DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Kerry Rothschild, J.D.
Director, DDMAC Liaison
US Regulatory Affairs
Aventis Pharmaceuticals
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800

RE: NDA # 20-449
Taxotere® (docetaxel) for Injection
MACMIS ID# 10989

Dear Mr. Rothschild:

This letter notifies Aventis Pharmaceuticals (Aventis) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified a sales aid (TXT-SA-2594-1) and three billboards (TXT-CP-2698-1, TXT-AM-3171-1 and one that was not submitted on FDA Form 2253 at the time of initial dissemination) for Taxotere (docetaxel) for Injection (Taxotere) that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. These promotional pieces were used at the thirty-eighth American Society of Clinical Oncology (ASCO) Meeting held in Orlando, Florida in May 2002. These promotional pieces are false or misleading because they omit material facts with regard to the indication for Taxotere, make misleading efficacy claims, and omit safety information. Our specific objections follow:

Omission of Material Facts Regarding Approved Indication and Use

The sales aid contains false or misleading claims regarding Taxotere because it omits material facts regarding the use of Taxotere for non-small cell lung cancer (NSCLC). At the time the sales aid was disseminated, the approved product labeling (PI) for Taxotere stated as follows:[1] "Taxotere is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer **after failure of prior platinum-based chemotherapy**" (emphasis added). The PI also stated that in the two randomized, controlled trials that established Taxotere use in NSCLC, patients had a history of prior treatment with a platinum-based chemotherapy regimen. However, the sales aid includes claims such as "Significant survival advantages in patients with advanced non-small cell lung cancer," "Improved clinical benefits for patients with NSCLC," and "At the center of more strategies every day." The sales aid fails to convey that these patients had failed prior platinum-based chemotherapy

[1] On November 27, 2002, Taxotere received approval, in combination with cisplatin, for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition. It is worth noting that even under your current labeling, the claims in your sales aid would be misleading because they suggest that Taxotere can be used as first-line monotherapy for NSCLC.

and falsely or misleadingly implies that Taxotere, as a single agent, may be used as first-line treatment of patients with NSCLC, contrary to its approved labeling as noted above.

This implication is particularly troublesome because 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 Food and Drug Administration (FDA) proposing that Taxotere's indication be changed to "..[ ] On April 26, 2000, Aventis sent the FDA correspondence to withdraw this SNDA. As noted in FDA's December 21, 2000, letter to Aventis:

> *This application's single randomized, controlled trial, [ ] did not establish the evidence of safety and efficacy of docetaxel [Taxotere] in the setting of first-line treatment of non-small cell lung carcinoma with a high level of confidence for the following reasons:*
>
> - *The FDA has approved therapies for first-line treatment of non-small cell lung cancer. The median survival and rate of one year survival associated with these therapies consistently surpass those reported with docetaxel [Taxotere] in [ ] The efficacy and safety results presented in [ ] do not provide a level of confidence necessary to recommend single agent docetaxel [Taxotere] at the dose studied for first line treatment of non-small cell lung cancer.*
>
> - *The treatment related mortality in [ ] was 6.5% (assessment of FDA). Our review of the data from the phase 2 studies utilizing [ ] in the application supported that rate of treatment mortality.*

Based on the data Aventis submitted in this SNDA, clinical trials with Taxotere in patients with advanced NSCLC failed to demonstrate improved survival benefits for these patients 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 [ ] 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. Taxotere's approved labeling contains a boxed warning regarding the risk of severe adverse reactions and death associated with its use in specific patient populations. With minimal survival benefits in patients with newly-diagnosed NSCLC (compared to existing combination regimens approved in this patient population) and the potential for increased toxicity with its use, Taxotere as a single agent was not indicated as first-line therapy and certainly was not "at the center of more strategies every day" as claimed in your sales aid. Therefore, Aventis' false or misleading promotion in the sales aid may compromise patient survival and safety.

