CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-449/S054

Trade Name: Taxotere

Generic Name: docetaxel

Sponsor: Sanofi-Aventis

Approval Date: August 2, 2010

Indications:

TAXOTERE is a microtubule inhibitor indicated for:

• Breast Cancer: single agent for locally advanced or metastatic after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive

• Non-Small Cell Lung Cancer: single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC

• Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer

• Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction

• Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN (1.5)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449/S054

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020449/S-054

APPROVAL LETTER

Linda Gustavson, Ph.D., RAC.
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U.S. Assoc. Therapeutic Axis Head, Oncology
Corporate Regulatory Affairs
sanofi-aventis US Inc.
Mail code: BX4-212C
200 Crossing Blvd.
Bridgewater, NJ 08890-0890

Dear Dr. Gustavson:

Please refer to your Supplemental New Drug Application (sNDA) dated December 22, 2008, received December 22, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Taxotere (docetaxel) Injection Concentrate, 20 mg and 80 mg.

We acknowledge receipt of your amendments dated September 14 and December 1, 2009; January 8, 14, and 20; April 6, 26, and 29; May 18; June 15, and 25; and July 21, and 27; and August 2, 2010.

The September 14, 2009, submission constituted a complete response to our June 22, 2009, action letter.

This "Changes Being Effected" supplemental new drug application provides for the approval of a new one-vial formulation in addition to the already approved two-vial marketed formulation and associated labeling (Package Insert, Patient Package Insert, Carton and Container).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

We acknowledge your August 2, 2010, submission containing final printed carton and container labels.

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 Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Deputy Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures:
Package Insert, Patient Package Insert
Carton and Container Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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

/s/

AMNA IBRAHIM
08/02/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449/S054

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TAXOTERE safely and effectively. See full prescribing information for TAXOTERE.

TAXOTERE (docetaxel) Injection Concentrate, Intravenous Infusion (IV). Initial U.S. Approval: 1996

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, and FLUID RETENTION
See full prescribing information for complete boxed warning

- **Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with NSCLC and prior platinum-based therapy receiving TAXOTERE at 100 mg/m^2 (5.1)**
- **Should not be given if bilirubin > ULN, or if AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. LFT elevations increase risk of severe or life-threatening complications. Obtain LFTs before each treatment cycle (8.6)**
- **Should not be given if neutrophil counts are < 1500 cells/mm^3. Obtain frequent blood counts to monitor for neutropenia (4)**
- **Severe hypersensitivity, including very rare fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of TAXOTERE and administration of appropriate therapy (5.4)**
- **Contraindicated if history of severe hypersensitivity reactions to TAXOTERE or to drugs formulated with polysorbate 80 (4)**
- **Severe fluid retention may occur despite dexamethasone (5.5)**

----------RECENT MAJOR CHANGES----------
- Dosage and administration (2.8, 2.9) 08/2010
- Contraindications (4) 05/2010
- Warnings and Precautions (5.2) 05/2010
- Drug interactions (7) 04/2010

----------INDICATIONS AND USAGE----------
TAXOTERE is a microtubule inhibitor indicated for:

- **Breast Cancer (BC)**: single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC (1.1)
- **Non-Small Cell Lung Cancer (NSCLC)**: single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC (1.2)
- **Hormone Refractory Prostate Cancer (HRPC)**: with prednisone in androgen independent (hormone refractory) metastatic prostate cancer (1.3)
- **Gastric Adenocarcinoma (GC)**: with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction (1.4)
- **Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN)**: with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN (1.5)

----------DOSAGE AND ADMINISTRATION----------
Administer in a facility equipped to manage possible complications (e.g., anaphylaxis).Administer intravenously (IV) over 1 hr every 3 weeks. PVC equipment is not recommended.

- BC locally advanced or metastatic: 60 mg/m^2 to 100 mg/m^2 single agent (2.1)
- BC adjuvant: 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles (2.1)
- NSCLC: after platinum therapy failure: 75 mg/m^2 single agent (2.2)
- NSCLC: chemotherapy-naive: 75 mg/m^2 followed by cisplatin 75 mg/m^2 (2.2)
- HRPC: 75 mg/m^2 with 5 mg prednisone twice a day continuously (2.3)
- GC: 75 mg/m^2 followed by cisplatin 75 mg/m^2 (both on day 1 only) followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion (2.4)
- SCCHN: 75 mg/m^2 followed by cisplatin 75 mg/m^2 IV (day 1), followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion; for 4 cycles (2.5)
- SCCHN: 75 mg/m^2 followed by cisplatin 100 mg/m^2 IV (day 1), followed by fluorouracil 1000 mg/m^2 per day as a 24-hr IV (days 1-4); for 3 cycles (2.5)

For all patients:

- Premedicate with oral corticosteroids (2.6)
- Adjust dose as needed (2.7)

----------DOSAGE FORMS AND STRENGTHS----------
- One vial TAXOTERE: Single use vials 80 mg/4 mL and 20 mg/mL (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to docetaxel or polysorbate 80 (4)
- Neutrophil counts of <1500 cells/mm^3 (4)

----------WARNINGS AND PRECAUTIONS----------
- Acute myeloid leukemia: In patients who received TAXOTERE, doxorubicin and cyclophosphamide, monitor for delayed myelodysplasia or myeloid leukemia (5.6)
- Cutaneous reactions: Reactions including erythema of the extremities with edema followed by desquamation may occur. Severe skin toxicity may require dose adjustment (5.7)
- Neurologic reactions: Reactions including. paresthesia, dysesthesia, and pain may occur. Severe neurosensory symptoms require dose adjustment or discontinuation if persistent. (5.8)
- Asthenia: Severe asthenia may occur and may require treatment discontinuation. (5.9)
- Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant when receiving TAXOTERE (5.10, 8.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions across all TAXOTERE indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, myalgia (6)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------DRUG INTERACTIONS----------
- Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, and FLUID RETENTION

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 as a single agent at a dose of 100 mg/m^2 *[see Warnings and Precautions (5.1)]*.

TAXOTERE should not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >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, AST or ALT, and alkaline phosphatase values should be obtained prior to each cycle of TAXOTERE therapy *[see Warnings and Precautions (5.2)]*.

TAXOTERE therapy should not be given to patients with neutrophil counts of <1500 cells/mm^3. 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 *[see Warnings and Precautions (5.3)]*.

Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who

received a 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the TAXOTERE infusion and administration of appropriate therapy *[see Warnings and Precautions (5.4)]*. 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 Contraindications (4)]*.

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 Warnings and Precautions (5.5)]*.

1. INDICATIONS AND USAGE

1.1 Breast Cancer

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

TAXOTERE in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

1.2 Non-Small Cell Lung Cancer

TAXOTERE as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.

TAXOTERE in combination with cisplatin is indicated 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.

1.3 Prostate Cancer

TAXOTERE in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

1.4 Gastric Adenocarcinoma

TAXOTERE in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

1.5 Head and Neck Cancer

TAXOTERE in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

2. DOSAGE AND ADMINISTRATION

For all indications, toxicities may warrant dosage adjustments *[see Dosage and Administration (2.7)]*.
Administer in a facility equipped to manage possible complications (e.g. anaphylaxis).

2.1 Breast Cancer

- For locally advanced or metastatic breast cancer after failure of prior chemotherapy, the recommended dose of TAXOTERE is 60 mg/m^2 to 100 mg/m^2 administered intravenously over 1 hour every 3 weeks.
- For the adjuvant treatment of operable node-positive breast cancer, the recommended TAXOTERE dose is 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities *[see Dosage and Administration (2.7)]*.

2.2 Non-Small Cell Lung Cancer

- For treatment after failure of prior platinum-based chemotherapy, TAXOTERE was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials *[see Boxed Warning, Dosage and Administration (2.7), Warnings and Precautions (5), Clinical Studies (14)]*.
- For chemotherapy-naïve patients, TAXOTERE was evaluated in combination with cisplatin. The recommended dose of TAXOTERE is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks *[see Dosage and Administration (2.7)]*.

2.3 Prostate cancer

- For hormone-refractory metastatic prostate cancer, the recommended dose of TAXOTERE is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5 mg orally twice daily is administered continuously *[see Dosage and Administration (2.7)]*.

2.4 Gastric adenocarcinoma

- For gastric adenocarcinoma, the recommended dose of TAXOTERE is 75 mg/m^2 as a 1 hour intravenous infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as a 24-hour continuous intravenous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration *[see Dosage and Administration (2.7)]*.

2.5 Head and Neck Cancer

Patients must receive premedication with antiemetics, and appropriate hydration (prior to and after cisplatin administration). Prophylaxis for neutropenic infections should be administered. All patients treated on the TAXOTERE containing arms of the TAX323 and TAX324 studies received prophylactic antibiotics.

- *Induction chemotherapy followed by radiotherapy (TAX323)*

  For the induction treatment of locally advanced inoperable SCCHN, the recommended dose of TAXOTERE is 75 mg/m^2 as a 1 hour intravenous infusion followed by cisplatin 75 mg/m^2 intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy. *[see Dosage and Administration (2.7)]*.

- *Induction chemotherapy followed by chemoradiotherapy (TAX324)*

  For the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN, the recommended dose of TAXOTERE is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemoradiotherapy *[see Dosage and Administration (2.7)]*.

2.6 Premedication Regimen

All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) 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 (5.4)]*.

For hormone-refractory metastatic prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the TAXOTERE infusion *[see Warnings and Precautions (5.4)]*.

2.7 Dosage Adjustments During Treatment

Breast Cancer

Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions during TAXOTERE therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m^2 and who do not experience febrile neutropenia, neutrophils <500 cells/mm^3 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.

Combination Therapy with TAXOTERE in the Adjuvant Treatment of Breast Cancer

TAXOTERE in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is ≥1,500 cells/mm^3. Patients who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their TAXOTERE dose reduced to 60 mg/m². Patients who experience grade 3 or 4 stomatitis should have their TAXOTERE dose decreased to 60 mg/m². Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during TAXOTERE therapy should have their dosage of TAXOTERE reduced from 75 mg/m² to 60 mg/m². If the patient continues to experience these reactions at 60 mg/m², treatment should be discontinued.

Non-Small Cell Lung Cancer

Monotherapy with TAXOTERE for NSCLC treatment after failure of prior platinum-based chemotherapy

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 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/m^2. Patients who develop ≥grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Combination therapy with TAXOTERE for chemotherapy-naïve NSCLC

For patients who are dosed initially at TAXOTERE 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm^3, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the TAXOTERE dosage in subsequent cycles should be reduced to 65 mg/m^2. In patients who require a further dose reduction, a dose of 50 mg/m^2 is recommended. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Prostate Cancer

Combination therapy with TAXOTERE for hormone-refractory metastatic prostate cancer

TAXOTERE should be administered when the neutrophil count is ≥1,500 cells/mm^3. Patients who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during TAXOTERE therapy should have the dosage of TAXOTERE reduced from 75 mg/m² to 60 mg/m². If the patient continues to experience these reactions at 60 mg/m², the treatment should be discontinued.

Gastric or Head and Neck Cancer

TAXOTERE in combination with cisplatin and fluorouracil in gastric cancer or head and neck cancer

Patients treated with TAXOTERE in combination with cisplatin and fluorouracil must receive antiemetics and appropriate hydration according to current institutional guidelines. In both studies, G-CSF was recommended during the second and/or subsequent cycles in case of febrile neutropenia, or documented infection with neutropenia, or neutropenia lasting more than 7 days. If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the TAXOTERE dose should be reduced from 75 mg/m^2 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the TAXOTERE dose should be reduced from 60 mg/m^2 to 45 mg/m^2. In case of grade 4 thrombocytopenia the TAXOTERE dose should be reduced from 75 mg/m^2 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of TAXOTERE until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. Discontinue treatment if these toxicities persist*. [see Warnings and Precautions (5.3)]*.

Recommended dose modifications for toxicities in patients treated with TAXOTERE in combination with cisplatin and fluorouracil are shown in Table 1.

Table 1 - Recommended Dose Modifications for Toxicities in Patients Treated with TAXOTERE in Combination with Cisplatin and Fluorouracil

Toxicity	Dosage adjustment
Diarrhea grade 3	First episode: reduce fluorouracil dose by 20%. Second episode: then reduce TAXOTERE dose by 20%.
Diarrhea grade 4	First episode: reduce TAXOTERE and fluorouracil doses by 20%. Second episode: discontinue treatment.
Stomatitis/mucositis grade 3	First episode: reduce fluorouracil dose by 20%. Second episode: stop fluorouracil only, at all subsequent cycles. Third episode: reduce TAXOTERE dose by 20%.
Stomatitis/mucositis grade 4	First episode: stop fluorouracil only, at all subsequent cycles. Second episode: reduce TAXOTERE dose by 20%.

Liver dysfunction:

In case of AST/ALT >2.5 to ≤5 x ULN and AP ≤2.5 x ULN, or AST/ALT >1.5 to ≤5 x ULN and AP >2.5 to ≤5 x ULN, TAXOTERE should be reduced by 20%.

In case of AST/ALT >5 x ULN and/or AP >5 x ULN TAXOTERE should be stopped.

The dose modifications for cisplatin and fluorouracil in the gastric cancer study are provided below:

Cisplatin dose modifications and delays

Peripheral neuropathy: A neurological examination should be performed before entry into the study, and then at least every 2 cycles and at the end of treatment. In the case of neurological signs or symptoms, more frequent examinations should be performed and the following dose modifications can be made according to NCIC-CTC grade:

• Grade 2: Reduce cisplatin dose by 20%.
• Grade 3: Discontinue treatment.

Ototoxicity: In the case of grade 3 toxicity, discontinue treatment.

