

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020449Orig1s017

Trade Name: TAXOTERE

Generic or Proper Name: docetaxel

Sponsor: Aventis Pharmaceuticals, Inc.

Approval Date: July 09, 2002

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

Non-Small Cell Lung Cancer: 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.

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020449Orig1s017

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020449Orig1s017

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-449/S-017, S-019, S-022

Aventis Pharmaceuticals, Inc.
200 Crossing Boulevard
P.O. Box 6890
Bridgewater, New Jersey 08807-0890

Attention: Jacqueline Little, M.Sc.
Regulatory Liaison

Dear Ms. Little:

Please refer to your supplemental new drug application dated November 6, 2002, received November 7, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taxotere® (docetaxel) for Injection Concentrate, 20 mg and 80 mg. We also refer to your final printed labeling dated November 6, 2002 (S-017 and S-019) submitted in response to our July 9 and 30, 2002 approval letters.

This "Changes Being Effected" supplemental new drug application (S-022) provides for the addition of new text to the ADVERSE REACTIONS, Post-marketing Experiences subsection of the package insert.

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on November 6, 2002. We have also reviewed the final printed labeling that you submitted in accordance with our July 9 and 30, 2002 letters, and we find it acceptable.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Ann Staten, Regulatory Project Manager, at (301) 594-0490.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Richard Pazdur

1/30/03 01:38:39 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020449Orig1s017

OTHER ACTION LETTERS



NDA 20-449/S-017

Aventis Pharmaceutical Products Inc.
Route 202-206
PO Box 6800
Bridgewater, New Jersey 08807-2800

Attention: Marion Ceruzzi, Ph.D.
US Regulatory Liaison

Dear Ms. Ceruzzi:

Please refer to your supplemental new drug application dated January 9, 2002, received January 10, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taxotere (docetaxel) for Injection Concentrate, 20 mg and 80 mg.

We also refer to your submissions dated May 28, June 5 and 28, 2002.

This "Changes Being Effected" supplemental new drug application provides for additions to the ADVERSE REACTIONS section, Post-Marketing Experience subsection of the package insert.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert and patient package insert submitted January 9, 2002). Accordingly, the supplemental application is approved effective on the date of this letter.

However, please make the following change in your labeling at the next printing:

Under **Post-marketing Experiences**, subsection **Gastrointestinal**, replace the last sentence (b) (4)

with the following:

“Gastrointestinal: abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, ischemic colitis, colitis, intestinal obstruction, ileus, neutropenic enterocolitis and dehydration as a consequence to gastrointestinal events have been reported.”

Under **Post-marketing Experiences**, subsection **Ophthalmologic**, replace the last sentence “ (b) (4)

(b) (4)

with the following:

“Excessive tearing which may be attributable to lacrimal duct obstruction has been reported.”

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Ann Staten, Project Manager, at (301) 594-5770.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Richard Pazdur

7/9/02 12:48:58 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020449Orig1s017

LABELING

Patient Information Leaflet

Detach and give to Patient

Rev. September 2002

Patient Information Leaflet

Questions and Answers About Taxotere® for Injection Concentrate

(generic name = docetaxel)

(pronounced as TAX-O-TEER)

What is Taxotere?

Taxotere is a medication to treat breast cancer and non-small cell lung cancer. It has severe side effects in some patients. This leaflet is designed to help you understand how to use Taxotere and avoid its side effects to the fullest extent possible. The more you understand your treatment, the better you will be able to participate in your care. If you have questions or concerns, be sure to ask your doctor or nurse. They are always your best source of information about your condition and treatment.

What is the most important information about Taxotere?

- Since this drug, like many other cancer drugs, affects your blood cells, your doctor will ask for routine blood tests. These will include regular checks of your white blood cell counts. About 5% of people with low blood counts have developed life-threatening infections. The earliest sign of infection may be fever, so if you experience a fever, tell your doctor right away.
- Occasionally, serious allergic reactions have occurred with this medicine. If you have any allergies, tell your doctor before receiving this medicine.
- A small number of people who take Taxotere have severe fluid retention, which can be life-threatening. To help avoid this problem, you must take another medication called dexamethasone (DECKS-A-METH-A-SONE) prior to each Taxotere treatment. You must follow the schedule and take the exact dose of dexamethasone prescribed (see schedule at end of brochure). If you forget to take a dose or do not take it on schedule you must tell the doctor or nurse prior to your Taxotere treatment.
- If you are using any other medicines, tell your doctor before receiving your infusions of Taxotere.

How does Taxotere work?

Taxotere works by attacking cancer cells in your body. Different cancer medications attack cancer cells in different ways.

Here's how Taxotere works: Every cell in your body contains a supporting structure (like a skeleton). If this "skeleton" is damaged, it cannot grow or reproduce. Taxotere makes the "skeleton" in cancer cells very stiff, so that the cells can no longer grow.

How will I receive Taxotere?

Taxotere is given by an infusion directly into your vein. Your treatment will take about 1 hour. Generally, people receive Taxotere every 3 weeks. The amount of Taxotere and the frequency of your infusions will be determined by your doctor.

As part of your treatment, to reduce side effects your doctor will prescribe another medicine called dexamethasone. Your doctor will tell you how and when to take this medicine. It is important that you take the dexamethasone on the schedule set by your doctor. If you forget to take your medication, or do not take it on schedule, make sure to tell your doctor or nurse **BEFORE** you receive your Taxotere treatment. **Included with this information leaflet is a chart to help you remember when to take your dexamethasone.**

What should be avoided while receiving Taxotere?

Taxotere can interact with other medicines. Use only medicines that are prescribed for you by your doctor and **be sure** to tell your doctor all the medicines that you use, including nonprescription drugs.

What are the possible side effects of Taxotere?

Low Blood Cell Count – Many cancer medications, including Taxotere, cause a temporary drop in the number of white blood cells. These cells help protect your body from infection. Your doctor will routinely check your blood count and tell you if it is too low. Although most people receiving Taxotere do not have an infection even if they have a low white blood cell count, the risk of infection is increased.

Fever is often one of the most common and earliest signs of infection. Your doctor will recommend that you take your temperature frequently, especially during the days after treatment with Taxotere. If you have a fever, tell your doctor or nurse immediately.

Allergic Reactions – This type of reaction, which occurs during the infusion of Taxotere, is infrequent. If you feel a warm sensation, a tightness in your chest, or itching during or shortly after your treatment, tell your doctor or nurse immediately.

Fluid Retention – This means that your body is holding extra water. If this fluid retention is in the chest or around the heart it can be life-threatening. If you notice swelling in the feet and legs or a slight weight gain, this may be the first warning sign. Fluid retention usually does not start immediately; but, if it occurs, it may start around your 5th treatment. Generally, fluid retention will go away within weeks or months after your treatments are completed.

Dexamethasone tablets may protect patients from significant fluid retention. It is important that you take this medicine on schedule. If you have not taken dexamethasone on schedule, you must tell your doctor or nurse before receiving your next Taxotere treatment.

Hair Loss – Loss of hair occurs in most patients taking Taxotere (including the hair on your head, underarm hair, pubic hair, eyebrows, and eyelashes). Hair loss will begin after the first few treatments and varies from patient to patient. Once you have completed all your treatments, hair generally grows back.

Your doctor or nurse can refer you to a store that carries wigs, hairpieces, and turbans for patients with cancer.