Misleading Efficacy Information

The sales aid is misleading because it uses subset analyses to imply a survival advantage and other clinical benefits of Taxotere in certain patient populations when, to the best of FDA's knowledge, such has not been demonstrated by substantial evidence or substantial clinical experience. As stated above, these misleading implications may result in patients receiving substandard treatment for advanced NSCLC. Following are the misleading presentations that use subset analyses to imply clinical benefit of Taxotere:

- The sales aid contains the claims "Significant survival advantages in patients with advanced non-small cell lung cancer (NSCLC)... and in patients previously treated with paclitaxel" and "Taxotere 75 mg/m^2 compared with V/I in patients with prior paclitaxel treatment" together with a graph depicting survival rates between patients who took Taxotere as compared with vinorelbine or ifosfamide. The data used to support these survival claims are derived from a *post hoc* subgroup analysis of a small patient population (i.e., patients with a history of prior paclitaxel exposure) within a large study (patients with a history of prior platinum-based chemotherapy). The primary endpoint of the large study was survival in NSCLC patients previously treated with a platinum-based chemotherapy regimen. The large study was not adequate in design to measure survival specifically in patients taking Taxotere who had been previously treated with paclitaxel as compared to the rest of the patient population. Therefore, this presentation misleadingly implies a survival advantage of Taxotere specifically in patients previously treated with paclitaxel when such has not been demonstrated by substantial evidence or substantial clinical experience. Additionally, this type of promotion is of concern because Aventis knew that these subset analyses were specifically not included in Taxotere's PI at the time of approval.

- The sales aid also contains a table titled "Response rates in patients with or without prior paclitaxel treatment (intent-to-treat population)" that compares partial response and stable disease in patients receiving Taxotere as compared with vinorelbine or ifosfamide. As stated above, these data are derived from a *post hoc* subgroup analysis of a small patient population (i.e., patients with a history of prior paclitaxel exposure) within a large study (i.e., patients with a history of prior platinum-based chemotherapy). Therefore, this table misleadingly implies that Taxotere will confer clinical benefits in patients previously treated with paclitaxel as compared to the rest of the patient population when such has not been demonstrated by substantial evidence or substantial clinical experience. Furthermore, the variable "stable disease" is not considered an appropriate measure of response in this setting and was also specifically not included in Taxotere's PI at the time of approval.

- Similarly, claims and graphic representations of "Improved clinical benefits for patients with NSCLC" are misleading because they are not supported by substantial evidence or substantial clinical experience. The sales aid misleadingly implies that patients taking Taxotere experienced less need for disease-related medications (i.e., opioid analgesic usage, nonopioid analgesic usage, and other disease-related medication usage) as compared to those patients receiving best supportive care (BSC). The sales aid also misleadingly implies that patients taking Taxotere needed less radiotherapy as compared to those patients receiving BSC. The data are derived from *post hoc* analyses and endpoints that were not prespecified. Analgesic use was evaluated in an unblinded

setting in an open-label study. Furthermore, patients on the BSC arm had a higher rate of starting morphine analgesics than those receiving Taxotere, which introduces obvious selection bias. Claims based on this type of inadequate study design do not constitute substantial evidence or substantial clinical experience, and were specifically not included in Taxotere's PI at the time of approval.

Finally, the sales aid is misleading because it uses graphs to distort and misrepresent the data. All the graphs used in this sales aid interrupt the X-axis (i.e., Percentage of patients) between 50 and 100. Such a presentation creates a misleading impression by enhancing the percentage bars in the graphs to appear closer to 100.

Omission of Safety Information

Aventis displayed three billboards promoting Taxotere at several Orlando, Florida locations[2,3,4] during the ASCO meeting. The first billboard, featuring the Taxotere product logo, the www.taxotere.com website address, a graphic of a queen chess piece, and the statement "Come see us at ASCO Booth #1001" was displayed at the baggage claim area of the Orlando International Airport. The second and third billboards containing the Taxotere logo, the website address, a depiction of a chess game featuring the queen piece in the middle of the claim "At the center of more strategies every day," and a statement "Please see full prescribing information including boxed WARNING at Booth 1001" appeared on the I-Trolly that transported attendees to and from the convention center (the meeting site), and as a "mobile billboard" that was driven slowly around the convention center and in a loop on the streets outside of the convention center.