Nephrotoxicity: In the event of a rise in serum creatinine ≥grade 2 (>1.5 x normal value) despite adequate rehydration, CrCl should be determined before each subsequent cycle and the following dose reductions should be considered (see Table 2).

For other cisplatin dosage adjustments, also refer to the manufacturers' prescribing information.

Table 2 – Dose Reductions for Evaluation of Creatinine Clearance

Creatinine clearance result before next cycle	Cisplatin dose next cycle
CrCl ≥60 mL/min	Full dose of cisplatin was given. CrCl was to be repeated before each treatment cycle.
CrCl between 40 and 59 mL/min	Dose of cisplatin was reduced by 50% at subsequent cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was reinstituted at the next cycle. If no recovery was observed, then cisplatin was omitted from the next treatment cycle.
CrCl <40 mL/min	Dose of cisplatin was omitted in that treatment cycle only. If CrCl was still <40 mL/min at the end of cycle, cisplatin was discontinued. If CrCl was >40 and <60 mL/min at end of cycle, a 50% cisplatin dose was given at the next cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was given at next cycle.

CrCl = Creatinine clearance

Fluorouracil dose modifications and treatment delays

For diarrhea and stomatitis, see Table 1.

In the event of grade 2 or greater plantar-palmar toxicity, fluorouracil should be stopped until recovery. The fluorouracil dosage should be reduced by 20%.

For other greater than grade 3 toxicities, except alopecia and anemia, chemotherapy should be delayed (for a maximum of 2 weeks from the planned date of infusion) until resolution to grade ≤1 and then recommenced, if medically appropriate.

For other fluorouracil dosage adjustments, also refer to the manufacturers' prescribing information.

Combination Therapy with Strong CYP3A4 inhibitors:
Avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require co-administration of a strong CYP3A4 inhibitor. *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

2.8 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 *[see How Supplied/ Storage and Handling (16.3)]*.

If TAXOTERE Injection 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 Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

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.

One-vial TAXOTERE (Injection Concentrate)
TAXOTERE Injection Concentrate requires NO prior dilution with a diluent and is ready to add to the infusion solution.
Please follow the preparation instructions provided below.

2.9 Preparation and Administration

DO NOT use the two-vial formulation (Injection Concentrate and diluent) with the one-vial formulation.

One-vial TAXOTERE (Injection Concentrate)

TAXOTERE Injection Concentrate (20 mg/mL) requires NO prior dilution with a diluent and is ready to add to the infusion solution.

1. TAXOTERE vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection Concentrate vials to stand at room temperature for approximately 5 minutes before use.
2. Aseptically withdraw the required amount of TAXOTERE injection concentrate (20 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 mg/mL 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
3. Thoroughly mix the infusion by gentle manual rotation.
4. 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 dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.

The TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature (below 25°C) and lighting conditions.

2.10 Stability

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

3. DOSAGE FORMS AND STRENGTHS

One-vial TAXOTERE (Injection Concentrate)

TAXOTERE 80 mg/4 mL

TAXOTERE (docetaxel) Injection Concentrate 80 mg/4 mL: 80 mg docetaxel in 4 mL 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol.

TAXOTERE 20 mg/mL

TAXOTERE (docetaxel) Injection Concentrate 20 mg/1 mL: 20 mg docetaxel in 1 mL in 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol.

4. CONTRAINDICATIONS

- TAXOTERE is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe reactions, including anaphylaxis, have occurred *[see Warnings and Precautions (5.4)]*.
- TAXOTERE should not be used in patients with neutrophil counts of <1500 cells/mm^3.

5. WARNINGS AND PRECAUTIONS

5.1 Toxic Deaths

Breast Cancer
TAXOTERE administered at 100 mg/m^2 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 (AST and/or ALT >1.5 times ULN together with AP >2.5 times ULN). Among patients dosed at 60 mg/m^2, 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/m^2 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/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had an ECOG PS of 2 at study entry *[see Dosage and Administration (2.2), Clinical Studies (14)]*.

5.2 Hepatic Impairment

Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with TAXOTERE *[see Boxed Warning, Use in Specific Populations (8.6), Clinical studies (14)]*.

5.3 Hematologic Effects

Perform frequent peripheral blood cell counts on all patients receiving TAXOTERE. Patients should not be retreated with subsequent cycles of TAXOTERE until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3.

A 25% reduction in the dose of TAXOTERE is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a TAXOTERE cycle *[see Dosage and Administration (2.7)]*.

Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60 mg/m^2 to 100 mg/m^2 of TAXOTERE and grade 4 neutropenia (<500 cells/mm^3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2. 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/mm^3.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

Three breast cancer patients with severe liver impairment (bilirubin >1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia. In gastric cancer patients treated with docetaxel in combination with cisplatin and fluorouracil (TCF), febrile neutropenia and/or neutropenic infection occurred in 12% of patients receiving G-CSF compared to 28% who did not. Patients receiving TCF should be closely monitored during the first and subsequent cycles for febrile neutropenia and neutropenic infection *[see Dosage and Administration (2.7), Adverse Reactions (6)]*.

5.4 Hypersensitivity Reactions

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the TAXOTERE infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with TAXOTERE.

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. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of TAXOTERE *[see Dosage and Administration (2.6)]***.**

5.5 Fluid Retention

Severe fluid retention has been reported following TAXOTERE therapy. 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 (2.6)]***.** 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/m^2. Nine of 92 patients (9.8%) 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/m^2. 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).

5.6 Acute Myeloid Leukemia

Treatment-related acute myeloid leukemia (AML) or myelodysplasia has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. In the adjuvant breast cancer trial *(TAX316)* AML occurred in 3 of 744 patients who received TAXOTERE, doxorubicin and cyclophosphamide (TAC) and in 1 of 736 patients who received fluorouracil, doxorubicin and cyclophosphamide *[see Clinical Studies (14.2)]*. In TAC-treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up.

5.7 Cutaneous Reactions

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 (2.7)]*. 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.

5.8 Neurologic Reactions

Severe neurosensory symptoms (*e.g.* 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 (2.7)]*. 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).

5.9 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.

5.10 Use in Pregnancy

TAXOTERE can cause fetal harm when administered to a pregnant woman. Docetaxel caused embryofetal toxicities including intrauterine mortality when administered to pregnant rats and rabbits during the period of organogenesis. Embryofetal effects in animals occurred at doses as low as 1/50 and 1/300 the recommended human dose on a body surface area basis.

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. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TAXOTERE *[see Use in Specific Populations (8.1)]***.**

6. ADVERSE REACTIONS

The most serious adverse reactions from TAXOTERE are:
- Toxic Deaths *[see Boxed Warning, Warning and Precautions (5.1)]*
- Hepatotoxicity *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Neutropenia *[see Boxed Warning, Warnings and Precautions (5.3)]*
- Hypersensitivity *[see Boxed Warning, Warnings and Precautions (5.4)]*
- Fluid Retention *[see Boxed Warning, Warnings and Precautions (5.5)]*

The most common adverse reactions across all TAXOTERE indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication.

Adverse reactions are described according to indication. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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.

6.1 Clinical Trial Experience

Breast Cancer

Monotherapy with TAXOTERE for locally advanced or metastatic breast cancer after failure of prior chemotherapy

TAXOTERE 100 mg/m^2: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received TAXOTERE administered at 100 mg/m^2 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 (See Table 3).

Table 3 - Summary of Adverse Reactions in Patients Receiving TAXOTERE at 100 mg/m^2

Adverse Reaction	**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	96	96	99
<500 cells/mm^3	75	88	86
Leukopenia			
<4000 cells/mm^3	96	98	99
<1000 cells/mm^3	32	47	44
Thrombocytopenia			
<100,000 cells/mm^3	8	25	9
Anemia			
<11 g/dL	90	92	94
<8 g/dL	9	31	8
Febrile Neutropenia***	11	26	12
Septic Death	2	5	1
Non-Septic Death	1	7	1
Infections			
Any	22	33	22
Severe	6	16	6
Fever in Absence of Infection			
Any	31	41	35
Severe	2	8	2
Hypersensitivity Reactions			
Regardless of Premedication			
Any	21	20	18
Severe	4	10	3
With 3-day Premedication	n=92	n=3	n=92
Any	15	33	15

Adverse Reaction	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
Severe	2	0	2
Fluid Retention			
Regardless of Premedication			
Any	47	39	60
Severe	7	8	9
With 3-day Premedication	n=92	n=3	n=92
Any	64	67	64
Severe	7	33	7
Neurosensory			
Any	49	34	58
Severe	4	0	6
Cutaneous			
Any	48	54	47
Severe	5	10	5
Nail Changes			
Any	31	23	41
Severe	3	5	4
Gastrointestinal			
Nausea	39	38	42
Vomiting	22	23	23
Diarrhea	39	33	43
Severe	5	5	6
Stomatitis			
Any	42	49	52
Severe	6	13	7
Alopecia	76	62	74
Asthenia			
Any	62	53	66
Severe	13	25	15
Myalgia			
Any	19	16	21
Severe	2	2	2
Arthralgia	9	7	8
Infusion Site Reactions	4	3	4

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

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

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

Hematologic Reactions

Reversible marrow suppression was the major dose-limiting toxicity of TAXOTERE *[see Warnings and Precautions (5.3)]*. The median time to nadir was 7 days, while the median duration of severe neutropenia (<500 cells/mm^3) 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/mm^3 with fever >38°C with intravenous 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/mm^3) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity Reactions

Severe hypersensitivity reactions have been reported *[see Boxed Warning, Warnings and Precautions (5.4)]*. 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 instituting appropriate therapy.

Fluid Retention.

Fluid retention can occur with the use of TAXOTERE *[see Boxed Warning, Dosage and Administration (2.6), Warnings and Precautions (5.5)]*.

Cutaneous Reactions

Severe skin toxicity is discussed elsewhere in the label *[see Warnings and Precautions (5.7)]*. 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 Reactions

Neurologic reactions are discussed elsewhere in the label *[see Warnings and Precautions (5.8)]*

Gastrointestinal Reactions

Nausea, vomiting, and 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 Reactions

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. Seven of 86 (8.1%) of metastatic breast cancer patients receiving TAXOTERE 100 mg/m^2 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 Reactions

In patients with normal LFTs at baseline, bilirubin values greater than the ULN occurred in 8.9% of patients. Increases in AST or ALT >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 AST and/or ALT >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.

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/m^2 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 AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN); and 174 patients in Japanese studies given TAXOTERE at 60 mg/m^2 who had normal LFTs (see Tables 4 and 5).

Table 4 - Hematologic Adverse Reactions in Breast Cancer Patients Previously Treated with Chemotherapy Treated at TAXOTERE 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

Adverse Reaction	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	100	95
Grade 4 <500 cells/mm^3	84	94	75
Thrombocytopenia			
Any <100,000 cells/mm^3	11	44	14
Grade 4 <20,000 cells/mm^3	1	17	1
Anemia <11 g/dL	95	94	65
Infection* **			
Any	23	39	1
Grade 3 and 4	7	33	0
Febrile Neutropenia**			
By Patient	12	33	0
By Course	2	9	0
Septic Death	2	6	1
Non-Septic Death	1	11	0

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

**Elevated Baseline LFTs: AST and/or ALT >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/m^2, ANC grade 4 and fever >38°C with intravenous antibiotics and/or hospitalization; for 60 mg/m^2, ANC grade 3/4 and fever >38.1°C

Table 5 - Non-Hematologic Adverse Reactions in Breast Cancer Patients Previously Treated with Chemotherapy Treated at TAXOTERE 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

Adverse Reaction	TAXOTERE 100 mg/m^2		TAXOTERE 60 mg/m^2
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
Acute Hypersensitivity Reaction Regardless of Premedication			
Any	13	6	1
Severe	1	0	0
Fluid Retention* Regardless of Premedication**			
Any	56	61	13
Severe	8	17	0
Neurosensory			
Any	57	50	20
Severe	6	0	0
Myalgia	23	33	3
Cutaneous			
Any	45	61	31
Severe	5	17	0
Asthenia			
Any	65	44	66
Severe	17	22	0
Diarrhea			
Any	42	28	NA
Severe	6	11	
Stomatitis			
Any	53	67	19
Severe	8	39	1

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

** Elevated Baseline Liver Function: AST and/or ALT >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/m^2 dose

NA = not available

In the three-arm monotherapy trial, TAX313, which compared TAXOTERE 60 mg/m^2, 75 mg/m^2 and 100 mg/m^2 in advanced breast cancer, grade 3/4 or severe adverse reactions occurred in 49.0% of patients treated with TAXOTERE 60 mg/m^2 compared to 55.3% and 65.9% treated with 75 mg/m^2 and 100 mg/m^2 respectively. Discontinuation due to adverse reactions was reported in 5.3% of patients treated with 60 mg/m^2 vs. 6.9% and 16.5% for patients treated at 75 and 100 mg/m^2 respectively. Deaths within 30 days of last treatment occurred in 4.0% of patients treated with 60 mg/m^2 compared to 5.3% and 1.6% for patients treated at 75 mg/m^2 and 100 mg/m^2 respectively.
The following adverse reactions were associated with increasing docetaxel doses: fluid retention (26%, 38%, and 46% at 60 mg/m^2, 75 mg/m^2, and 100 mg/m^2 respectively), thrombocytopenia (7%, 11% and 12% respectively), neutropenia (92%, 94%, and 97% respectively), febrile neutropenia (5%, 7%, and 14% respectively), treatment-related grade 3/4 infection (2%, 3%, and 7% respectively) and anemia (87%, 94%, and 97% respectively).

Combination therapy with TAXOTERE in the adjuvant treatment of breast cancer
The following table presents treatment emergent adverse reactions observed in 744 patients, who were treated with TAXOTERE 75 mg/m² every 3 weeks in combination with doxorubicin and cyclophosphamide (see Table 6).