Fatigue – A number of patients (about 10%) receiving Taxotere feel very tired following their treatments. If you feel tired or weak, allow yourself extra rest before your next treatment. If it is bothersome or lasts for longer than 1 week, inform your doctor or nurse.

Muscle Pain – This happens about 20% of the time, but is rarely severe. You may feel pain in your muscles or joints. Tell your doctor or nurse if this happens. They may suggest ways to make you more comfortable.

Rash – This side effect occurs commonly but is severe in about 5%. You may develop a rash that looks like a blotchy, hive-like reaction. This usually occurs on the hands and feet but may also appear on the arms, face, or body. Generally, it will appear between treatments and will go away before the next treatment. Inform your doctor or nurse if you experience a rash. They can help you avoid discomfort.

Odd Sensations – About half of patients getting Taxotere will feel numbness, tingling, or burning sensations in their hands and feet. If you do experience this, tell your doctor or nurse. Generally, these go away within a few weeks or months after your treatments are completed. About 14% of patients may also develop weakness in their hands and feet.

Nail Changes – Color changes to your fingernails or toenails may occur while taking Taxotere. In extreme, but rare, cases nails may fall off. After you have finished Taxotere treatments, your nails will generally grow back.

Other Possible Side Effects – Less severe side effects include nausea and vomiting. Severe diarrhea may occasionally occur. If you experience these or any other unusual effects, tell your doctor or nurse.

If you are interested in learning more about this drug, ask your doctor for a copy of the package insert.

Aventis Pharmaceuticals Products Inc.
Bridgewater, NJ 08807 USA
www.aventispharma-us.com

Rev. September 2002

Date _____

Day 1

Start

Dexamethasone tablets

2 times per day

AM

PM

Date _____

Day 2

Taxotere
Treatment Day

Take
Dexamethasone tablets
2 times per day
AM
PM

Date _____

Day 3

Take
Dexamethasone tablets
2 times per day
AM
PM

Prescribing Information as of September 2002

R_x only
TAXOTERE[®]
(docetaxel)
for Injection Concentrate

WARNING

TAXOTERE[®] (docetaxel) for Injection Concentrate should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

The incidence of treatment-related mortality associated with TAXOTERE therapy is increased 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 at a dose of 100 mg/m² (see **WARNINGS**).

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 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase > 1.5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, SGOT or SGPT, and alkaline phosphatase values should be obtained prior to each cycle of TAXOTERE therapy and reviewed by the treating physician.

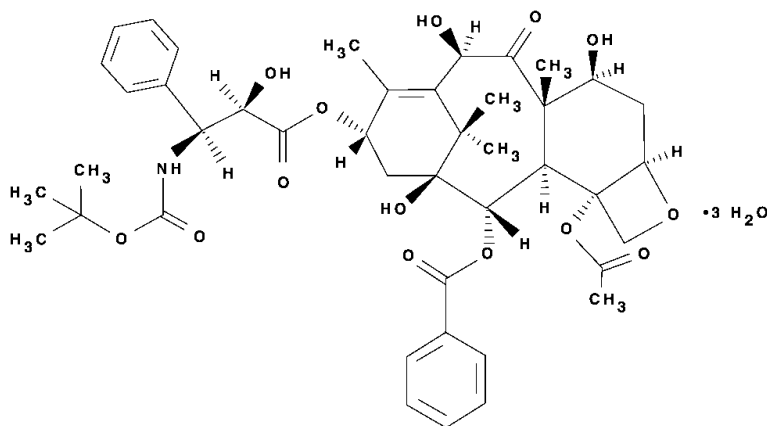
TAXOTERE therapy should not be given to patients with neutrophil counts of < 1500 cells/mm³. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving TAXOTERE.

Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% (2/92) of patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of the TAXOTERE infusion were reported in five patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy. TAXOTERE must not be given to patients who have a history of severe hypersensitivity reactions to TAXOTERE or to other drugs formulated with polysorbate 80 (see **WARNINGS**).

Severe fluid retention occurred in 6.5% (6/92) of patients despite use of a 3-day dexamethasone premedication regimen. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites) (see **PRECAUTIONS**).

DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5 β -20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14} \cdot 3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. TAXOTERE (docetaxel) for Injection Concentrate is a clear yellow to brownish-yellow viscous solution. TAXOTERE is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2.0 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

TAXOTERE for Injection Concentrate requires dilution prior to use. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. The diluent for TAXOTERE contains 13% ethanol in Water for Injection, and is supplied in 1.5 mL (to be used with 20 mg TAXOTERE for Injection Concentrate) and 6.0 mL (to be used with 80 mg TAXOTERE for Injection Concentrate) vials.

CLINICAL PHARMACOLOGY

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

HUMAN PHARMACOKINETICS

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m² in phase I studies. The area under the curve (AUC) was dose proportional following doses of 70-115 mg/m² with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α , β , and γ phases of 4 min, 36 min, and 11.1 hr, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean values for total body clearance and steady state volume of distribution were 21 L/h/m² and 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of 10-90 mg/m² was similar to that of European/American populations dosed at 100 mg/m², suggesting no significant difference in the elimination of docetaxel in the two populations.

A study of ¹⁴C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

A population pharmacokinetic analysis was carried out after TAXOTERE treatment of 535 patients dosed at 100 mg/m². Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase I studies. The pharmacokinetics of docetaxel were not influenced by age or gender and docetaxel total body clearance was not modified by pretreatment with dexamethasone. In patients with clinical chemistry data suggestive of mild to moderate liver function impairment (SGOT and/or SGPT >1.5 times the upper limit of normal [ULN] concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should, in general, not be treated with TAXOTERE.

In vitro studies showed that docetaxel is about 94% protein bound, mainly to α_1 -acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism can be inhibited by CYP3A4 inhibitors, such as ketoconazole, erythromycin, troleandomycin, and nifedipine. Based on *in vitro* findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood concentrations. No clinical studies have been performed to evaluate this finding (see **PRECAUTIONS**).

CLINICAL STUDIES

Breast Cancer: The efficacy and safety of TAXOTERE have been evaluated in locally advanced or metastatic breast cancer after failure of previous chemotherapy (alkylating agent-containing regimens or anthracycline-containing regimens), primarily at a dose of 100 mg/m² given as a 1-hour infusion every 3 weeks, but with some experience at 60 mg/m², in two large randomized trials and a number of smaller single arm studies.

Randomized Trials: In one randomized trial, patients with a history of prior treatment with an anthracycline-containing regimen were assigned to treatment with TAXOTERE or the combination of mitomycin (12 mg/m² every 6 weeks) and vinblastine (6 mg/m² every 3 weeks). 203 patients were randomized to TAXOTERE and 189 to the comparator arm. Most patients had received prior chemotherapy for metastatic disease; only 27 patients on the TAXOTERE arm and 33 patients on the comparator arm entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The following table summarizes the study results:

**Efficacy of TAXOTERE in the Treatment of Breast Cancer Patients
Previously Treated with an Anthracycline-Containing Regimen
(Intent-to-Treat Analysis)**

Efficacy Parameter	Docetaxel (n=203)	Mitomycin/ Vinblastine (n=189)	p-value
Median Survival	11.4 months	8.7 months	p=0.01 Log Rank
Risk Ratio*, Mortality (Docetaxel: Control)	0.73		
95% CI (Risk Ratio)	0.58-0.93		
Median Time to Progression	4.3 months	2.5 months	p=0.01 Log Rank
Risk Ratio*, Progression (Docetaxel: Control)	0.75		
95% CI (Risk Ratio)	0.61-0.94		
Overall Response Rate	28.1%	9.5%	p<0.0001 Chi Square
Complete Response Rate	3.4%	1.6%	

*For the risk ratio, a value less than 1.00 favors docetaxel.