None of these billboards promoting Taxotere provided a brief summary or the approved product labeling. Although the first billboard made no representations or suggestions about the product, it was not acceptable as a reminder piece because Taxotere's approved labeling contains a boxed warning. Reminder promotion is not permitted for products with boxed warnings. The second and third billboards contained product claims about Taxotere ("At the center of more strategies every day"), but failed to provide the brief summary or the approved product labeling. The statement directing the reader to a booth at a convention, removed from the location of the billboard itself, is not considered adequate to provide this information. Even for the attendees of the meeting, who presumably would have understood the reference and would have had access to the convention center, there was a temporal delay between reading the message on the billboard about Taxotere and being able to access the full prescribing information. That information should have been provided as part of or with the promotional billboards themselves (e.g., brief summary or product labeling on the billboard itself or on an adjacent billboard).

Moreover, the claim "At the center of more strategies every day" on the mobile billboard and on the billboard on the trolley is misleading for the same reasons discussed above with respect to the use of that claim in the promotional sales aid. As with the sales aid, these billboards misrepresented the approved indication of the product, in addition to failing to convey any of the important information from the boxed warning for Taxotere regarding its

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[2] Taxotere Billboard (not submitted on FDA Form 2253). United Airlines baggage claim area. Orlando International Airport. May 17, 2002.
[3] Taxotere Mobile Billboard. (TXT-CP-2698-1). Anytime Anywhere Mobile Billboards. May 18, 2002.
[4] Taxotere Billboard (TXT-AM-3171-1). Orlando I-Trolly. May 18, 2002.

safe administration, the risk of severe adverse reactions and death associated with its use in specific patient populations, important monitoring parameters, and important information regarding severe hypersensitivity reactions associated with its use. It misrepresents the drug to suggest that Taxotere is like the queen piece in a chess game (i.e., the most powerful and versatile player in the game strategy) and is "at the center of more strategies every day," when, according to its approved PI at the time, Taxotere was not indicated for first-line use, showed minimal survival benefits in patients with newly-diagnosed NSCLC compared to other approved regimens, and had the potential for increased toxicity.

Failure to Comply with CFR 314.81(b)(3)(i)

The Taxotere billboard at the baggage claim area of the Orlando Airport was not submitted on Form FDA 2253 at the time of initial use, in violation of the post-marketing reporting requirements of the Act.

Requested Action

Aventis should immediately cease the distribution of these and other similar promotional materials for Taxotere that contain the same or similar claims or presentations. Please submit a written response to DDMAC on or before January 2, 2003, describing your intent and plans to comply with the above. In its letter to DDMAC, Aventis should include the date on which this and other similarly violative materials were discontinued.

Aventis should direct its response to me by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS ID # 10989 in addition to the NDA number. DDMAC reminds Aventis that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

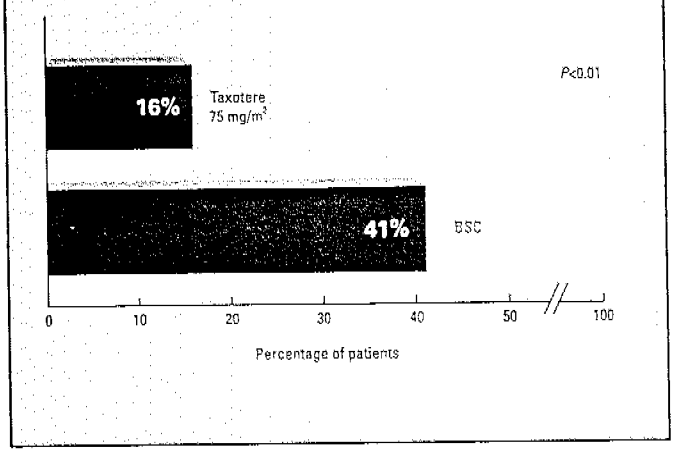
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