Table 6- Clinically Important Treatment Emergent Adverse Reactions Regardless of Causal Relationship in Patients Receiving TAXOTERE in Combination with Doxorubicin and Cyclophosphamide (TAX316).

	TAXOTERE 75 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (TAC) n=744 %		**Fluorouracil 500 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (FAC) n=736 %**	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Anemia	92	4	72	2
Neutropenia	71	66	82	49
Fever in absence of infection	47	1	17	0
Infection	39	4	36	2
Thrombocytopenia	39	2	28	1
Febrile neutropenia	25	N/A	3	N/A
Neutropenic infection	12	N/A	6	N/A
Hypersensitivity reactions	13	1	4	0
Lymphedema	4	0	1	0
Fluid Retention*	35	1	15	0
Peripheral edema	27	0	7	0
Weight gain	13	0	9	0
Neuropathy sensory	26	0	10	0
Neuro-cortical	5	1	6	1

	TAXOTERE 75 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (TAC) n=744 %		Fluorouracil 500 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (FAC) n=736 %	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Neuropathy motor	4	0	2	0
Neuro-cerebellar	2	0	2	0
Syncope	2	1	1	0
Alopecia	98	N/A	97	N/A
Skin toxicity	27	1	18	0
Nail disorders	19	0	14	0
Nausea	81	5	88	10
Stomatitis	69	7	53	2
Vomiting	45	4	59	7
Diarrhea	35	4	28	2
Constipation	34	1	32	1
Taste perversion	28	1	15	0
Anorexia	22	2	18	1
Abdominal Pain	11	1	5	0
Amenorrhea	62	N/A	52	N/A
Cough	14	0	10	0
Cardiac dysrhythmias	8	0	6	0
Vasodilatation	27	1	21	1
Hypotension	2	0	1	0
Phlebitis	1	0	1	0
Asthenia	81	11	71	6
Myalgia	27	1	10	0
Arthralgia	19	1	9	0
Lacrimation disorder	11	0	7	0
Conjunctivitis	5	0	7	0

* COSTART term and grading system for events related to treatment.

Of the 744 patients treated with TAC, 36.3% experienced severe treatment emergent adverse reactions compared to 26.6% of the 736 patients treated with FAC. Dose reductions due to hematologic toxicity occurred in 1% of cycles in the TAC arm versus 0.1% of cycles in the FAC arm. Six percent of patients treated with TAC discontinued treatment due to adverse reactions, compared to 1.1% treated with FAC; fever in the absence of infection and allergy being the most common reasons for withdrawal among TAC-treated patients. Two patients died in each arm within 30 days of their last study treatment; 1 death per arm was attributed to study drugs.

Fever and Infection
Fever in the absence of infection was seen in 46.5% of TAC-treated patients and in 17.1% of FAC-treated patients. Grade 3/4 fever in the absence of infection was seen in 1.3% and 0% of TAC- and FAC-treated patients respectively. Infection was seen in 39.4% of TAC-treated patients compared to 36.3% of FAC-treated patients. Grade 3/4 infection was seen in 3.9% and 2.2% of TAC-treated and FAC-treated patients respectively. There were no septic deaths in either treatment arm.

Gastrointestinal Reactions
In addition to gastrointestinal reactions reflected in the table above, 7 patients in the TAC arm were reported to have colitis/enteritis/large intestine perforation vs. one patient in the FAC arm. Five of the 7 TAC-treated patients required treatment discontinuation; no deaths due to these events occurred.

Cardiovascular Reactions
More cardiovascular reactions were reported in the TAC arm vs. the FAC arm; dysrhythmias, all grades (7.9% vs. 6.0%), hypotension, all grades (2.6% vs. 1.1%) and CHF (2.3% vs. 0.9%, at 70 months median follow-up). One patient in each arm died due to heart failure.

Acute Myeloid Leukemia (AML)
Treatment-related acute myeloid leukemia or myelodysplasia is known to occur in patients treated with anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. AML occurs at a higher frequency when these agents are given in combination with radiation therapy. AML occurred in the adjuvant breast cancer trial (TAX316). The cumulative risk of developing treatment-related AML at 5 years in TAX316 was 0.4% for TAC-treated patients and 0.1% for FAC-treated patients. This risk of AML is comparable to the risk observed for other anthracyclines/cyclophosphamide containing adjuvant breast chemotherapy regimens.

Lung Cancer
Monotherapy with TAXOTERE for unresectable, locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy
TAXOTERE 75 mg/m^2: Treatment emergent adverse drug reactions are shown in Table 7. 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 where otherwise noted.

Table 7 - Treatment Emergent Adverse Reactions Regardless of Relationship to Treatment in Patients Receiving TAXOTERE as Monotherapy for Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy*

Adverse Reaction	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Neutropenia			
Any	84	14	83
Grade 3/4	65	12	57
Leukopenia			
Any	84	6	89
Grade 3/4	49	0	43
Thrombocytopenia			
Any	8	0	8
Grade 3/4	3	0	2
Anemia			
Any	91	55	91
Grade 3/4	9	12	14
Febrile Neutropenia**	6	NA†	1
Infection			
Any	34	29	30
Grade 3/4	10	6	9
Treatment Related Mortality	3	NA†	3
Hypersensitivity Reactions			
Any	6	0	1
Grade 3/4	3	0	0
Fluid Retention			
Any	34	ND††	23
Severe	3		3
Neurosensory			
Any	23	14	29
Grade 3/4	2	6	5
Neuromotor			
Any	16	8	10
Grade 3/4	5	6	3
Skin			
Any	20	6	17
Grade 3/4	1	2	1

Adverse Reaction	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Gastrointestinal			
Nausea			
Any	34	31	31
Grade 3/4	5	4	8
Vomiting			
Any	22	27	22
Grade 3/4	3	2	6
Diarrhea			
Any	23	6	12
Grade 3/4	3	0	4
Alopecia	56	35	50
Asthenia			
Any	53	57	54
Severe***	18	39	23
Stomatitis			
Any	26	6	8
Grade 3/4	2	0	1
Pulmonary			
Any	41	49	45
Grade 3/4	21	29	19
Nail Disorder			
Any	11	0	2
Severe***	1	0	0
Myalgia			
Any	6	0	3
Severe***	0	0	0
Arthralgia			
Any	3	2	2
Severe***	0	0	1
Taste Perversion			
Any	6	0	0
Severe***	1	0	0

*Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤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°C with intravenous antibiotics and/or hospitalization

***COSTART term and grading system

†Not Applicable; †† Not Done

Combination therapy with TAXOTERE in chemotherapy-naïve advanced unresectable or metastatic NSCLC

Table 8 presents safety data from two arms of an open label, randomized controlled trial (TAX326) that enrolled patients with unresectable stage IIIB or IV non-small cell lung cancer and no history of prior chemotherapy. Adverse reactions were described using the NCI Common Toxicity Criteria except where otherwise noted.

Table 8 - Adverse Reactions Regardless of Relationship to Treatment in Chemotherapy-Naïve Advanced Non-Small Cell Lung Cancer Patients Receiving TAXOTERE in Combination with Cisplatin

Adverse Reaction	**TAXOTERE 75 mg/m^2 + Cisplatin 75 mg/m^2 n=406 %**	**Vinorelbine 25 mg/m^2 + Cisplatin 100 mg/m^2 n=396 %**
Neutropenia		
Any	91	90
Grade 3/4	74	78
Febrile Neutropenia	5	5
Thrombocytopenia		
Any	15	15
Grade 3/4	3	4
Anemia		
Any	89	94
Grade 3/4	7	25
Infection		
Any	35	37
Grade 3/4	8	8
Fever in absence of infection		
Any	33	29
Grade 3/4	< 1	1
Hypersensitivity Reaction*		
Any	12	4
Grade 3/4	3	< 1
Fluid Retention**		
Any	54	42
All severe or life-threatening events	2	2
Pleural effusion		
Any	23	22
All severe or life-threatening events	2	2
Peripheral edema		
Any	34	18
All severe or life-threatening events	<1	<1
Weight gain		
Any	15	9

Adverse Reaction	TAXOTERE 75 mg/m^2 + Cisplatin 75 mg/m^2 n=406 %	Vinorelbine 25 mg/m^2 + Cisplatin 100 mg/m^2 n=396 %
All severe or life-threatening events	<1	<1
Neurosensory		
Any	47	42
Grade 3/4	4	4
Neuromotor		
Any	19	17
Grade 3/4	3	6
Skin		
Any	16	14
Grade 3/4	<1	1
Nausea		
Any	72	76
Grade 3/4	10	17
Vomiting		
Any	55	61
Grade 3/4	8	16
Diarrhea		
Any	47	25
Grade 3/4	7	3
Anorexia**		
Any	42	40
All severe or life-threatening events	5	5
Stomatitis		
Any	24	21
Grade 3/4	2	1
Alopecia		
Any	75	42
Grade 3	<1	0
Asthenia**		
Any	74	75
All severe or life-threatening events	12	14
Nail Disorder**		
Any	14	<1
All severe events	<1	0
Myalgia**		
Any	18	12
All severe events	<1	<1

* Replaces NCI term “Allergy”
** COSTART term and grading system

Deaths within 30 days of last study treatment occurred in 31 patients (7.6%) in the docetaxel+cisplatin arm and 37 patients (9.3%) in the vinorelbine+cisplatin arm. Deaths within 30 days of last study treatment attributed to study drug occurred in 9 patients (2.2%) in the docetaxel+cisplatin arm and 8 patients (2.0%) in the vinorelbine+cisplatin arm.
The second comparison in the study, vinorelbine+cisplatin versus TAXOTERE+carboplatin (which did not demonstrate a superior survival associated with TAXOTERE, *[see Clinical Studies (14.3)]*) demonstrated a higher incidence of thrombocytopenia, diarrhea, fluid retention, hypersensitivity reactions, skin toxicity, alopecia and nail changes on the TAXOTERE+carboplatin arm, while a higher incidence of anemia, neurosensory toxicity, nausea, vomiting, anorexia and asthenia was observed on the vinorelbine+cisplatin arm.

Prostate Cancer

Combination therapy with TAXOTERE in patients with prostate cancer

The following data are based on the experience of 332 patients, who were treated with TAXOTERE 75 mg/m² every 3 weeks in combination with prednisone 5 mg orally twice daily (see Table 9).

Table 9 - Clinically Important Treatment Emergent Adverse Reactions (Regardless of Relationship) in Patients with Prostate Cancer who Received TAXOTERE in Combination with Prednisone (TAX327)

	TAXOTERE 75 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=332 %		**Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=335 %**	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Anemia	67	5	58	2
Neutropenia	41	32	48	22
Thrombocytopenia	3	1	8	1
Febrile neutropenia	3	N/A	2	N/A
Infection	32	6	20	4
Epistaxis	6	0	2	0
Allergic Reactions	8	1	1	0
Fluid Retention*	24	1	5	0
Weight Gain*	8	0	3	0
Peripheral Edema*	18	0	2	0
Neuropathy Sensory	30	2	7	0
Neuropathy Motor	7	2	3	1
Rash/Desquamation	6	0	3	1
Alopecia	65	N/A	13	N/A
Nail Changes	30	0	8	0

	TAXOTERE 75 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=332 %		Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=335 %	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Nausea	41	3	36	2
Diarrhea	32	2	10	1
Stomatitis/Pharyngitis	20	1	8	0
Taste Disturbance	18	0	7	0
Vomiting	17	2	14	2
Anorexia	17	1	14	0
Cough	12	0	8	0
Dyspnea	15	3	9	1
Cardiac left ventricular function	10	0	22	1
Fatigue	53	5	35	5
Myalgia	15	0	13	1
Tearing	10	1	2	0
Arthralgia	8	1	5	1

*Related to treatment

Gastric Cancer

Combination therapy with TAXOTERE in gastric adenocarcinoma

Data in the following table are based on the experience of 221 patients with advanced gastric adenocarcinoma and no history of prior chemotherapy for advanced disease, who were treated with TAXOTERE 75 mg/m^2 in combination with cisplatin and fluorouracil (see Table 10).

Table 10 - Clinically Important Treatment Emergent Adverse Reactions Regardless of Relationship to Treatment in the Gastric Cancer Study

	TAXOTERE 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=221		Cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 n=224	
Adverse Reaction	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Anemia	97	18	93	26
Neutropenia	96	82	83	57
Fever in the absence of infection	36	2	23	1

	TAXOTERE 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=221		Cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 n=224	
Adverse Reaction	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Thrombocytopenia	26	8	39	14
Infection	29	16	23	10
Febrile neutropenia	16	N/A	5	N/A
Neutropenic infection	16	N/A	10	N/A
Allergic reactions	10	2	6	0
Fluid retention*	15	0	4	0
Edema*	13	0	3	0
Lethargy	63	21	58	18
Neurosensory	38	8	25	3
Neuromotor	9	3	8	3
Dizziness	16	5	8	2
Alopecia	67	5	41	1
Rash/itch	12	1	9	0
Nail changes	8	0	0	0
Skin desquamation	2	0	0	0
Nausea	73	16	76	19
Vomiting	67	15	73	19
Anorexia	51	13	54	12
Stomatitis	59	21	61	27
Diarrhea	78	20	50	8
Constipation	25	2	34	3
Esophagitis/dysphagia/ odynophagia	16	2	14	5
Gastrointestinal pain/cramping	11	2	7	3
Cardiac dysrhythmias	5	2	2	1
Myocardial ischemia	1	0	3	2
Tearing	8	0	2	0
Altered hearing	6	0	13	2

Clinically important treatment emergent adverse reactions were determined based upon frequency, severity, and clinical impact of the adverse reaction.
*Related to treatment

Head and Neck Cancer

Combination therapy with TAXOTERE in head and neck cancer

Table 11 summarizes the safety data obtained from patients that received induction chemotherapy with TAXOTERE 75 mg/m^2 in combination with cisplatin and fluorouracil followed by radiotherapy (TAX323; 174 patients) or chemoradiotherapy (TAX324; 251 patients). The treatment regimens are described in Section 14.6.