In a second randomized trial, patients previously treated with an alkylating-containing regimen were assigned to treatment with TAXOTERE or doxorubicin (75 mg/m² every 3 weeks). 161 patients were randomized to TAXOTERE and 165 patients to doxorubicin. Approximately one-half of patients had received prior chemotherapy for metastatic disease, and one-half entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The study results are summarized below:

**Efficacy of TAXOTERE in the Treatment of Breast Cancer Patients
Previously Treated with an Alkylating-Containing Regimen
(Intent-to-Treat Analysis)**

Efficacy Parameter	Docetaxel (n=161)	Doxorubicin (n=165)	p-value
Median Survival	14.7 months	14.3 months	p=0.39 Log Rank
Risk Ratio*, Mortality (Docetaxel: Control)	0.89		
95% CI (Risk Ratio)	0.68-1.16		
Median Time to Progression	6.5 months	5.3 months	p=0.45 Log Rank
Risk Ratio*, Progression (Docetaxel: Control)	0.93		
95% CI (Risk Ratio)	0.71-1.16		
Overall Response Rate	45.3%	29.7%	p=0.004 Chi Square
Complete Response Rate	6.8%	4.2%	

*For the risk ratio, a value less than 1.00 favors docetaxel.

Single Arm Studies: TAXOTERE at a dose of 100 mg/m² was studied in six single arm studies involving a total of 309 patients with metastatic breast cancer in whom previous chemotherapy had failed. Among these, 190 patients had anthracycline-resistant breast cancer, defined as progression during an anthracycline-containing chemotherapy regimen for metastatic disease, or relapse during an anthracycline-containing adjuvant regimen. In anthracycline-resistant patients, the overall response rate was 37.9% (72/190; 95% C.I.: 31.0-44.8) and the complete response rate was 2.1%.

TAXOTERE was also studied in three single arm Japanese studies at a dose of 60 mg/m², in 174 patients who had received prior chemotherapy for locally advanced or metastatic breast cancer. Among 26 patients whose best response to an anthracycline had been progression, the response rate was 34.6% (95% C.I.: 17.2-55.7), similar to the response rate in single arm studies of 100 mg/m².

Hematologic and Other Toxicity: Relation to dose and baseline liver chemistry abnormalities. Hematologic and other toxicity is increased at higher doses and in patients with elevated baseline liver function tests (LFTs). In the following tables, adverse drug reactions are compared for three populations: 730 patients with normal LFTs given TAXOTERE at 100 mg/m² in the randomized and single arm studies of metastatic breast cancer after failure of previous chemotherapy; 18 patients in these studies who had abnormal baseline LFTs (defined as SGOT and/or SGPT > 1.5 times ULN concurrent with alkaline phosphatase > 2.5 times ULN); and 174 patients in Japanese studies given TAXOTERE at 60 mg/m² who had normal LFTs.

**Hematologic Adverse Events in Breast Cancer Patients
Previously Treated with Chemotherapy
Treated at TAXOTERE 100 mg/m² with Normal
or Elevated Liver Function Tests or
60 mg/m² with Normal Liver Function Tests**

Adverse Event	TAXOTERE 100 mg/m ²		TAXOTERE 60 mg/m ²
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
Neutropenia			
Any <2000 cells/mm ³	98.4	100	95.4
Grade 4 <500 cells/mm ³	84.4	93.8	74.9
Thrombocytopenia			
Any <100,000 cells/mm ³	10.8	44.4	14.4
Grade 4 <20,000 cells/mm ³	0.6	16.7	1.1
Anemia <11 g/dL	94.6	94.4	64.9
Infection***			
Any	22.5	38.9	1.1
Grade 3 and 4	7.1	33.3	0
Febrile Neutropenia****			
By Patient	11.8	33.3	0
By Course	2.4	8.6	0
Septic Death	1.5	5.6	1.1
Non-Septic Death	1.1	11.1	0

*Normal Baseline LFTs: Transaminases \leq 1.5 times ULN or alkaline phosphatase \leq 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

**Elevated Baseline LFTs: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN

***Incidence of infection requiring hospitalization and/or intravenous antibiotics was 8.5% (n=62) among the 730 patients with normal LFTs at baseline; 7 patients had concurrent grade 3 neutropenia, and 46 patients had grade 4 neutropenia.

****Febrile Neutropenia: For 100 mg/m², ANC grade 4 and fever > 38°C with IV antibiotics and/or hospitalization; for 60 mg/m², ANC grade 3/4 and fever > 38.1°C

**Non-Hematologic Adverse Events in Breast Cancer Patients
Previously Treated with Chemotherapy
Treated at TAXOTERE 100 mg/m² with Normal or Elevated Liver Function Tests or
60 mg/m² with Normal Liver Function Tests**

Adverse Event	TAXOTERE 100 mg/m²		TAXOTERE 60 mg/m²
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
Acute Hypersensitivity Reaction Regardless of Premedication			
Any	13.0	5.6	0.6
Severe	1.2	0	0
Fluid Retention*** Regardless of Premedication			
Any	56.2	61.1	12.6
Severe	7.9	16.7	0
Neurosensory			
Any	56.8	50	19.5
Severe	5.8	0	0
Myalgia	22.7	33.3	3.4
Cutaneous			
Any	44.8	61.1	30.5
Severe	4.8	16.7	0
Asthenia			
Any	65.2	44.4	65.5
Severe	16.6	22.2	0
Diarrhea			
Any	42.2	27.8	NA
Severe	6.3	11.1	
Stomatitis			
Any	53.3	66.7	19.0
Severe	7.8	38.9	0.6

***Normal Baseline LFTs: Transaminases \leq 1.5 times ULN or alkaline phosphatase \leq 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN**

**** Elevated Baseline Liver Function: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN**

*****Fluid Retention includes (by COSTART): edema (peripheral, localized, generalized, lymphedema, pulmonary edema, and edema otherwise not specified) and effusion (pleural, pericardial, and ascites); no premedication given with the 60 mg/m² dose**

NA = not available

Non-Small Cell Lung Cancer (NSCLC): The efficacy and safety of TAXOTERE in non-small cell lung cancer have been evaluated in patients with locally advanced or metastatic disease and a history of prior treatment with a platinum-based chemotherapy regimen. Two randomized, controlled trials established that a TAXOTERE dose of 75 mg/m² was tolerable and yielded a favorable outcome (see below). TAXOTERE at a dose of 100 mg/m², however, was associated with unacceptable hematologic toxicity, infections, and treatment-related mortality and this dose should not be used (see **BOXED WARNING**, **WARNINGS**, and **DOSAGE AND ADMINISTRATION** sections).

One trial (TAX317), randomized patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, no history of taxane exposure, and an ECOG performance status ≤2 to TAXOTERE or best supportive care. The primary endpoint of the study was survival. Patients were initially randomized to TAXOTERE 100 mg/m² or best supportive care, but early toxic deaths at this dose led to a dose reduction to TAXOTERE 75 mg/m². A total of 104 patients were randomized in this amended study to either TAXOTERE 75 mg/m² or best supportive care.

