% CI, 1.33-2.02, P<.0001)**"
- "Median time to progression, evaluable population: Taxotere 5.5 months vs paclitaxel 3.6 months (P<.0001)"

Similar claims are also presented on the back cover of the reprint carrier.

These claims misleadingly suggest that Taxotere is superior to paclitaxel in the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy, and overstate the efficacy of Taxotere. FDA is unaware of substantial evidence to support these claims.

The claims in the reprint carrier reference the Jones, et al. reprint included with the carrier, which describes an open label, randomized study of Taxotere (docetaxel) 100 mg/m^2 versus paclitaxel 175 mg/m^2, administered every 21 days. The patients (449 randomized, 225 given Taxotere and 224 given paclitaxel) included in the study must have had histologically proven adenocarcinoma of the breast, metastatic or locally advanced inoperable disease, bi-dimensionally measurable disease and an ECOG performance status of 0, 1, or 2. Prior therapy must not have included any taxane, and patients continued therapy until disease progression, unacceptable toxicity or patient request to discontinue. The primary efficacy endpoint for the study was objective response and secondary endpoints included duration of response, time to progression, and overall survival.

The reference cited in support of these claims, as is further detailed below, does not constitute substantial evidence or substantial clinical experience to support these claims and representations because, among other factors, the study failed to demonstrate statistical significance on the primary endpoint and has not been replicated.

Regarding the first factor, the superiority analysis of the primary endpoint (e.g., objective response rate in the intent-to-treat population) failed to demonstrate a statistically significant difference between the two study arms. In the absence of a finding of statistical significance for the primary endpoint, any further analysis conducted on this study, including secondary endpoints and subpopulations, are all considered exploratory and do not generally constitute substantial evidence.

Regarding the second factor, a claim of superiority generally must be supported by <u>two</u> well-designed, head-to-head clinical trials comparing appropriate doses and dose regimens of your drug and the comparator drug. We are not aware of any study replicating the result achieved in this trial.

FDA is not aware of substantial evidence or substantial clinical experience to support the claims made in the carrier regarding Taxotere's level of efficacy or superiority to paclitaxel. If you have such evidence, please submit it to FDA for review.

Conclusion and Requested Actions

For the reasons discussed above, the professional reprint carrier misbrands Taxotere in violation of the Act, 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(6)(i), (ii) & (e)(7)(ii).

DDMAC requests that sanofi-aventis immediately cease the dissemination of violative promotional materials for Taxotere such as those described above. Please submit a written response to this letter on or before April 30, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Taxotere as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266 or by facsimile at (301) 847-8444. In all future correspondence regarding this matter, please refer to the MACMIS ID #17379 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 Taxotere comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Keith Olin, Pharm.D.
Regulatory Review Officer
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/

Keith Olin
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