Table 11 – Clinically Important Treatment Emergent Adverse Reactions (Regardless of Relationship) in Patients with SCCHN Receiving Induction Chemotherapy with TAXOTERE in Combination with cisplatin and fluorouracil followed by radiotherapy (TAX323) or chemoradiotherapy (TAX324)

	TAX323 (n=355)				**TAX324 (n=494)**			
	TAXOTERE arm (n=174)		**Comparator arm (n=181)**		**TAXOTERE arm (n=251)**		**Comparator arm (n=243)**	
Adverse Reaction (by Body System)	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Neutropenia	93	76	87	53	95	84	84	56
Anemia	89	9	88	14	90	12	86	10
Thrombocytopenia	24	5	47	18	28	4	31	11
Infection	27	9	26	8	23	6	28	5
Febrile neutropenia*	5	N/A	2	N/A	12	N/A	7	N/A
Neutropenic infection	14	N/A	8	N/A	12	N/A	8	N/A
Cancer pain	21	5	16	3	17	9	20	11
Lethargy	41	3	38	3	61	5	56	10
Fever in the absence of infection	32	1	37	0	30	4	28	3
Myalgia	10	1	7	0	7	0	7	2
Weight loss	21	1	27	1	14	2	14	2
Allergy	6	0	3	0	2	0	0	0
Fluid retention**	20	0	14	1	13	1	7	2
Edema only	13	0	7	0	12	1	6	1
Weight gain only	6	0	6	0	0	0	1	0
Dizziness	2	0	5	1	16	4	15	2
Neurosensory	18	1	11	1	14	1	14	0
Altered hearing	6	0	10	3	13	1	19	3
Neuromotor	2	1	4	1	9	0	10	2
Alopecia	81	11	43	0	68	4	44	1
Rash/itch	12	0	6	0	20	0	16	1
Dry skin	6	0	2	0	5	0	3	0
Desquamation	4	1	6	0	2	0	5	0
Nausea	47	1	51	7	77	14	80	14
Stomatitis	43	4	47	11	66	21	68	27
Vomiting	26	1	39	5	56	8	63	10
Diarrhea	33	3	24	4	48	7	40	3
Constipation	17	1	16	1	27	1	38	1

	TAX323 (n=355)				TAX324 (n=494)			
	TAXOTERE arm (n=174)		Comparator arm (n=181)		TAXOTERE arm (n=251)		Comparator arm (n=243)	
Adverse Reaction (by Body System)	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Anorexia	16	1	25	3	40	12	34	12
Esophagitis/dysphagia/ Odynophagia	13	1	18	3	25	13	26	10
Taste, sense of smell altered	10	0	5	0	20	0	17	1
Gastrointestinal pain/cramping	8	1	9	1	15	5	10	2
Heartburn	6	0	6	0	13	2	13	1
Gastrointestinal bleeding	4	2	0	0	5	1	2	1
Cardiac dysrhythmia	2	2	2	1	6	3	5	3
Venous* **	3	2	6	2	4	2	5	4
Ischemia myocardial	2	2	1	0	2	1	1	1
Tearing	2	0	1	0	2	0	2	0
Conjunctivitis	1	0	1	0	1	0	0.4	0

Clinically important treatment emergent adverse reactions based upon frequency, severity, and clinical impact.
*Febrile neutropenia: grade ≥2 fever concomitant with grade 4 neutropenia requiring intravenous antibiotics and/or hospitalization.
**Related to treatment.
*** Includes superficial and deep vein thrombosis and pulmonary embolism

6.2 Post-marketing Experiences

The following adverse reactions 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: very rare cases of cutaneous lupus erythematosus and rare cases of bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and Scleroderma-like changes usually preceded by peripheral lymphedema. In some cases multiple factors may have contributed to the development of these effects. Severe hand and foot syndrome has been reported.

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. Disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure, has been reported. Cases of acute myeloid leukemia and myelodysplasic syndrome have been reported in association with TAXOTERE when used in combination with other chemotherapy agents and/or radiotherapy.

Hypersensitivity: rare cases of anaphylactic shock have been reported. Very rarely these cases resulted in a fatal outcome in patients who received premedication.

Hepatic: rare cases of hepatitis, sometimes fatal primarily in patients with pre-existing liver disorders, 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. Rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion.

Hearing: rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported, including cases associated with other ototoxic drugs.

Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome, interstitial pneumonia. Pulmonary fibrosis has been rarely reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

Renal: renal insufficiency and renal failure have been reported, the majority of these cases were associated with concomitant nephrotoxic drugs.

7. DRUG INTERACTIONS

Docetaxel is a CYP3A4 substrate. *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.

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of TAXOTERE and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with TAXOTERE, close monitoring for toxicity and a TAXOTERE

dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see 'Warnings and Precautions' section]*
Based on its mechanism of action and findings in animals, TAXOTERE can cause fetal harm when administered to a pregnant woman. 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. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TAXOTERE.

TAXOTERE can cause fetal harm when administered to a pregnant woman. 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/m^2 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.

8.3 Nursing Mothers

It is not known whether docetaxel 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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The efficacy of TAXOTERE in pediatric patients as monotherapy or in combination has not been established. The overall safety profile of TAXOTERE in pediatric patients receiving monotherapy or TCF was consistent with the known safety profile in adults.

TAXOTERE has been studied in a total of 289 pediatric patients: 239 in 2 trials with monotherapy and 50 in combination treatment with cisplatin and 5-fluoruracil (TCF).

TAXOTERE Monotherapy
TAXOTERE monotherapy was evaluated in a dose-finding phase 1 trial in 61 pediatric patients (median age 12.5 years, range 1-22 years) with a variety of refractory solid tumors. The recommended dose was 125 mg/m^2 as a 1-hour intravenous infusion every 21 days. The primary dose limiting toxicity was neutropenia.

The recommended dose for TAXOTERE monotherapy was evaluated in a phase 2 single-arm trial in 178 pediatric patients (median age 12 years, range 1-26 years) with a variety of

recurrent/refractory solid tumors. Efficacy was not established with tumor response rates ranging from one complete response (CR) (0.6%) in a patient with undifferentiated sarcoma to four partial responses (2.2%) seen in one patient each with Ewing Sarcoma, neuroblastoma, osteosarcoma, and squamous cell carcinoma.

TAXOTERE in Combination

TAXOTERE was studied in combination with cisplatin and 5-fluorouracil (TCF) versus cisplatin and 5-fluorouracil (CF) for the induction treatment of nasopharyngeal carcinoma (NPC) in pediatric patients prior to chemoradiation consolidation. Seventy-five patients (median age 16 years, range 9 to 21 years) were randomized (2:1) to TAXOTERE (75 mg/m²) in combination with cisplatin (75 mg/m²) and 5-fluorouracil (750 mg/m²) (TCF) or to cisplatin (80 mg/m²) and 5-fluorouracil (1000 mg/m²/day) (CF). The primary endpoint was the CR rate following induction treatment of NPC. One patient out of 50 in the TCF group (2%) had a complete response while none of the 25 patients in the CF group had a complete response.

Pharmacokinetics:

Pharmacokinetic parameters for docetaxel were determined in 2 pediatric solid tumor trials. Following docetaxel administration at 55 mg/m^2 to 235 mg/m^2 in a 1-hour intravenous infusion every 3 weeks in 25 patients aged 1 to 20 years (median 11 years), docetaxel clearance was 17.3±10.9 L/h/m^2 .

Docetaxel was administered in combination with cisplatin and 5-fluorouracil (TCF), at dose levels of 75 mg/m^2 in a 1-hour intravenous infusion day 1 in 28 patients aged 10 to 21 years (median 16 years, 17 patients were older than 16). Docetaxel clearance was 17.9±8.75 L/h/m^2, corresponding to an AUC of 4.20±2.57 μg.h/mL.

In summary, the body surface area adjusted clearance of docetaxel monotherapy and TCF combination in children were comparable to those in adults *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

Non-Small Cell Lung Cancer

In a study conducted in chemotherapy-naïve patients with NSCLC (TAX326), 148 patients (36%) in the TAXOTERE+cisplatin group were 65 years of age or greater. There were 128 patients (32%) in the vinorelbine+cisplatin group 65 years of age or greater. In the TAXOTERE+cisplatin group, patients less than 65 years of age had a median survival of 10.3 months (95% CI: 9.1 months, 11.8 months) and patients 65 years or older had a median survival of 12.1 months (95% CI: 9.3 months, 14 months). In patients 65 years of age or greater treated with TAXOTERE+cisplatin, diarrhea (55%), peripheral edema (39%) and stomatitis (28%) were observed more frequently than in the vinorelbine+cisplatin group (diarrhea 24%, peripheral edema 20%, stomatitis 20%). Patients treated with TAXOTERE+cisplatin who were 65 years of age or greater were more likely to experience diarrhea (55%), infections (42%),

peripheral edema (39%) and stomatitis (28%) compared to patients less than the age of 65 administered the same treatment (43%, 31%, 31% and 21%, respectively).

When TAXOTERE was combined with carboplatin for the treatment of chemotherapy-naïve, advanced non-small cell lung carcinoma, patients 65 years of age or greater (28%) experienced higher frequency of infection compared to similar patients treated with TAXOTERE+cisplatin, and a higher frequency of diarrhea, infection and peripheral edema than elderly patients treated with vinorelbine+cisplatin.

Prostate Cancer

Of the 333 patients treated with TAXOTERE every three weeks plus prednisone in the prostate cancer study (TAX327), 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with TAXOTERE every three weeks, the following treatment emergent adverse reactions occurred at rates ≥10% higher in patients 65 years of age or greater compared to younger patients: anemia (71% vs. 59%), infection (37% vs. 24%), nail changes (34% vs. 23%), anorexia (21% vs. 10%), weight loss (15% vs. 5%) respectively.

Breast Cancer

In the adjuvant breast cancer trial (TAX316), TAXOTERE in combination with doxorubicin and cyclophosphamide was administered to 744 patients of whom 48 (6%) were 65 years of age or greater. The number of elderly patients who received this regimen was not sufficient to determine whether there were differences in safety and efficacy between elderly and younger patients.

Gastric Cancer

Among the 221 patients treated with TAXOTERE in combination with cisplatin and fluorouracil in the gastric cancer study, 54 were 65 years of age or older and 2 patients were older than 75 years. In this study, the number of patients who were 65 years of age or older was insufficient to determine whether they respond differently from younger patients. However, the incidence of serious adverse reactions was higher in the elderly patients compared to younger patients. The incidence of the following adverse reactions (all grades, regardless of relationship): lethargy, stomatitis, diarrhea, dizziness, edema, febrile neutropenia/neutropenic infection occurred at rates ≥10% higher in patients who were 65 years of age or older compared to younger patients. Elderly patients treated with TCF should be closely monitored.

Head and Neck Cancer

Among the 174 and 251 patients who received the induction treatment with TAXOTERE in combination with cisplatin and fluorouracil (TPF) for SCCHN in the TAX323 and TAX324 studies, 18 (10%) and 32 (13%) of the patients were 65 years of age or older, respectively.

These clinical studies of TAXOTERE in combination with cisplatin and fluorouracil in patients with SCCHN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience with this treatment regimen has not identified differences in responses between elderly and younger patients.

8.6 Hepatic Impairment

Patients with bilirubin >ULN should not receive TAXOTERE. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive TAXOTERE *[see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

10. OVERDOSAGE

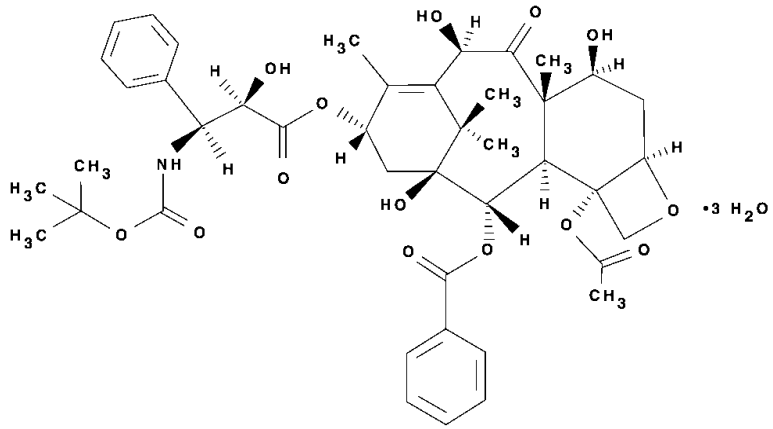
There is no known antidote for TAXOTERE overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should 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 intravenous doses that were ≥154 mg/kg (about 4.5 times the human dose of 100 mg/m^2 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 human dose of 100 mg/m^2 basis). In male and female rats, lethality was observed at a dose of 20 mg/kg (comparable to the human dose of 100 mg/m^2 on a mg/m^2 basis) and was associated with abnormal mitosis and necrosis of multiple organs.

11. 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 5β-20-epoxy-1,2α,4,7β,10β,13α-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 $C_{43}H_{53}NO_{14}$• $3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

One-vial TAXOTERE (Injection Concentrate)

TAXOTERE (docetaxel) Injection Concentrate is a sterile, non-pyrogenic, pale yellow to brownish-yellow solution at 20 mg/mL concentration.

Each mL contains 20 mg docetaxel (anhydrous) in 0.54 grams polysorbate 80 and 0.395 grams dehydrated alcohol solution.