In a second randomized trial (TAX320), 373 patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, and an ECOG performance status ≤2 were randomized to TAXOTERE 75 mg/m², TAXOTERE 100 mg/m² and a treatment in which the investigator chose either vinorelbine 30 mg/m² days 1, 8, and 15 repeated every 3 weeks or ifosfamide 2 g/m² days 1-3 repeated every 3 weeks. Forty percent of the patients in this study had a history of prior paclitaxel exposure. The primary endpoint was survival in both trials. The efficacy data for the TAXOTERE 75 mg/m² arm and the comparator arms are summarized in the table below and in figures 1 and 2 showing the survival curves for the two studies.

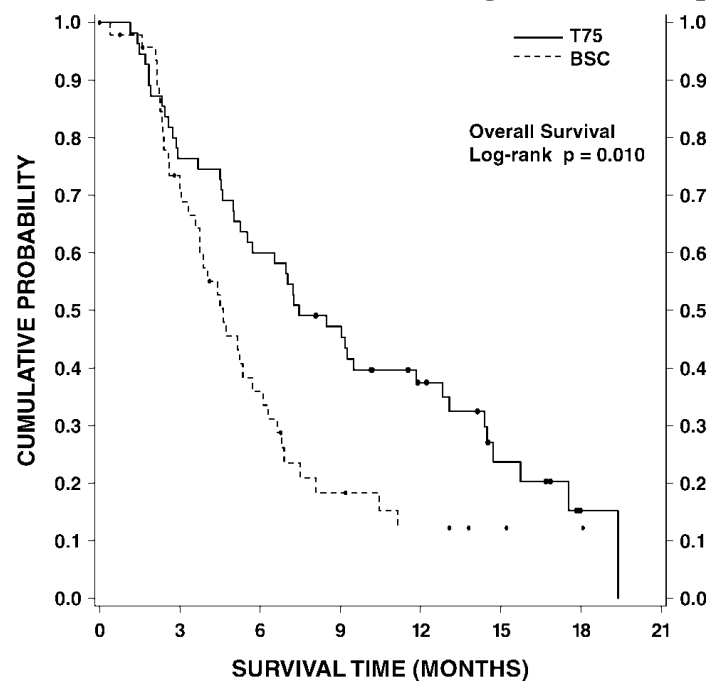
**Efficacy of TAXOTERE in the Treatment of Non-Small Cell Lung
Cancer Patients Previously Treated with a Platinum-Based
Chemotherapy Regimen (Intent-to-Treat Analysis)**

	TAX317		TAX320	
	Docetaxel 75 mg/m² n=55	Best Supportive Care/75 n=49	Docetaxel 75 mg/m² n=125	Control (V/I) n=123
Overall Survival Log-rank Test	p=0.01		p=0.13	
Risk Ratio ^{††} , Mortality (Docetaxel: Control) 95% CI (Risk Ratio)	0.56 (0.35, 0.88)		0.82 (0.63, 1.06)	
Median Survival 95% CI	7.5 months* (5.5, 12.8)	4.6 months (3.7, 6.1)	5.7 months (5.1, 7.1)	5.6 months (4.4, 7.9)
% 1-year Survival 95% CI	37%* [†] (24, 50)	12% (2, 23)	30%* [†] (22, 39)	20% (13, 27)
Time to Progression 95% CI	12.3 weeks* (9.0, 18.3)	7.0 weeks (6.0, 9.3)	8.3 weeks (7.0, 11.7)	7.6 weeks (6.7, 10.1)
Response Rate 95% CI	5.5% (1.1, 15.1)	Not Applicable	5.7% (2.3, 11.3)	0.8% (0.0, 4.5)

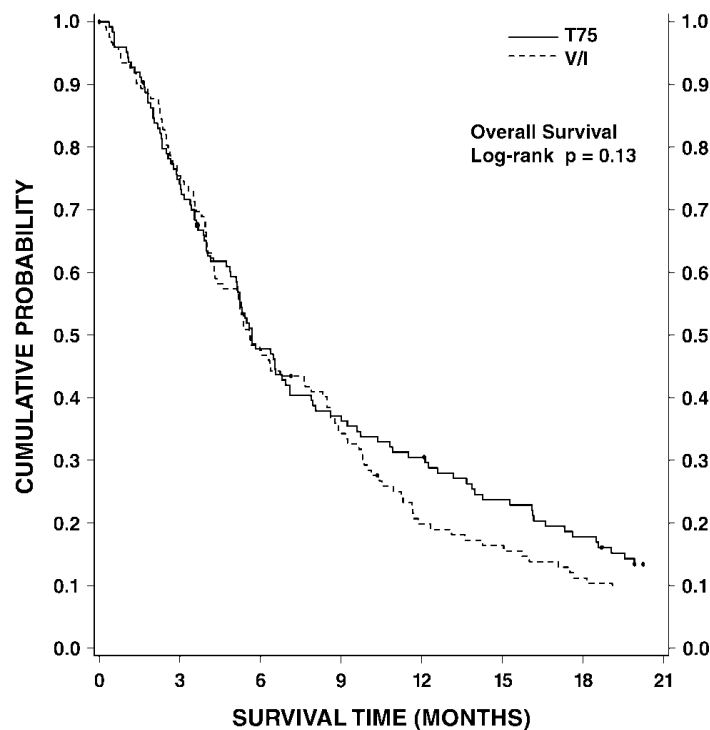
* p≤0.05; [†] uncorrected for multiple comparisons; ^{††} a value less than 1.00 favors docetaxel.

Only one of the two trials (TAX317) showed a clear effect on survival, the primary endpoint; that trial also showed an increased rate of survival to one year. In the second study (TAX320) the rate of survival at one year favored TAXOTERE 75 mg/m².

TAX317 Survival K-M Curves - Docetaxel 75 mg/m² vs. Best Supportive Care



TAX320 Survival K-M Curves - Docetaxel 75 mg/m² vs. Vinorelbine or Ifosfamide Control



Patients treated with TAXOTERE at a dose of 75 mg/m² experienced no deterioration in performance status and body weight relative to the comparator arms used in these trials.

INDICATIONS AND USAGE

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

Non-Small Cell Lung Cancer: 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.

CONTRAINDICATIONS

TAXOTERE is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80.

TAXOTERE should not be used in patients with neutrophil counts of <1500 cells/mm³.

WARNINGS

TAXOTERE should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Toxic Deaths

Breast Cancer: TAXOTERE administered at 100 mg/m² was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function (SGOT and/or SGPT > 1.5 times ULN together with AP > 2.5 times ULN). Among patients dosed at 60 mg/m², mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Non-Small Cell Lung Cancer: TAXOTERE administered at a dose of 100 mg/m² in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m² dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m² dose level, 3 of 5 patients had a PS of 2 at study entry (see **BOXED WARNING**, **CLINICAL STUDIES**, and **DOSAGE AND ADMINISTRATION** sections).

Premedication Regimen: All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (*e.g.*, 8 mg BID) for 3 days starting 1 day prior to TAXOTERE to reduce the severity of fluid retention and hypersensitivity reactions (see **DOSAGE AND ADMINISTRATION** section). This regimen was evaluated in 92 patients with metastatic breast cancer previously treated with chemotherapy given TAXOTERE at a dose of 100 mg/m² every 3 weeks.