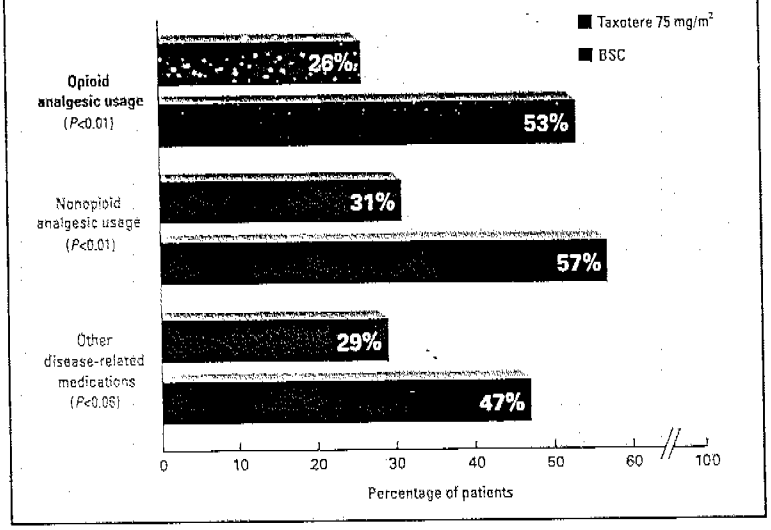
Joseph Grillo
12/18/02 04:06:47 PM

Improved clinical benefits for patients with NSCLC[5]

Need for radiotherapy



Need for disease-related medications



- Only 2% of Taxotere-treated patients experienced weight loss ≥10%, compared with 23% of patients who received BSC
- 49% of Taxotere-treated patients either had no change or an improvement in their performance status, compared with only 37% of patients who received BSC

Taxotere has a predictable and generally manageable safety profile[1]

- Among advanced NSCLC patients receiving Taxotere at a dose of 75 mg/m², the most common severe side effects were myelosuppression and asthenia; nonsevere side effects included nausea and alopecia

Important safety considerations[1]

- All patients treated with Taxotere on an every-3-week schedule should receive a premedication regimen (such as dexamethasone 8 mg PO b.i.d.) for 3 days starting 1 day prior to treatment. H_1 or H_2 antagonists are not required
  — In the clinical trials of **NSCLC** patients receiving Taxotere 75 mg/m² and pretreatment with oral corticosteroids, the incidences of severe fluid retention and severe hypersensitivity were each 2.8%
- Taxotere should generally not be given to patients with bilirubin >upper limit of normal (ULN) or to patients with SGOT and/or SGPT >1.5 × ULN **concomitant with** alkaline phosphatase >2.5 × ULN
  — These patients are at increased risk for treatment-related mortality and adverse events
- Patients with neutrophil counts <1500 cells/mm³ should not receive Taxotere
- Patients with a history of severe hypersensitivity reactions to Taxotere or to other drugs formulated with polysorbate 80 should not receive Taxotere

References: 1. Prescribing Information. Aventis Pharmaceuticals Inc. **2.** Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol.* 2000;18:2095-2103. **3.** Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. *J Clin Oncol.* 2000;18:2354-2362. **4.** Fossella FV. Second-line chemotherapy for non-small-cell lung cancer. *Lung Cancer Updates.* 2001;1:1-7. **5.** Data on file. Aventis Pharmaceuticals Inc.