TAXOTERE is available in single use vials containing 20 mg (1 mL) or 80 mg (4 mL) docetaxel (anhydrous).

TAXOTERE Injection Concentrate requires NO prior dilution with a diluent and is ready to add to the infusion solution.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.3 Human Pharmacokinetics

Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 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. Mean total body clearance was 21 L/h/m^2.

Distribution: 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 steady state volume of distribution was 113 L. *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.

Metabolism: *In vitro* drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4 *[see Drug Interactions (7)]*.

Elimination: A study of ^{14}C-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.

Effect of Age: A population pharmacokinetic analysis was carried out after TAXOTERE treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age.

Effect of Gender: The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel.

Hepatic Impairment: The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times 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 not be treated with TAXOTERE. Patients with severe hepatic impairment have not been studied. *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*

Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/m^2 to 90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

Effect of Ketoconazole: The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were randomized to receive either docetaxel (100 mg/m² intravenous) alone or docetaxel (10 mg/m² intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was co-administration with ketoconazole *[see Dosage and Administration (2.7) and Drug-Drug Interactions (7)]*.

Effect of Combination Therapies:

- Dexamethasone: Docetaxel total body clearance was not modified by pretreatment with dexamethasone.

- Cisplatin: Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

- Cisplatin and Fluorouracil: The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.

- Prednisone: A population pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone.

- Cyclophosphamide and Doxorubicin: A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with docetaxel have not been performed.

Docetaxel was clastogenic in the *in vitro* chromosome aberration test in CHO-K_1 cells and in the *in vivo* micronucleus test in mice administered doses of 0.39 to 1.56 mg/kg (about $1/60^{th}$ to $1/15^{th}$ the recommended human dose on a mg/m^2 basis). Docetaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assays.

Docetaxel did not reduce fertility in rats when administered in multiple intravenous doses of up to 0.3 mg/kg (about $1/50^{th}$ the recommended human dose on a mg/m^2 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 intravenous doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about $1/3^{rd}$ and $1/15^{th}$ the recommended human dose on a mg/m^2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

14. CLINICAL STUDIES

14.1 Locally Advanced or Metastatic 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).

Randomized Trials

In one randomized trial, patients with a history of prior treatment with an anthracycline-containing regimen were assigned to treatment with TAXOTERE (100 mg/m^2 every 3 weeks) or the combination of mitomycin (12 mg/m^2 every 6 weeks) and vinblastine (6 mg/m^2 every 3 weeks). Two hundred three 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 (See Table 12).

Table 12 - 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	
Risk Ratio*, Mortality (Docetaxel: Control)	0.73		p=0.01 Log Rank
95% CI (Risk Ratio)	0.58-0.93		
Median Time to	4.3 months	2.5 months	

Progression			
Risk Ratio*, Progression (Docetaxel: Control) 95% CI (Risk Ratio)	0.75 0.61-0.94		p=0.01 Log Rank
Overall Response Rate Complete Response Rate	28.1% 3.4%	9.5% 1.6%	p<0.0001 Chi Square

*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 (100 mg/m^2) or doxorubicin (75 mg/m^2) every 3 weeks. One hundred sixty-one 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 (See Table 13).

Table 13 - 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	
Risk Ratio*, Mortality (Docetaxel: Control) 95% CI (Risk Ratio)	0.89 0.68-1.16		p=0.39 Log Rank
Median Time to Progression	6.5 months	5.3 months	
Risk Ratio*, Progression (Docetaxel: Control) 95% CI (Risk Ratio)	0.93 0.71-1.16		p=0.45 Log Rank
Overall Response Rate Complete Response Rate	45.3% 6.8%	29.7% 4.2%	p=0.004 Chi Square

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

In another multicenter open-label, randomized trial (TAX313), in the treatment of patients with advanced breast cancer who progressed or relapsed after one prior chemotherapy regimen, 527 patients were randomized to receive TAXOTERE monotherapy 60 mg/m^2 (n=151), 75 mg/m^2 (n=188) or 100 mg/m^2 (n=188). In this trial, 94% of patients had metastatic disease and 79% had received prior anthracycline therapy. Response rate was the primary endpoint.

Response rates increased with TAXOTERE dose: 19.9% for the 60 mg/m^2 group compared to 22.3% for the 75 mg/m^2 and 29.8% for the 100 mg/m^2 group; pair-wise comparison between the 60 mg/m^2 and 100 mg/m^2 groups was statistically significant (p=0.037).

Single Arm Studies

TAXOTERE at a dose of 100 mg/m^2 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/m^2, 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/m^2.

14.2 Adjuvant Treatment of Breast Cancer

A multicenter, open-label, randomized trial (TAX316) evaluated the efficacy and safety of TAXOTERE for the adjuvant treatment of patients with axillary-node-positive breast cancer and no evidence of distant metastatic disease. After stratification according to the number of positive lymph nodes (1-3, 4+), 1491 patients were randomized to receive either TAXOTERE 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC arm), or doxorubicin 50 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclosphosphamide 500 mg/m^2 (FAC arm). Both regimens were administered every 3 weeks for 6 cycles. TAXOTERE was administered as a 1-hour infusion; all other drugs were given as intravenous bolus on day 1. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC.

Results from a second interim analysis (median follow-up 55 months) are as follows: In study TAX316, the docetaxel-containing combination regimen TAC showed significantly longer disease-free survival (DFS) than FAC (hazard ratio=0.74; 2-sided 95% CI=0.60, 0.92, stratified log rank p=0.0047). The primary endpoint, disease-free survival, included local and distant recurrences, contralateral breast cancer and deaths from any cause. The overall reduction in risk of relapse was 25.7% for TAC-treated patients. (See Figure 1).

At the time of this interim analysis, based on 219 deaths, overall survival was longer for TAC than FAC (hazard ratio=0.69, 2-sided 95% CI=0.53, 0.90). (See Figure 2). There will be further analysis at the time survival data mature.

Figure 1 - TAX316 Disease Free Survival K-M curve

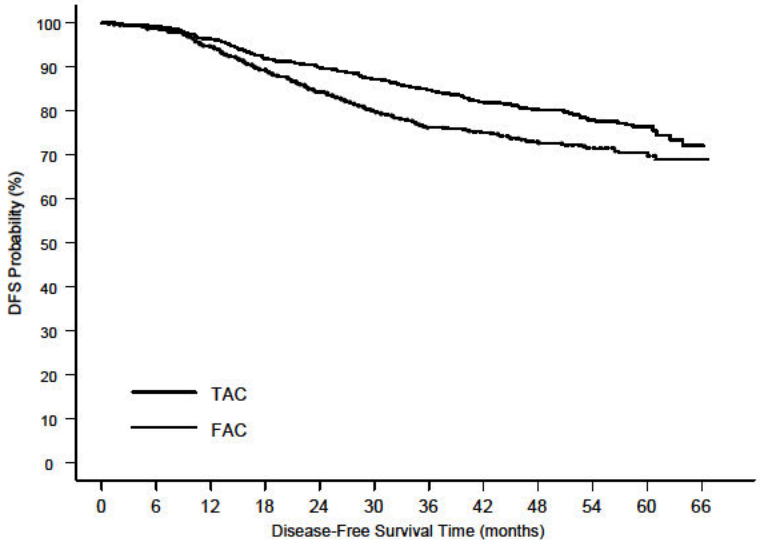
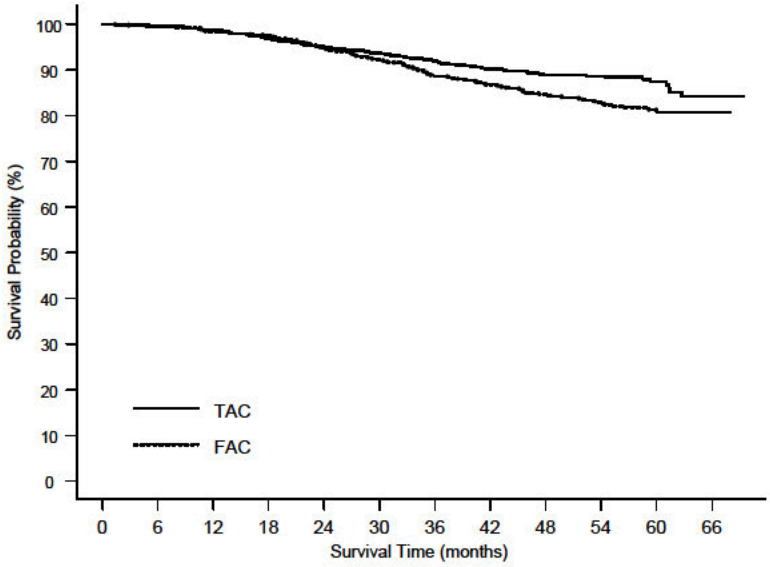


Figure 2 - TAX316 Overall Survival K-M Curve



The following table describes the results of subgroup analyses for DFS and OS (See Table 14).

Table 14 - Subset Analyses-Adjuvant Breast Cancer Study

		Disease Free Survival		Overall Survival	
Patient subset	**Number of patients**	**Hazard ratio***	**95% CI**	**Hazard ratio***	**95% CI**
No. of positive nodes					
Overall	744	0.74	(0.60, 0.92)	0.69	(0.53, 0.90)

1-3	467	0.64	(0.47, 0.87)	0.45	(0.29, 0.70)
4+	277	0.84	(0.63, 1.12)	0.93	(0.66, 1.32)
Receptor status					
Positive	566	0.76	(0.59, 0.98)	0.69	(0.48, 0.99)
Negative	178	0.68	(0.48, 0.97)	0.66	(0.44, 0.98)

*****a hazard ratio of less than 1 indicates that TAC is associated with a longer disease free survival or overall survival compared to FAC.

14.3 Non-Small Cell Lung Cancer (NSCLC)

The efficacy and safety of TAXOTERE has been evaluated in patients with unresectable, locally advanced or metastatic non-small cell lung cancer whose disease has failed prior platinum-based chemotherapy or in patients who are chemotherapy-naïve.

Monotherapy with TAXOTERE for NSCLC Previously Treated with Platinum-Based Chemotherapy

Two randomized, controlled trials established that a TAXOTERE dose of 75 mg/m^2 was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy (see below). TAXOTERE at a dose of 100 mg/m^2, however, was associated with unacceptable hematologic toxicity, infections, and treatment-related mortality and this dose should not be used *[see Boxed Warning, Dosage and Administration (2.7), Warnings and Precautions (5.3)]*.

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/m^2 or best supportive care, but early toxic deaths at this dose led to a dose reduction to TAXOTERE 75 mg/m^2. A total of 104 patients were randomized in this amended study to either TAXOTERE 75 mg/m^2 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/m^2, TAXOTERE 100 mg/m^2 and a treatment in which the investigator chose either vinorelbine 30 mg/m^2 days 1, 8, and 15 repeated every 3 weeks or ifosfamide 2 g/m^2 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/m^2 arm and the comparator arms are summarized in Table 15 and Figures 3 and 4 showing the survival curves for the two studies.

Table 15 - 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/m^2 n=55	**Best Supportive Care n=49**	**Docetaxel 75 mg/m^2 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)

* Vinorelbine/Ifosfamide

** 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/m^2.

Figure 3 - TAX317 Survival K-M Curves - TAXOTERE 75 mg/m^2 vs. Best Supportive Care

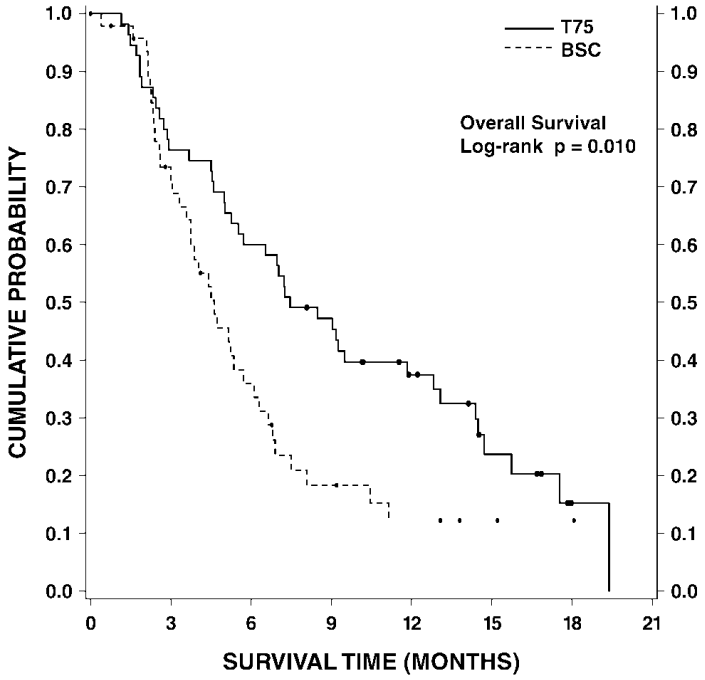
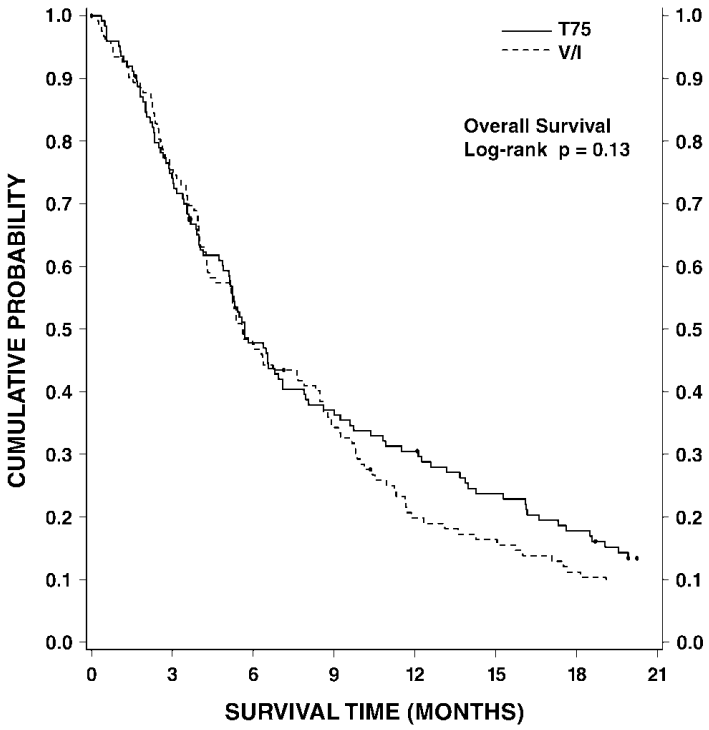


Figure 4 - TAX320 Survival K-M Curves - TAXOTERE 75 mg/m^2 vs. Vinorelbine or Ifosfamide Control



Patients treated with TAXOTERE at a dose of 75 mg/m^2 experienced no deterioration in performance status and body weight relative to the comparator arms used in these trials.