Hypersensitivity Reactions: Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% of the 92 patients premedicated with 3-day corticosteroids. Hypersensitivity reactions requiring discontinuation of the TAXOTERE infusion were reported in 5 out of 1260 patients with various tumor types who did not receive premedication, but in 0/92 patients premedicated with 3-day corticosteroids. Patients with a history of severe hypersensitivity reactions should not be rechallenged with TAXOTERE.

Hematologic Effects: Neutropenia (< 2000 neutrophils/mm³) occurs in virtually all patients given 60-100 mg/m² of TAXOTERE and grade 4 neutropenia (< 500 cells/mm³) occurs in 85% of patients given 100 mg/m² and 75% of patients given 60 mg/m². Frequent monitoring of blood

counts is, therefore, essential so that dose can be adjusted. TAXOTERE should not be administered to patients with neutrophils < 1500 cells/mm³.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m² but was very uncommon in patients given 60 mg/m². Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related and are described in **CLINICAL STUDIES**.

Three breast cancer patients with severe liver impairment (bilirubin > 1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia.

Hepatic Impairment: (see **BOXED WARNING**).

Fluid Retention: (see **BOXED WARNING**).

Pregnancy: TAXOTERE can cause fetal harm when administered to pregnant women. Studies in both rats and rabbits at doses ≥ 0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m² basis), administered during the period of organogenesis, have shown that TAXOTERE is embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity.

There are no adequate and well-controlled studies in pregnant women using TAXOTERE. If TAXOTERE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TAXOTERE.

PRECAUTIONS

General: Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

Hematologic Effects: In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOTERE. Patients should not be retreated with subsequent cycles of TAXOTERE until neutrophils recover to a level > 1500 cells/mm³ and platelets recover to a level $> 100,000$ cells/mm³.

A 25% reduction in the dose of TAXOTERE is recommended during subsequent cycles following severe neutropenia (< 500 cells/mm³) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a TAXOTERE cycle (see **DOSAGE AND ADMINISTRATION** section).

Hypersensitivity Reactions: Hypersensitivity reactions may occur within a few minutes following initiation of a TAXOTERE infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. More severe reactions, however, require the immediate discontinuation of TAXOTERE and aggressive therapy. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of TAXOTERE (see **BOXED WARNING** and **WARNINGS: Premedication Regimen**).

Cutaneous: Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended (see **DOSAGE AND ADMINISTRATION** section). The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued TAXOTERE due to skin toxicity.

Fluid Retention: Severe fluid retention has been reported following TAXOTERE therapy (see **BOXED WARNING** and **WARNINGS: Premedication Regimen**). Patients should be premedicated with oral corticosteroids prior to each TAXOTERE administration to reduce the incidence and severity of fluid retention (see **DOSAGE AND ADMINISTRATION** section).

Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m². 9.8% (9/92) of patients discontinued treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m². Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the last infusion of TAXOTERE to resolution (range: 0 to 42+ weeks). Patients developing peripheral edema may be treated with standard measures, *e.g.*, salt restriction, oral diuretic(s).

Neurologic: Severe neurosensory symptoms (paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued (see **DOSAGE AND ADMINISTRATION** section). Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

Asthenia: Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

Information for Patients: For additional information, see the accompanying Patient Information Leaflet.

Drug Interactions: There have been no formal clinical studies to evaluate the drug interactions of TAXOTERE with other medications. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. Caution should be exercised with these drugs when treating patients receiving TAXOTERE as there is a potential for a significant interaction.

Carcinogenicity, Mutagenicity, Impairment of Fertility: No studies have been conducted to assess the carcinogenic potential of TAXOTERE. TAXOTERE has been shown to be clastogenic in the *in vitro* chromosome aberration test in CHO-K₁ cells and in the *in vivo* micronucleus test in the mouse, but it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assays. TAXOTERE produced no impairment of fertility in rats when administered in multiple IV doses of up to 0.3 mg/kg (about 1/50 the recommended human dose on a mg/m² basis), but decreased testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at IV doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/3 and 1/15 the recommended human dose on a mg/m² basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

Pregnancy: Pregnancy Category D (see **WARNINGS** section).

Nursing Mothers: It is not known whether TAXOTERE is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse

reactions in nursing infants from TAXOTERE, mothers should discontinue nursing prior to taking the drug.

Pediatric Use: The safety and effectiveness of TAXOTERE in pediatric patients have not been established.

ADVERSE REACTIONS

The adverse reactions are described separately for TAXOTERE 100 mg/m², the maximum dose approved for breast cancer, and 75 mg/m², the dose approved for advanced non-small cell lung carcinoma after prior platinum-based chemotherapy.

TAXOTERE 100 mg/m²: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received TAXOTERE administered at 100 mg/m² as a 1-hour infusion every 3 weeks: 2045 patients with various tumor types and normal baseline liver function tests; the subset of 965 patients with locally advanced or metastatic breast cancer, both previously treated and untreated with chemotherapy, who had normal baseline liver function tests; and an additional 61 patients with various tumor types who had abnormal liver function tests at baseline. These reactions were described using COSTART terms and were considered possibly or probably related to TAXOTERE. At least 95% of these patients did not receive hematopoietic support. The safety profile is generally similar in patients receiving TAXOTERE for the treatment of breast cancer and in patients with other tumor types.

Summary of Adverse Events in Patients Receiving TAXOTERE at 100 mg/m²

Adverse Event	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
Hematologic			
Neutropenia			
<2000 cells/mm ³	95.5	96.4	98.5
<500 cells/mm ³	75.4	87.5	85.9
Leukopenia			
<4000 cells/mm ³	95.6	98.3	98.6
<1000 cells/mm ³	31.6	46.6	43.7
Thrombocytopenia			
<100,000 cells/mm ³	8.0	24.6	9.2
Anemia			
<11 g/dL	90.4	91.8	93.6
<8 g/dL	8.8	31.1	7.7
Febrile Neutropenia***	11.0	26.2	12.3
Septic Death	1.6	4.9	1.4
Non-Septic Death	0.6	6.6	0.6
Infections			
Any	21.6	32.8	22.2
Severe	6.1	16.4	6.4

Fever in Absence of Infection			
Any	31.2	41.0	35.1
Severe	2.1	8.2	2.2
Hypersensitivity Reactions			
Regardless of Premedication			
Any	21.0	19.7	17.6
Severe	4.2	9.8	2.6
With 3-day Premedication	n=92	n=3	n=92
Any	15.2	33.3	15.2
Severe	2.2	0	2.2
Fluid Retention			
Regardless of Premedication			
Any	47.0	39.3	59.7
Severe	6.9	8.2	8.9
With 3-day Premedication	n=92	n=3	n=92
Any	64.1	66.7	64.1
Severe	6.5	33.3	6.5
Neurosensory			
Any	49.3	34.4	58.3
Severe	4.3	0	5.5
Cutaneous			
Any	47.6	54.1	47.0
Severe	4.8	9.8	5.2
Nail Changes			
Any	30.6	23.0	40.5
Severe	2.5	4.9	3.7
Gastrointestinal			
Nausea	38.8	37.7	42.1
Vomiting	22.3	23.0	23.4
Diarrhea	38.7	32.8	42.6
Severe	4.7	4.9	5.5
Stomatitis			
Any	41.7	49.2	51.7
Severe	5.5	13.0	7.4
Alopecia	75.8	62.3	74.2
Asthenia			
Any	61.8	52.5	66.3
Severe	12.8	24.6	14.9
Myalgia			
Any	18.9	16.4	21.1
Severe	1.5	1.6	1.8