Aventis

ONCOLOGY

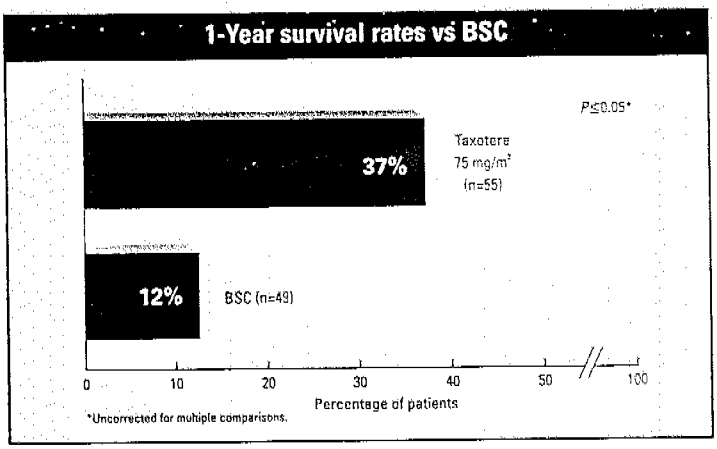
Aventis Pharmaceuticals
Bridgewater, NJ 08807

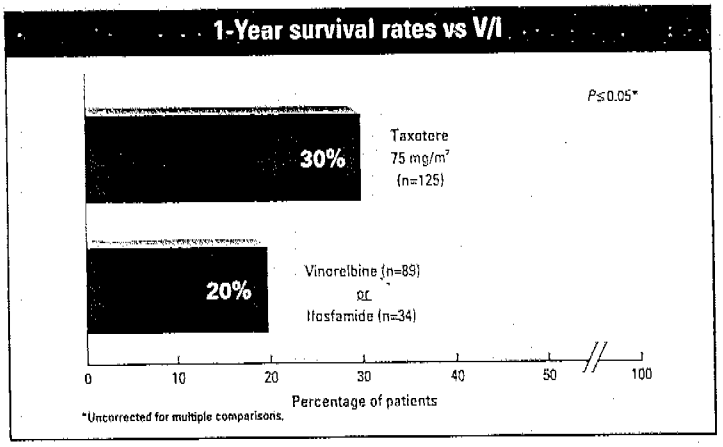
TXT-SA-2594-1 05/02 Printed in U.S.A.

TAXOTERE® (docetaxel)
for Injection Concentrate

www.taxotere.com

Significant survival advantages in patients with advanced non-small cell lung cancer (NSCLC)[1-3] ...

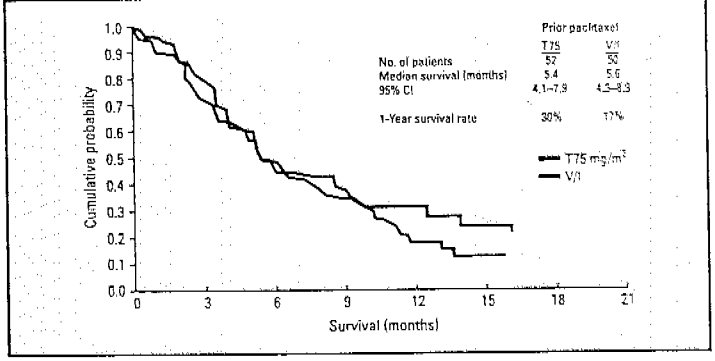




- Taxotere 75 mg/m² prolongs median survival
  — 7.5 months for Taxotere vs 4.6 months for best supportive care (BSC)

...and in patients previously treated with paclitaxel[4,5]

Kaplan-Meier plot of overall survival: Taxotere 75 mg/m² compared with V/I in patients with prior paclitaxel treatment



Response rates in patients with or without prior paclitaxel treatment (intent-to-treat population)

Prior paclitaxel	Taxotere 75 mg/m²	Vinorelbine or ifosfamide
Yes	(n=52)	(n=50)
Partial response	13%	2%
Stable disease	31%	31%
No	(n=73)	(n=73)
Partial response	3%	0
Stable disease	37%	30%

- Taxotere 75 mg/m² demonstrates increased overall and 1-year survival rates vs V/I
  — Survival was comparable in Taxotere-treated patients irrespective of prior treatment with paclitaxel
- Taxotere improves response rates vs V/I