Combination Therapy with TAXOTERE for Chemotherapy-Naïve NSCLC

In a randomized controlled trial (TAX326), 1218 patients with unresectable stage IIIB or IV NSCLC and no prior chemotherapy were randomized to receive one of three treatments: TAXOTERE 75 mg/m^2 as a 1 hour infusion immediately followed by cisplatin 75 mg/m^2 over 30 to 60 minutes every 3 weeks; vinorelbine 25 mg/m^2 administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100 mg/m^2 administered on day 1 of cycles repeated every 4 weeks; or a combination of TAXOTERE and carboplatin.

The primary efficacy endpoint was overall survival. Treatment with TAXOTERE+cisplatin did not result in a statistically significantly superior survival compared to vinorelbine+cisplatin (see table below). The 95% confidence interval of the hazard ratio (adjusted for interim analysis and multiple comparisons) shows that the addition of TAXOTERE to cisplatin results in an outcome ranging from a 6% inferior to a 26% superior survival compared to the addition of vinorelbine to cisplatin. The results of a further statistical analysis showed that at least (the lower bound of the 95% confidence interval) 62% of the known survival effect of vinorelbine when added to cisplatin (about a 2-month increase in median survival; Wozniak et al. JCO, 1998) was maintained. The efficacy data for the TAXOTERE+cisplatin arm and the comparator arm are summarized in Table 16.

Table 16 - Survival Analysis of TAXOTERE in Combination Therapy for Chemotherapy-Naïve NSCLC

Comparison	Taxotere+Cisplatin n=408	Vinorelbine+Cisplatin n=405
Kaplan-Meier Estimate of Median Survival	10.9 months	10.0 months
p-value[a]	0.122	
Estimated Hazard Ratio[b]	0.88	
Adjusted 95% CI[c]	(0.74, 1.06)	

[a] From the superiority test (stratified log rank) comparing TAXOTERE+cisplatin to vinorelbine+cisplatin

[b] Hazard ratio of TAXOTERE+cisplatin vs. vinorelbine+cisplatin. A hazard ratio of less than 1 indicates that TAXOTERE+cisplatin is associated with a longer survival.

[c] Adjusted for interim analysis and multiple comparisons.

The second comparison in the same three-arm study, vinorelbine+cisplatin versus TAXOTERE+carboplatin, did not demonstrate superior survival associated with the TAXOTERE arm (Kaplan-Meier estimate of median survival was 9.1 months for TAXOTERE+carboplatin compared to 10.0 months on the vinorelbine+cisplatin arm) and the TAXOTERE+carboplatin arm did not demonstrate preservation of at least 50% of the survival effect of vinorelbine added to cisplatin. Secondary endpoints evaluated in the trial included objective response and time to progression. There was no statistically significant difference between TAXOTERE+cisplatin and vinorelbine+cisplatin with respect to objective response and time to progression (see Table 17).

Table 17 - Response and TTP Analysis of TAXOTERE in Combination Therapy for Chemotherapy-Naïve NSCLC

Endpoint	TAXOTERE+Cisplatin	Vinorelbine+Cisplatin	p-value
Objective Response Rate	31.6%	24.4%	Not Significant

(95% CI)[a]	(26.5%, 36.8%)	(19.8%, 29.2%)	
Median Time to Progression[b] (95% CI)[a]	21.4 weeks (19.3, 24.6)	22.1 weeks (18.1, 25.6)	Not Significant

[a]Adjusted for multiple comparisons.

[b]Kaplan-Meier estimates.

14.4 Hormone Refractory Prostate Cancer

The safety and efficacy of TAXOTERE in combination with prednisone in patients with androgen independent (hormone refractory) metastatic prostate cancer were evaluated in a randomized multicenter active control trial. A total of 1006 patients with Karnofsky Performance Status (KPS) ≥60 were randomized to the following treatment groups:

- TAXOTERE 75 mg/m^2 every 3 weeks for 10 cycles.
- TAXOTERE 30 mg/m^2 administered weekly for the first 5 weeks in a 6-week cycle for 5 cycles.
- Mitoxantrone 12 mg/m^2 every 3 weeks for 10 cycles.

All 3 regimens were administered in combination with prednisone 5 mg twice daily, continuously.

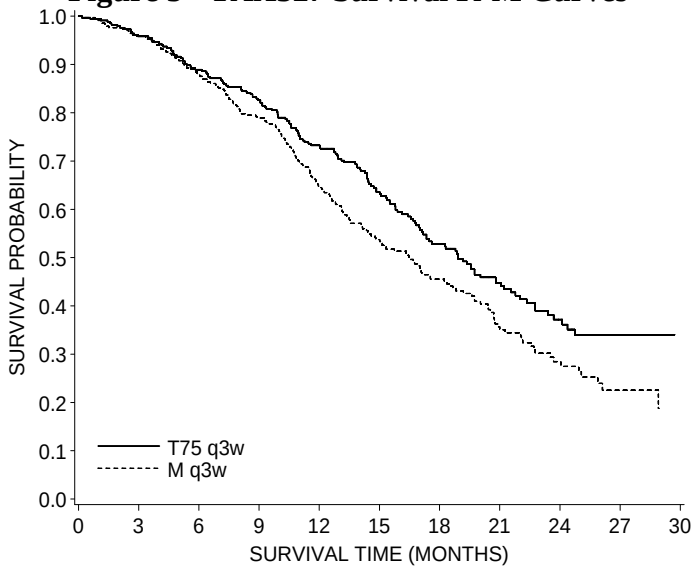
In the TAXOTERE every three week arm, a statistically significant overall survival advantage was demonstrated compared to mitoxantrone. In the TAXOTERE weekly arm, no overall survival advantage was demonstrated compared to the mitoxantrone control arm. Efficacy results for the TAXOTERE every 3 week arm versus the control arm are summarized in Table 18 and Figure 5.

Table 18 - Efficacy of TAXOTERE in the Treatment of Patients with Androgen Independent (Hormone Refractory) Metastatic Prostate Cancer (Intent-to-Treat Analysis)

	TAXOTERE+ Prednisone every 3 weeks	**Mitoxantrone+ Prednisone every 3 weeks**
Number of patients	335	337
Median survival (months)	18.9	16.5
95% CI	(17.0-21.2)	(14.4-18.6)
Hazard ratio	0.761	--
95% CI	(0.619-0.936)	--
p-value*	0.0094	--

*Stratified log rank test. Threshold for statistical significance = 0.0175 because of 3 arms.

Figure 5 - TAX327 Survival K-M Curves



14.5 Gastric Adenocarcinoma

A multicenter, open-label, randomized trial was conducted to evaluate the safety and efficacy of TAXOTERE for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for advanced disease. A total of 445 patients with KPS >70 were treated with either TAXOTERE (T) (75 mg/m^2 on day 1) in combination with cisplatin (C) (75 mg/m^2 on day 1) and fluorouracil (F) (750 mg/m^2 per day for 5 days) or cisplatin (100 mg/m^2 on day 1) and fluorouracil (1000 mg/m^2 per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The demographic characteristics were balanced between the two treatment arms. The median age was 55 years, 71% were male, 71% were Caucasian, 24% were 65 years of age or older, 19% had a prior curative surgery and 12% had palliative surgery. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint and was defined as time from randomization to disease progression or death from any cause within 12 weeks of the last evaluable tumor assessment or within 12 weeks of the first infusion of study drugs for patients with no evaluable tumor assessment after randomization. The hazard ratio (HR) for TTP was 1.47 (CF/TCF, 95% CI: 1.19-1.83) with a significantly longer TTP (p=0.0004) in the TCF arm. Approximately 75% of patients had died at the time of this analysis. Overall survival was significantly longer (p=0.0201) in the TCF arm with a HR of 1.29 (95% CI: 1.04-1.61). Efficacy results are summarized in Table 19 and Figures 6 and 7.

Table 19 - Efficacy of TAXOTERE in the treatment of patients with gastric adenocarcinoma

Endpoint	TCF n=221	CF n=224
Median TTP (months)	5.6	3.7
(95%CI)	(4.86-5.91)	(3.45-4.47)
Hazard ratio†	0.68	
(95%CI)	(0.55-0.84)	
*p-value	0.0004	
Median survival (months)	9.2	8.6
(95%CI)	(8.38-10.58)	(7.16-9.46)
Hazard ratio†	0.77	
(95%CI)	(0.62-0.96)	
*p-value	0.0201	
Overall Response Rate (CR+PR) (%)	36.7	25.4
p-value	0.0106	

*Unstratified log-rank test

†For the hazard ratio (TCF/CF), values less than 1.00 favor the TAXOTERE arm.

Subgroup analyses were consistent with the overall results across age, gender and race.

Figure 6 - Gastric Cancer Study (TAX325) Time to Progression K-M Curve

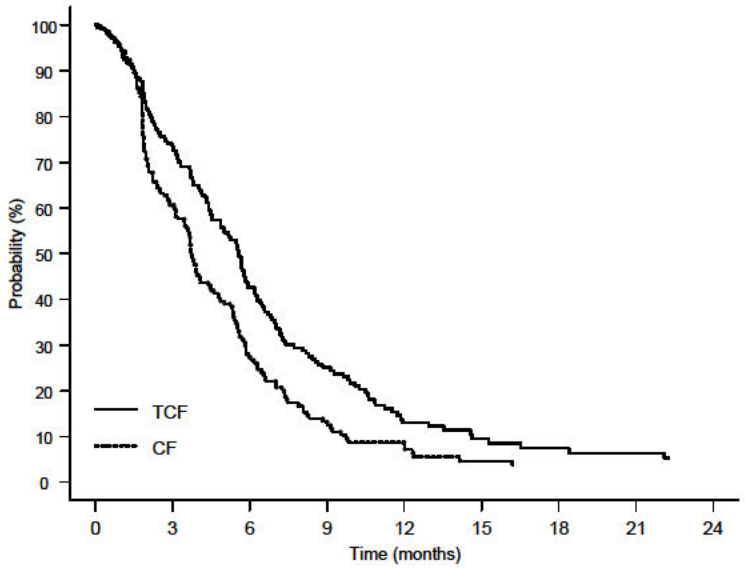
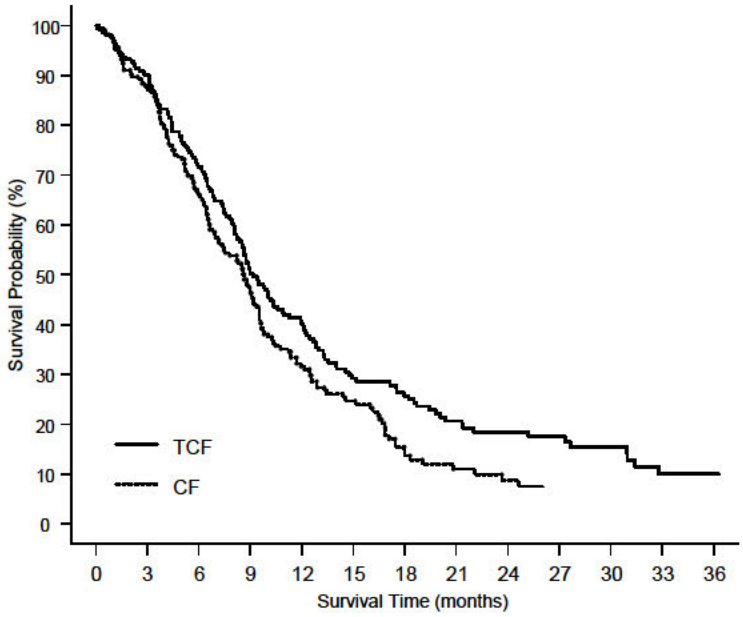


Figure 7 - Gastric Cancer Study (TAX325) Survival K-M Curve



14.6 Head and Neck Cancer

Induction chemotherapy followed by radiotherapy (TAX323)

The safety and efficacy of TAXOTERE in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a multicenter, open-label, randomized trial (TAX323). In this study, 358 patients with inoperable locally advanced SCCHN, and WHO performance status 0 or 1, were randomized to one of two treatment arms. Patients on the TAXOTERE arm received TAXOTERE (T) 75 mg/m^2 followed by cisplatin (P) 75 mg/m^2 on Day 1, followed by fluorouracil (F) 750 mg/m^2 per day as a continuous infusion on Days 1-5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines (TPF/RT). Patients on the comparator arm received cisplatin (P) 100 mg/m^2 on Day 1, followed by fluorouracil (F) 1000 mg/m^2/day as a continuous infusion on Days 1-5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received RT according to institutional guidelines (PF/RT). At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines. Locoregional therapy with radiation was delivered either with a conventional fraction regimen (1.8 Gy-2.0 Gy once a day, 5 days per week for a total dose of 66 to 70 Gy) or with an accelerated/hyperfractionated regimen (twice a day, with a minimum interfraction interval of 6 hours, 5 days per week, for a total dose of 70 to 74 Gy, respectively). Surgical resection was allowed following chemotherapy, before or after radiotherapy.