Arthralgia	9.2	6.6	8.2
Infusion Site Reactions	4.4	3.3	4.0

***Normal Baseline LFTs: Transaminases \leq 1.5 times ULN or alkaline phosphatase \leq 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN**

****Elevated Baseline LFTs: SGOT and/or SGPT > 1.5 times ULN concurrent with alkaline phosphatase > 2.5 times ULN**

*****Febrile Neutropenia: ANC grade 4 with fever > 38°C with IV antibiotics and/or hospitalization**

Hematologic: (see **WARNINGS**). Reversible marrow suppression was the major dose-limiting toxicity of TAXOTERE. The median time to nadir was 7 days, while the median duration of severe neutropenia (<500 cells/mm³) was 7 days. Among 2045 patients with solid tumors and normal baseline LFTs, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles.

Febrile neutropenia (<500 cells/mm³ with fever > 38°C with IV antibiotics and/or hospitalization) occurred in 11% of patients with solid tumors, in 12.3% of patients with metastatic breast cancer, and in 9.8% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Severe infectious episodes occurred in 6.1% of patients with solid tumors, in 6.4% of patients with metastatic breast cancer, and in 5.4% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Thrombocytopenia (<100,000 cells/mm³) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity Reactions: Severe hypersensitivity reactions are discussed in the **BOXED WARNING**, **WARNINGS**, and **PRECAUTIONS** sections. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after discontinuing the infusion and appropriate therapy.

Fluid Retention: (see **BOXED WARNING**, **WARNINGS: Premedication Regimen**, and **PRECAUTIONS** sections).

Cutaneous: Severe skin toxicity is discussed in **PRECAUTIONS**. Reversible cutaneous reactions characterized by a rash including localized eruptions, mainly on the feet and/or hands, but also on the arms, face, or thorax, usually associated with pruritus, have been observed. Eruptions generally occurred within 1 week after TAXOTERE infusion, recovered before the next infusion, and were not disabling.

Severe nail disorders were characterized by hypo- or hyperpigmentation, and occasionally by onycholysis (in 0.8% of patients with solid tumors) and pain.

Neurologic: (see **PRECAUTIONS**).

Gastrointestinal: Gastrointestinal reactions (nausea and/or vomiting and/or diarrhea) were generally mild to moderate. Severe reactions occurred in 3-5% of patients with solid tumors and to a similar extent among metastatic breast cancer patients. The incidence of severe reactions was 1% or less for the 92 breast cancer patients premedicated with 3-day corticosteroids.

Severe stomatitis occurred in 5.5% of patients with solid tumors, in 7.4% of patients with metastatic breast cancer, and in 1.1% of the 92 breast cancer patients premedicated with 3-day corticosteroids.

Cardiovascular: Hypotension occurred in 2.8% of patients with solid tumors; 1.2% required treatment. Clinically meaningful events such as heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension occurred rarely. 8.1% (7/86)

of metastatic breast cancer patients receiving TAXOTERE 100 mg/m² in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF by ≥ 10% associated with a drop below the institutional lower limit of normal.

Infusion Site Reactions: Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, or swelling of the vein.

Hepatic: In patients with normal LFTs at baseline, bilirubin values greater than the ULN occurred in 8.9% of patients. Increases in SGOT or SGPT > 1.5 times the ULN, or alkaline phosphatase > 2.5 times ULN, were observed in 18.9% and 7.3% of patients, respectively. While on TAXOTERE, increases in SGOT and/or SGPT > 1.5 times ULN concomitant with alkaline phosphatase > 2.5 times ULN occurred in 4.3% of patients with normal LFTs at baseline. (Whether these changes were related to the drug or underlying disease has not been established.)

TAXOTERE 75 mg/m²: Treatment emergent adverse drug reactions are shown below. Included in this table are safety data for a total of 176 patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who were treated in two randomized, controlled trials. These reactions were described using NCI Common Toxicity Criteria regardless of relationship to study treatment, except for the hematologic toxicities or otherwise noted.

**Treatment Emergent Adverse Events in Non-Small Cell Lung Cancer Patients
Receiving TAXOTERE Regardless of Relationship to Treatment***

Adverse Event	TAXOTERE 75 mg/m² n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Neutropenia			
Any	84.1	14.3	83.2
Grade 3/4	65.3	12.2	57.1
Leukopenia			
Any	83.5	6.1	89.1
Grade 3/4	49.4	0	42.9
Thrombocytopenia			
Any	8.0	0	7.6
Grade 3/4	2.8	0	1.7
Anemia			
Any	91.0	55.1	90.8
Grade 3/4	9.1	12.2	14.3
Febrile Neutropenia**	6.3	NA [†]	0.8
Infection			
Any	33.5	28.6	30.3
Grade 3/4	10.2	6.1	9.2
Treatment Related Mortality	2.8	NA [†]	3.4
Hypersensitivity Reactions			
Any	5.7	0	0.8
Grade 3/4	2.8	0	0

Fluid Retention			
Any	33.5	ND ^{††}	22.7
Severe	2.8		3.4
Neurosensory			
Any	23.3	14.3	28.6
Grade 3/4	1.7	6.1	5.0
Neuromotor			
Any	15.9	8.2	10.1
Grade 3/4	4.5	6.1	3.4
Skin			
Any	19.9	6.1	16.8
Grade 3/4	0.6	2.0	0.8
Gastrointestinal			
Nausea			
Any	33.5	30.6	31.1
Grade 3/4	5.1	4.1	7.6
Vomiting			
Any	21.6	26.5	21.8
Grade 3/4	2.8	2.0	5.9
Diarrhea			
Any	22.7	6.1	11.8
Grade 3/4	2.8	0	4.2
Alopecia	56.3	34.7	49.6
Asthenia			
Any	52.8	57.1	53.8
Severe***	18.2	38.8	22.7
Stomatitis			
Any	26.1	6.1	7.6
Grade 3/4	1.7	0	0.8
Pulmonary			
Any	40.9	49.0	45.4
Grade 3/4	21.0	28.6	18.5
Nail Disorder			
Any	11.4	0	1.7
Severe***	1.1	0	0
Myalgia			
Any	6.3	0	2.5
Severe***	0	0	0
Arthralgia			
Any	3.4	2.0	1.7
Severe***	0	0	0.8

Taste Perversion			
Any	5.7	0	0
Severe***	0.6	0	0

***Normal Baseline LFTs: Transaminases \leq 1.5 times ULN or alkaline phosphatase \leq 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN**

****Febrile Neutropenia: ANC grade 4 with fever $> 38^{\circ}\text{C}$ with IV antibiotics and/or hospitalization**

*****COSTART term and grading system**

†Not Applicable; †† Not Done

Post-marketing Experiences

The following adverse events have been identified from clinical trials and/or post-marketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.

Body as a whole: diffuse pain, chest pain, radiation recall phenomenon

Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction

Cutaneous: rare cases of bullous eruption such as erythema multiforme or Stevens-Johnson syndrome. Multiple factors may have contributed to the development of these effects.