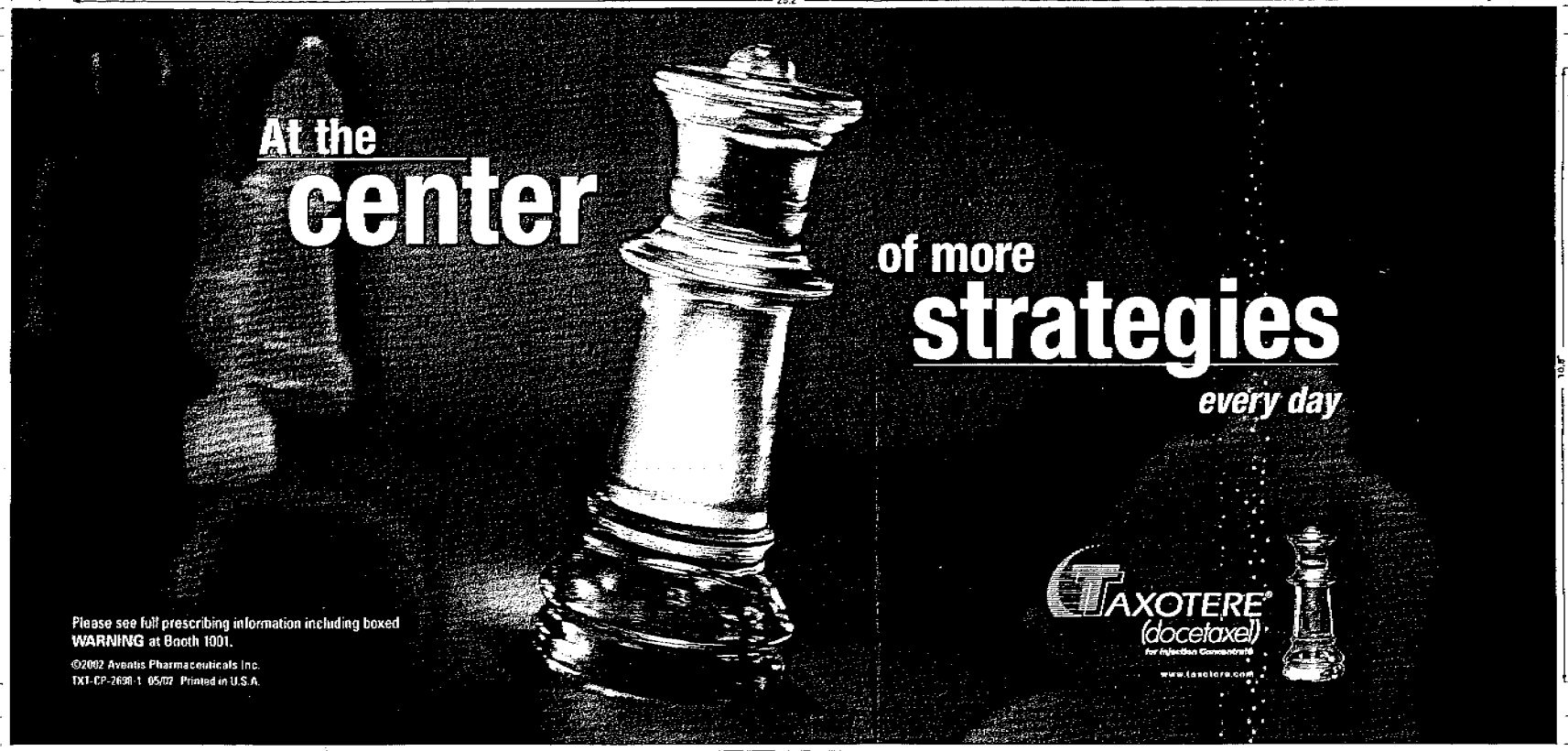
TAXOTERE®
(docetaxel)
for Injection Concentrate

Please see enclosed full prescribing information including boxed **WARNING.**

Front of Bus →

Quark file is 1/8 of actual size

Passenger side
Bus direction →



DOCUMENT SET @ 10% OF FINAL SIZE.

TAXPR-1737
1Pg + 4/C + 200 LS
ASCO Billboard 120" x 264"
harrisonmstar