The primary endpoint in this study, progression-free survival (PFS), was significantly longer in the TPF arm compared to the PF arm, p=0.0077 (median PFS: 11.4 vs. 8.3 months respectively)

with an overall median follow up time of 33.7 months. Median overall survival with a median follow-up of 51.2 months was also significantly longer in favor of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.2 months respectively). Efficacy results are presented in Table 20 and Figures 8 and 9.

Table 20 - Efficacy of TAXOTERE in the induction treatment of patients with inoperable locally advanced SCCHN (Intent-to-Treat Analysis)

ENDPOINT	TAXOTERE+ Cisplatin+ Fluorouracil n=177	Cisplatin+ Fluorouracil n=181
Median progression free survival (months) (95%CI)	11.4 (10.1-14.0)	8.3 (7.4-9.1)
Adjusted Hazard ratio (95%CI) *p-value	0.71 (0.56-0.91) 0.0077	
Median survival (months) (95%CI)	18.6 (15.7-24.0)	14.2 (11.5-18.7)
Hazard ratio (95%CI) **p-value	0.71 (0.56-0.90) 0.0055	
Best overall response (CR + PR) to chemotherapy (%) (95%CI)	67.8 (60.4-74.6)	53.6 (46.0-61.0)
***p-value	0.006	
Best overall response (CR + PR) to study treatment [chemotherapy +/- radiotherapy] (%) (95%CI)	72.3 (65.1-78.8)	58.6 (51.0-65.8)
***p-value	0.006	

A Hazard ratio of less than 1 favors TAXOTERE+Cisplatin+Fluorouracil
* Stratified log-rank test based on primary tumor site
** Stratified log-rank test, not adjusted for multiple comparisons
*** Chi square test, not adjusted for multiple comparisons

Figure 8 - TAX323 Progression-Free Survival K-M Curve

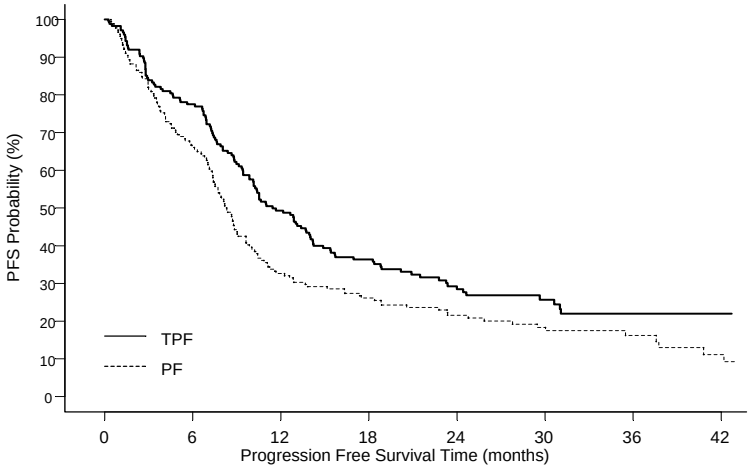
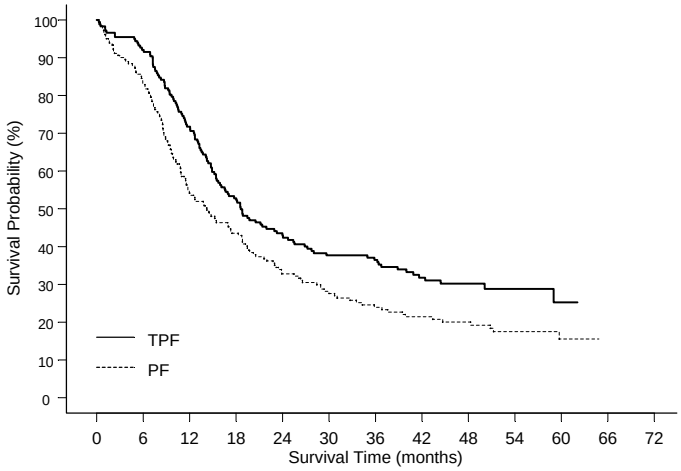


Figure 9 - TAX323 Overall Survival K-M Curve



Induction chemotherapy followed by chemoradiotherapy (TAX324)

The safety and efficacy of TAXOTERE in the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN was evaluated in a randomized, multicenter open-label trial (TAX324). In this study, 501 patients, with locally advanced SCCHN, and a WHO performance status of 0 or 1, were randomized to one of two treatment arms. Patients on the TAXOTERE arm received TAXOTERE (T) 75 mg/m² by intravenous infusion on day 1 followed by cisplatin (P) 100 mg/m² administered as a 30-minute to three-hour intravenous infusion, followed by the continuous intravenous infusion of fluorouracil (F) 1000 mg/m²/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 cycles. Patients on the comparator arm received cisplatin (P) 100 mg/m² as a 30-minute to three-hour intravenous infusion on day 1 followed by the continuous intravenous infusion of fluorouracil (F) 1000 mg/m²/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 cycles.

All patients in both treatment arms who did not have progressive disease were to receive 7 weeks of chemoradiotherapy (CRT) following induction chemotherapy 3 to 8 weeks after the start of the last cycle. During radiotherapy, carboplatin (AUC 1.5) was given weekly as a one-hour intravenous infusion for a maximum of 7 doses. Radiation was delivered with megavoltage equipment using once daily fractionation (2 Gy per day, 5 days per week for 7 weeks for a total dose of 70-72 Gy). Surgery on the primary site of disease and/or neck could be considered at anytime following completion of CRT.

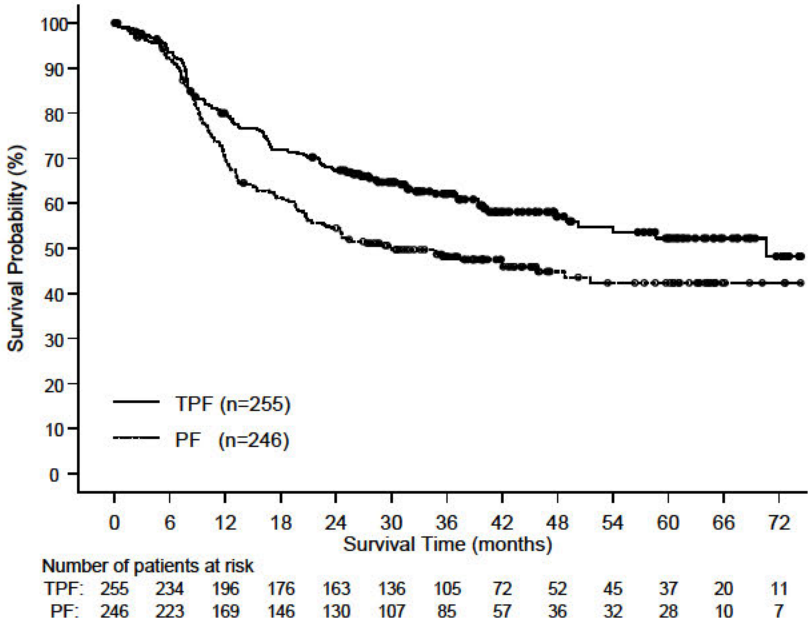
The primary efficacy endpoint, overall survival (OS), was significantly longer (log-rank test, p=0.0058) with the TAXOTERE-containing regimen compared to PF [median OS: 70.6 versus 30.1 months respectively, hazard ratio (HR)=0.70, 95% confidence interval (CI)= 0.54 – 0.90]. Overall survival results are presented in Table 21 and Figure 10.

Table 21 - Efficacy of TAXOTERE in the induction treatment of patients with locally advanced SCCHN (Intent-to-Treat Analysis)

ENDPOINT	TAXOTERE+ Cisplatin+ Fluorouracil n=255	Cisplatin+ Fluorouracil n=246
Median overall survival (months) (95% CI)	70.6 (49.0-NE)	30.1 (20.9-51.5)
Hazard ratio: (95% CI) *p-value	0.70 (0.54-0.90) 0.0058	

A Hazard ratio of less than 1 favors TAXOTERE+cisplatin+fluorouracil
* un-adjusted log-rank test
NE - not estimable

Figure 10 - TAX324 Overall Survival K-M Curve



15. REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193

4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

One-vial TAXOTERE (Injection Concentrate)

TAXOTERE Injection Concentrate is supplied in a single use vial as a sterile, pyrogen-free, non-aqueous solution.

TAXOTERE 80 mg/4 mL (NDC 0075-8004-04)
TAXOTERE (docetaxel) Injection Concentrate 80 mg/4 mL: 80 mg docetaxel in 4 mL 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol..
The vial is in a blister pack in one carton.

TAXOTERE 20 mg/mL (NDC 0075-8003-01)
TAXOTERE (docetaxel) Injection Concentrate 20 mg/1 mL: 20 mg docetaxel in 1 mL in 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol.
The vial is in a blister pack in one carton.

16.2 Storage

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

16.3 Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*.

17. PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

- TAXOTERE may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Women of childbearing potential should use effective contraceptives if receiving TAXOTERE *[see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)]*.
- Obtain detailed allergy and concomitant drug information from the patient prior to TAXOTERE administration.
- Explain the significance of oral corticosteroids such as dexamethasone administration to the patient to help facilitate compliance. Instruct patients to report if they were not compliant with oral corticosteroid regimen.
- Instruct patients to immediately report signs of a hypersensitivity reaction.
- Tell patients to watch for signs of fluid retention such as peripheral edema in the lower extremities, weight gain and dyspnea.
- Explain the significance of routine blood cell counts. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever.
- Instruct patients to report myalgia, cutaneous, or neurologic reactions.
- Explain to patients that side effects such as nausea, vomiting, diarrhea, constipation, fatigue, excessive tearing, infusion site reactions, and hair loss are associated with docetaxel administration.

Patient Information

TAXOTERE (pronounced as TAX-O-TEER)
(generic name = docetaxel)

Read this Patient Information before you receive your first treatment with TAXOTERE and each time before you are treated. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about TAXOTERE?

TAXOTERE can cause serious side effects, including death.

1. **The chance of death in people who receive TAXOTERE is higher if you:**
   - have liver problems
   - receive high doses of TAXOTERE
   - have non-small cell lung cancer and have been treated with chemotherapy medicines that contain platinum
2. **TAXOTERE can affect your blood cells.** Your doctor should do routine blood tests during treatment with TAXOTERE. This will include regular checks of your white blood cell counts. If your white blood cells are too low, your doctor may not treat you with TAXOTERE until you have enough white blood cells. People with low white blood counts can develop life-threatening infections. The earliest sign of infection may be fever. Follow your doctor's instructions for how often to take your temperature while taking TAXOTERE. Call your doctor right away if you have a fever.
3. **Serious allergic reactions** can happen in people who take TAXOTERE. Serious allergic reactions are medical emergencies that can lead to death and must be treated right away.

   Tell your doctor right away if you have any of these signs of a serious allergic reaction:

   - trouble breathing
   - sudden swelling of your face, lips, tongue, throat, or trouble swallowing
   - hives (raised bumps), rash, or redness all over your body
4. **Your body may hold too much fluid (severe fluid retention)** during treatment with TAXOTERE. This can be life threatening. To decrease the chance of this happening, you must take another medicine, a corticosteroid, before each TAXOTERE treatment. You must take the corticosteroid exactly as your doctor tells you. Tell your doctor or nurse before your TAXOTERE treatment if you forget to take corticosteroid dose or do not take it as your doctor tells you.

What is TAXOTERE?

TAXOTERE is a prescription anti-cancer medicine used to treat certain people with:

- breast cancer
- non-small cell lung cancer
- prostate cancer
- stomach cancer
- head and neck cancer

The effectiveness of TAXOTERE in children has not been established.

Who should not take TAXOTERE?

Do not take TAXOTERE if you:

- have had a severe allergic reaction to:
    - docetaxel, the active ingredient in TAXOTERE, **or**
    - any other medicines that contain polysorbate 80. Ask your doctor or pharmacist if you are not sure.

    See "What is the most important information I should know about TAXOTERE?" for the signs and symptoms of a severe allergic reaction.
- have a low white blood cell count.

What should I tell my doctor before receiving TAXOTERE?

Before you receive TAXOTERE, tell your doctor if you:

- are allergic to any medicines. See "Who should not take TAXOTERE?" Also, see the end of this leaflet for a list of the ingredients in TAXOTERE.
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. TAXOTERE can harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if TAXOTERE passes into your breast milk. You and your doctor should decide if you will take TAXOTERE or breast-feed.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. TAXOTERE may affect the way other medicines work, and other medicines may affect the way TAXOTERE works.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How will I receive TAXOTERE?

- TAXOTERE will be given to you as an intravenous (IV) injection into your vein, usually over 1 hour.
- TAXOTERE is usually given every 3 weeks.
- Your doctor will decide how long you will receive treatment with TAXOTERE.
- Your doctor will check your blood cell counts and other blood tests during your treatment with TAXOTERE to check for side effects of TAXOTERE.
- Your doctor may stop your treatment, change the timing of your treatment, or change the dose of your treatment if you have certain side effects while taking TAXOTERE.

What are the possible side effects of TAXOTERE?

TAXOTERE may cause serious side effects including death.