Gastrointestinal: abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, ischemic colitis, colitis, intestinal obstruction, ileus, neutropenic enterocolitis and dehydration as a consequence to gastrointestinal events have been reported.

Hematologic: bleeding episodes

Hepatic: rare cases of hepatitis have been reported.

Neurologic: confusion, rare cases of seizures or transient loss of consciousness have been observed, sometimes appearing during the infusion of the drug.

Ophthalmologic: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis.. Excessive tearing which may be attributable to lacrimal duct obstruction has been reported.

Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome, interstitial pneumonia. Pulmonary fibrosis has been rarely reported.

Urogenital: renal insufficiency

OVERDOSAGE

There is no known antidote for TAXOTERE overdose. In case of overdose, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdose include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

In two reports of overdose, one patient received 150 mg/m^2 and the other received 200 mg/m^2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.

In mice, lethality was observed following single IV doses that were $\geq 154 \text{ mg/kg}$ (about 4.5 times the recommended human dose on a mg/m^2 basis); neurotoxicity associated with paralysis, non-extension of hind limbs, and myelin degeneration was observed in mice at 48 mg/kg (about 1.5 times the recommended human dose on a mg/m^2 basis). In male and female rats, lethality was

observed at a dose of 20 mg/kg (comparable to the recommended human dose on a mg/m² basis) and was associated with abnormal mitosis and necrosis of multiple organs.

DOSAGE AND ADMINISTRATION

Breast Cancer: The recommended dose of TAXOTERE is 60-100 mg/m² administered intravenously over 1 hour every 3 weeks.

Non-Small Cell Lung Cancer: The recommended dose of TAXOTERE is 75 mg/m² administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m² in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials (see **BOXED WARNING, WARNINGS** and **CLINICAL STUDIES** sections).

Premedication Regimen: All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to TAXOTERE administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (see **BOXED WARNING, WARNINGS**, and **PRECAUTIONS** sections).

Dosage Adjustments During Treatment

Breast Cancer: Patients who are dosed initially at 100 mg/m² and who experience either febrile neutropenia, neutrophils < 500 cells/mm³ for more than 1 week, or severe or cumulative cutaneous reactions during TAXOTERE therapy should have the dosage adjusted from 100 mg/m² to 75 mg/m². If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m² to 55 mg/m² or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m² and who do not experience febrile neutropenia, neutrophils < 500 cells/mm³ for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during TAXOTERE therapy may tolerate higher doses. Patients who develop ≥ grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Non-Small Cell Lung Cancer: Patients who are dosed initially at 75 mg/m² and who experience either febrile neutropenia, neutrophils < 500 cells/mm³ for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during TAXOTERE treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m². Patients who develop ≥ grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Special Populations:

Hepatic Impairment: Patients with bilirubin > ULN should generally not receive TAXOTERE. Also, patients with SGOT and/or SGPT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN should generally not receive TAXOTERE.

Children: The safety and effectiveness of docetaxel in pediatric patients below the age of 16 years have not been established.

Elderly: No dosage adjustments are required for use in elderly.

PREPARATION AND ADMINISTRATION PRECAUTIONS

TAXOTERE is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXOTERE solutions. The use of gloves is recommended. Please refer to **Handling and Disposal** section.

If TAXOTERE concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If TAXOTERE concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

TAXOTERE for Injection Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. **Note:** Both the TAXOTERE for Injection Concentrate and the diluent vials contain an overfill.

A. Preparation of the Initial Diluted Solution

1. Remove the appropriate number of vials of TAXOTERE for Injection Concentrate and diluent (13% Ethanol in Water for Injection) from the refrigerator. Allow the vials to stand at room temperature for approximately 5 minutes.
2. Aseptically withdraw the entire contents of the appropriate diluent vial into a syringe by partially inverting the vial, and transfer it to the appropriate vial of TAXOTERE for Injection Concentrate. **If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.**
3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4. The initial diluted TAXOTERE solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

B. Preparation of the Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted TAXOTERE solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.

If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.

2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE for Injection initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

The final TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

Contact of the TAXOTERE concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TAXOTERE dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Stability: TAXOTERE infusion solution, if stored between 2 and 25°C (36 and 77°F) is stable for 4 hours. Fully prepared TAXOTERE infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour i.v. administration).

HOW SUPPLIED

TAXOTERE for Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in Water for Injection) vial. The following strengths are available:

TAXOTERE 80 MG (NDC 0075-8001-80)

TAXOTERE (docetaxel) 80 mg Concentrate for Infusion: 80 mg docetaxel in 2 mL polysorbate 80 and diluent for TAXOTERE 80 mg. 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton.

TAXOTERE 20 MG (NDC 0075-8001-20)

TAXOTERE (docetaxel) 20 mg Concentrate for Infusion: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for TAXOTERE 20 mg. 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton.

Storage: Store between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published¹⁻⁷. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. OSHA Work-Practice Guidelines for Controlling Occupational Exposure to Hazardous Drugs. *Am J Health-Syst Pharm.* 1996; 53: 1669-1685.
2. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm.* 1990; 47(95): 1033-1049.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA.* 1985; 253 (11): 1590-1592.
4. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
5. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffry, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
6. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Austr.* 1983; 426-428.
7. Jones, RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from the Mt. Sinai Medical Center. *CA-A Cancer Journal for Clinicians.* 1983; Sept/Oct: 258-263.

Prescribing Information as of September 2002

Manufactured by Aventis Pharma Ltd.
Dagenham, Essex RM10 7XS
United Kingdom

Manufactured for
Aventis Pharmaceuticals Products Inc.
Bridgewater, NJ 08807 USA
www.aventispharma-us.com

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020449Orig1s017

OTHER REVIEW(S)

PROJECT MANAGER REVIEW OF LABELING

NDA 20-449/S-017

Drug: Taxotere (docetaxel) Injection, 20mg and 80mg

Applicant: Aventis Pharmaceutical Products, Inc.

Submission Date: January 9, 2002 CBE

Receipt Date: January 10, 2002

Additional Submissions: May 28, June 5 and 28, 2002

FDA Facsimiles: March 27, May 29 and June 20, 2002

BACKGROUND:

On January 31, 2001, the sponsor submission dated July 28, 2000 containing FPL for supplement 011 was acknowledged and retained.

Aventis submitted a "Changes Being Effected" (CBE) labeling supplement (S-017) dated January 9, 2002 to provide for additions to the ADVERSE REACTIONS section, Post-Marketing Experience subsection of the package insert.

The following new adverse events include: anorexia, bleeding episodes, conjunctivitis, and lacrimation or lacrimation with or without conjunctivitis associated with the use of Taxotere.

Additionally, the following new events, (b) (4) have been added to the ADVERSE REACTIONS section, Post-marketing Experience subsection: bullous eruption such as erythema multiforme or Stevens-Johnson syndrome, ischemic colitis, colitis, hepatitis, transient loss of consciousness and lacrimal duct obstruction resulting in excessive tearing.

DOCUMENTS REVIEWED:

I compared the approved July 28, 2000 FPL against the FPL in the CBE supplement dated January 9, 2002.

REVIEW:

The following changes were identified:

1. ADVERSE REACTIONS section, Ongoing Evaluations subsection:
(see attachment 1 for the tracked changes version of this section in the package insert)

- The "**Ongoing Evaluation**" subsection has been changed to "**Post-marketing Experiences**". The introductory paragraph "The following serious adverse events of uncertain relationship to TAXOTERE have been reported." has been replaced with " The following adverse events have been identified from clinical trials and/or post-marketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made. "
- In the subsection **Body as a Whole**, the event "Abdominal pain" has been moved to the **Gastrointestinal** subsection.
- The subsection **Cutaneous** has been added with the following statement "rare cases of bullous eruption such as erythema multiforme or Stevens-Johnson syndrome. Multiple factors may have contributed to the development of these effects. "
- The subsection **Digestive** has been renamed **Gastrointestinal**. The event "abdominal pain " has been relocated to this subsection from the subsection **Body as a Whole**. The event "anorexia" was added.

The following events that currently are reported as "of uncertain relationship to Taxotere" (b) (4): "dehydration as a consequence to gastrointestinal events" (currently, this event is listed as "dehydration in relation to digestive disorders"), "gastrointestinal perforation", "intestinal obstruction", "ileus", and "neutropenic enterocolitis ". Additionally, the following new events (b) (4) have been added "ischemic colitis" and "colitis". The following statement has been inserted to reflect these revisions:

(b) (4)
 " "

Medical Reviewer comment:

The sponsor was requested to remove the reference to (b) (4) in the following sentence to read as:

(b) (4)

The sponsor proposed the following alternate wording and the reviewer concurs with the change:

"Gastrointestinal: abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, ischemic colitis, colitis, intestinal obstruction, ileus, neutropenic

enterocolitis and dehydration as a consequence to gastrointestinal events have been reported."

- The subsection **Hematologic** has been added to include a new adverse event "bleeding episodes".
- The subsection **Hepatic** has been added to include the adverse event "rare cases of hepatitis".
- The subsection **Nervous** has been changed to **Neurologic**. The adverse event "seizures" has been changed to "rare cases of seizures". The event "transient loss of consciousness have been observed, sometimes during the infusion of the drug" has been added.
- The subsection **Ophthalmologic** has been added and contained the following events: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis. (b) (4) The addition of this event has been described in the following statement: " (b) (4)

Medical Reviewer comment:

The sponsor was requested to change the following sentence to read:

Excessive tearing which may be attributable to lacrimal duct obstruction has been reported.

These changes are acceptable; however, the sponsor should make the two labeling changes to the Gastrointestinal and Ophthalmologic subsections at the next printing.

Medical Reviewer Concurrence *[See appended electronic signature page]*

Ramzi Dagher, MD

In addition to the safety changes, the following editorial revisions have been made:

- The revision date and the designation "IN-5493H" have been deleted and the date of the most recent revision "Prescribing Information as of (b) (4)" has been added in accordance with to 21 CFR § 201.56(e).
- The following manufacturing information has been added "Manufactured by Aventis Pharma (b) (4) Ltd, Dagenham, Essex RM10 7XS, United Kingdom"

- The Aventis Pharmaceuticals website has been added
[REDACTED] (b) (4)
- The Aventis Pharmaceuticals Products Inc. address has been changed from "Collegeville, PA 19426" to "Bridgewater, NJ 08807"

These changes are acceptable.

The following editorial revisions have been made to the Patient Information Leaflet

- The revision date has been changed from "[REDACTED] (b) (4) " to "[REDACTED] (b) (4) "and the designation "IN-5493H" has been deleted.
- The Aventis Pharmaceuticals Products Inc. address has been changed from "Collegeville, PA 19426" to "Bridgewater, NJ 0880 7, USA "
- The Aventis Pharmaceuticals website has been added "www.aventispharmna-us.com"

These changes are acceptable.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

This supplement should be approved after concurrence from the medical reviewer and the changes to the **Gastrointestinal** and **Ophthalmologic** subsections should be requested to occur at the next printing.

____ *{See appended electronic signature page}*____
Ann Staten, Regulatory Health Project Manager

____ *{See appended electronic signature page}*____
Dotti Pease, Chief, Project Manager Staff

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/s/

Ann Staten
7/3/02 11:19:35 AM
CSO

Ramzi Dagher
7/3/02 11:35:53 AM
MEDICAL OFFICER

Dotti Pease
7/9/02 12:40:49 PM
CSO

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020449Orig1s017

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Marion Ceruzzi, Ph.D., Aventis

From: Ann Staten, Project Manager

Fax: 908-304-6317

Fax: 301-827-4590

Phone: 908-231-5828

Phone: 301-594-5770

Pages: 1

Date: June 20, 2002

Re: NDA 20-449/s-017

☐ **Urgent**

☐ **For Review**

☐ **Please Comment**

☐ **Please Reply**

☐ **Please Recycle**

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Dear Marion:

Please refer to your submission dated June 5, 2002.

Thank you for your clarification with respect to the typographical error related to comment #1. We still have the position that (b) (4) should be removed from the beginning of the paragraph under discussion since (b) (4).

Please call me with any questions.

Sincerely,

Ann

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/s/

Ann Staten

6/20/02 02:10:55 PM

CSO

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Martha Propsner, Aventis

From: Ann Staten, Project Manager

Fax: 908-304-6317

Fax: 301-827-4590

Phone: 908-231-5828

Phone: 301-594-5770

Pages: 1

Date: May 29, 2002

Re: NDA 20-449/s-017

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Dear Marion:

Please refer to your submission dated May 28, 2002. We have the following request:

1. [REDACTED] (b) (4)
Please clarify.
2. With regard to your proposal for wording regarding excessive tearing, we suggest removing the reference to [REDACTED] (b) (4)
We propose the following "Excessive tearing which may be attributable to lacrimal duct obstruction has been reported."

Please call me with any questions.

Sincerely,

Ann

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/s/

Ann Staten

5/29/02 03:22:25 PM

CSO

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Martha Propsner, Aventis

From: Ann Staten, Project Manager

Fax: 908-231-3716

Fax: 301-827-4590

Phone: 908-231-3841

Phone: 301-594-5770

Pages: 1

Date: March 27, 2002

Re: NDA 20-449/s-017

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

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Dear Martha:

We have completed our review of the CBE supplement and have the following request for changes to be made at the next printing. Please let me know if you agree.

Under **Post-marketing Experiences**, subsection **Gastrointestinal**, replace the last sentence (b) (4) " with the following:

(b) (4)

Under **Post-marketing Experiences**, subsection **Ophthalmologic**, replace the last sentence (b) (4) " with the following:

(b) (4)

Sincerely,

Ann

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/s/

Ann Staten
3/27/02 09:22:51 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-449/S-017

CBE-0 SUPPLEMENT

Aventis Pharmaceuticals Products, Inc.
Route 202-206
PO Box 6800
Bridgewater, NJ 08807-2800

Attention: Martha Propsner, US Liaison
Drug Regulatory Affairs

Dear Ms. Propsner:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Taxotere® (docetaxel) for Injection Concentrate

NDA Number: 20-449

Supplement number: S-017

Date of supplement: January 9, 2002

Date of receipt: January 10, 2002

This supplemental application was submitted as a "Supplement - Changes Being Effected." The appropriateness of reporting the proposed changes as changes being effected is under review.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 11, 2002 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
1451 Rockville Pike
Rockville, Maryland 20852

If you have any question, call Ann Staten, Regulatory Project Manager, at (301) 594-5770.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Ann Staten
1/16/02 03:30:45 PM
Signed for Dottì Pease