- See "What is the most important information I should know about TAXOTERE?"
- **Acute Myeloid Leukemia (AML),** a type of blood cancer**,** can happen in people who take TAXOTERE along with certain other medicines. Tell your doctor about all the medicines you take.
- **Other Blood Disorders –** Changes in blood counts due to leukemia and other blood disorders may occur years after treatment with Taxotere.
- **Skin Reactions** including redness and swelling of your arms and legs with peeling of your skin.
- **Neurologic Symptoms** including numbness, tingling, or burning in your hands and feet.

The most common side effects of TAXOTERE include:

- changes in your sense of taste
- feeling short of breath
- constipation
- decreased appetite
- changes in your fingernails or toenails
- swelling of your hands, face or feet
- feeling weak or tired
- joint and muscle pain
- nausea and vomiting
- diarrhea
- mouth or lips sores
- hair loss
- rash
- redness of the eye, excess tearing

- skin reactions at the site of TAXOTERE administration such as increased skin pigmentation, redness, tenderness, swelling, warmth or dryness of the skin.
- tissue damage if TAXOTERE leaks out of the vein into the tissues

Tell your doctor if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of TAXOTERE. For more information ask your doctor or pharmacist.

Call your doctor or for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about TAXOTERE

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. This Patient Information leaflet summarizes the most important information about TAXOTERE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about TAXOTERE that is written for healthcare professionals.

For more information contact 1-800-633-1610

What are the ingredients in TAXOTERE?

Active ingredient: docetaxel
Inactive ingredients include: ethanol and polysorbate 80

Every three-week injection of TAXOTERE for breast, non-small cell lung and stomach, and head and neck cancers
Take your oral corticosteroid medicine as your doctor tells you.

Oral corticosteroid *dosing:*

Day 1 Date: _____ Time:_____ AM _____ PM

Day 2 Date: _____ Time:_____ AM _____ PM
(Taxotere Treatment Day)

Day 3 Date: Time: AM PM

Every three-week injection of TAXOTERE for prostate cancer
Take your oral corticosteroid medicine as your doctor tells you.

Oral corticosteroid dosing:

Date: _____ Time:_____

Date: _____ Time:_____
(Taxotere Treatment Day)
Time:_____

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Taxotere®
(docetaxel)
Injection Concentrate
20 mg/mL

Each mL contains 20 mg docetaxel in 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol.

Ready to add to infusion solution.

Withdraw the required amount of docetaxel concentrate **(20 mg/mL)** from the vial and add it directly into the infusion solution for administration. See package insert for complete instructions.

Single Use Vial. Discard unused contents appropriately.

Dosage and Administration: See package insert for dosage information, directions for use and handling.

WARNING: Cytotoxic agent. Keep out of reach of children.

Store between 2–25°C (36–77°F).
Protect from light.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807 ©2009
Origin United Kingdom 5008XXXX

N 3 00758 00301 9

AXOTERE® (docetaxel)
Injection Concentrate
20 mg/mL
Contains 1 mL

NDC 0075-8003-01

FOR FDA SUBMISSION ONLY

AXOTERE® (docetaxel)
Injection Concentrate
20 mg/mL
Contains 1 mL

NDC 0075-8003-01

sanofi aventis

Rx ONLY

Contains 1 mL

For Intravenous Infusion Only

READY TO ADD TO INFUSION SOLUTION

Pull to remove leaflet

AXOTERE® (docetaxel)
Injection Concentrate
20 mg/mL

NEW CONCENTRATION AND PREPARATION

NDC 0075-8003-01

Lot

Exp

AXOTERE® (docetaxel)
Injection Concentrate
20 mg/mL
Contains 1 mL

NDC 0075-8003-01

Taxotere®
(docetaxel)
Injection Concentrate
80 mg/4 mL (20 mg/mL)

Each mL contains 20 mg docetaxel in 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol.

Ready to add to infusion solution.

Withdraw the required amount of docetaxel concentrate **(20 mg/mL)** from the vial and add it directly into the infusion solution for administration. See package insert for complete instructions.

Single Use Vial. Discard unused contents appropriately.

Dosage and Administration: See package insert for dosage information, directions for use and handling.

WARNING: Cytotoxic agent. Keep out of reach of children.

Store between 2–25°C (36–77°F).
Protect from light.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807 ©2009
Origin United Kingdom 5008XXXX

N 3 00758 00404 7

AXOTERE® *(docetaxel)*
Injection Concentrate
80 mg/4 mL
(20 mg/mL)
Contains 4 mL

NDC 0075-8004-04

AXOTERE® *(docetaxel)*
Injection Concentrate
80 mg/4 mL
(20 mg/mL)
Contains 4 mL

NDC 0075-8004-04

AXOTERE® *(docetaxel)*
Injection Concentrate
80 mg/4 mL
(20 mg/mL)
Contains 4 mL

NDC 0075-8004-04

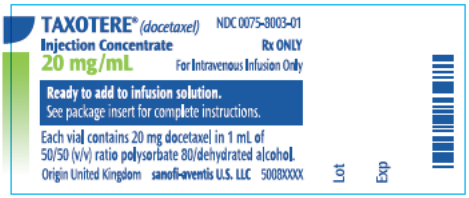
NEW CONCENTRATION AND PREPARATION

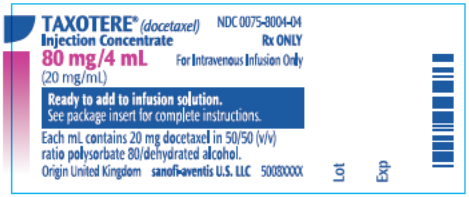
Pull to remove leaflet

READY TO ADD TO INFUSION SOLUTION
For Intravenous Infusion Only
Contains 4 mL
Rx ONLY

sanofi aventis

Lot Exp


TAXOTERE® (docetaxel)
NDC 0075-8003-01
Injection Concentrate
Rx ONLY
20 mg/mL
For Intravenous Infusion Only
Ready to add to infusion solution.
See package insert for complete instructions.
Each vial contains 20 mg docetaxel in 1 mL of
50/50 (v/v) ratio polysorbate 80/dehydrated alcohol.
Origin United Kingdom sanofi-aventis U.S. LLC 500BXXXX
Lot
Exp


TAXOTERE® (docetaxel)
Injection Concentrate
80 mg/4 mL
(20 mg/mL)
NDC 0075-8004-04
Rx ONLY
For Intravenous Infusion Only
Ready to add to infusion solution.
See package insert for complete instructions.
Each mL contains 20 mg docetaxel in 50/50 (v/v)
ratio polysorbate 80/dehydrated alcohol.
Origin United Kingdom sanofi-aventis U.S. LLC 50030XXX
Lot
Exp

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449/S054

SUMMARY REVIEW

Division of Drug Oncology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: 020449/S-054

Name of Drug: TAXOTERE (docetaxel) Injection Concentrate, 20 mg and 80 mg

Applicant: sanofi-aventis U.S.LLC

Material Reviewed:

Submission Date: 12/22/2008

Receipt Date: 12/22/2008

Link: < **\\FDSWA150\NONECTD\4061754>**

Background and Summary Description: NDA 020449 is approved for:

- **Breast Cancer (BC)**: single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC.
- **Non-Small Cell Lung Cancer (NSCLC)**: single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC.
- **Hormone Refractory Prostate Cancer (HRPC)**: with prednisone in androgen independent (hormone refractory) metastatic prostate cancer.
- **Gastric Adenocarcinoma (GC)**: with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction.
- **Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN)**: with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN.

S-054, a prior approval supplement, provides for the approval of a new one-vial formulation and associated labeling (Package Insert, Patient Package Insert, Carton and Container (b) (4) . This supplement has been reviewed **by:**

Clinical	Pharmacology/Toxicology	Clinical Pharmacology	CMC	DMEPA
Qin Ryan Ellen Maher Ke Liu	Margaret Brower Haleh Saber	Sophia Abraham Qi Liu	Cheng Yi Liang Liang Zhou Hasmukh Patel	Carol Holquist Loretta Holmes Denise Toyer

Review

The submitted draft package insert, identified as "proposeddpi.doc" was compared to the package insert, identified as "S-045", i.e., NDA 020449/SE1-045, approved on September 28, 2007. Updates from S-044 and S-053, approved on April 20, 2010, and S-059, approved on May 13, 2010, were included in the Final Package Insert and Patient Package Insert for this supplement S-054.

Note:

- September 14, 2009 Applicant submitted a Complete Response in response to the June 22, 2009, Complete Response letter.
- FDA Email Messages of January 7 and 13, April 23 and 28, 2010 - Conveyed DMEPA Recommendations to Applicant and Applicant responded January 20, and April 29, 2010, respectively.
- Applicant responded to FDA request to update S-054 with the approved S-044 and S-053 (two vials) - label of April 26, 2010.
- Applicant also responded to the FDA request to update the S-054 label with the approved S-059 (pediatric) label approved May 18, 2010.
- Final Carton and Container labeling submitted on January 8, 2010; final PI and PPI submitted on June 25, 2010.

{See appended electronic signature page}

Modupe Fagbami.
Regulatory Health Project Manager

{See appended electronic signature page}

Frank Cross Jr. CPMS
Chief, Project Management Staff

Attachments:
Package Insert, Patient Package Insert,
Carton and Container labeling.

143 pages immediately following withheld - Draft Labeling b(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

MODUPE O FAGBAMI
07/01/2010

LIANG ZHOU
07/01/2010
for BC Dr. H. Patel

KE LIU
07/01/2010

FRANK H Cross
07/16/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

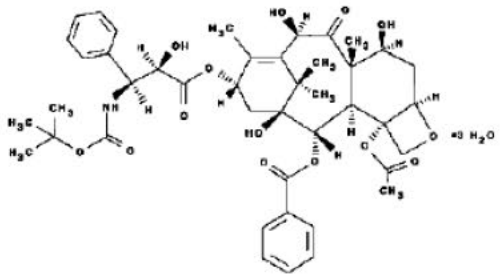
APPLICATION NUMBER:

20-449/S054

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #3	1. ORGANIZATION ONDQA/HFD-150	2. NDA NUMBER 20-449
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Sanofi-Aventis U. S. LLC 200 Crossing Boulevard Bridgewater, NJ 08807		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)
6. NAME OF DRUG Taxotere Injection Concentrate	7. NONPROPRIETARY NAME Docetaxel	SCF 054 Amendment 12/22/2008 4/6/2010
8. SUPPLEMENT PROVIDES FOR: a new one-vial formulation DP to replace the approved two-vial DP.		9. AMENDMENTS DATES
10. PHARMACOLOGICAL CATEGORY Antineoplastic	11. HOW DISPENSED RX √ OTC	12. RELATED IND/NDA/DMF None
13. DOSAGE FORM(S) Injection	14. POTENCY 20 mg and 80 mg/vial	

15. CHEMICAL NAME AND STRUCTURE



(2*R*,3*S*)-*N*-Carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β ,20-epoxy-1,2α,4α,7β,10β,8,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.
Molecular formula: $C_{43}H_{53}NO_{14}$. $3H_2O$. Molecular weight: 861.93

16. RECORDS AND REPORTS

CURRENT YES √ NO

REVIEWED YES √ NO

17. COMMENTS

The original supplement was to introduce one vial formulation (b) (4) CMC as well as labeling information about one vial DP was reviewed and this supplement was approved (see review 1). (b) (4)

No additional changes in CMC and vial/carton label were proposed in this amendment. Revised PI (b) (4) has also been reviewed and CMC related sections are found to be acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval is recommended based on the adequate CMC information.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.		4-22-2010

DISTRIBUTION	ORIGINAL JACKET	DIVISION FILE	Reviewer: C.Liang	CSO:	Branch Chief H. Patel

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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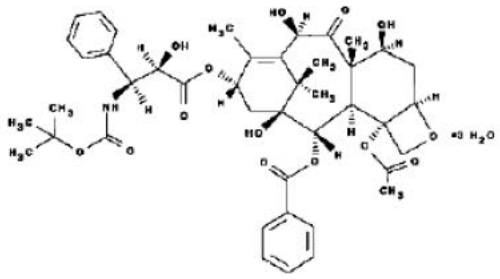
/s/

CHENG YI LIANG
04/23/2010

HASMUKH B PATEL
04/23/2010

CHEMIST'S REVIEW #2	1. ORGANIZATION ONDQA/HFD-150	2. NDA NUMBER 20-449
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Sanofi-Aventis U. S. LLC 200 Crossing Boulevard Bridgewater, NJ 08807		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)
6. NAME OF DRUG Taxotere Injection Concentrate	7. NONPROPRIETARY NAME Docetaxel	SCF 054 | 12/22/2008
8. SUPPLEMENT PROVIDES FOR: a new one-vial formulation DP to replace the approved two-vial DP.		9. AMENDMENTS DATES
10. PHARMACOLOGICAL CATEGORY Antineoplastic	11. HOW DISPENSED RX √ OTC	12. RELATED IND/NDA/DMF None
13. DOSAGE FORM(S) Injection	14. POTENCY 20 mg and 80 mg/vial	

15. CHEMICAL NAME AND STRUCTURE



(2*R*,3*S*)-*N*-Carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β ,20-epoxy-1,2α,4α,7β,10β,8,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.
Molecular formula: $C_{43}H_{53}NO_{14}$. $3H_2O$. Molecular weight: 861.93

16. RECORDS AND REPORTS

CURRENT YES √ NO

REVIEWED YES √ NO

17. COMMENTS

The original supplement was approved pending DMEPA consult (b) (4)

The final labeling review was completed by DEMEPA and found the revised DP name Taxotere (docetaxel) Injection Concentrate, Intravenous Infusion (IV) to be acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval is recommended based on the adequate CMC information and DMEPA consult.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.		1-14-2010

DISTRIBUTION	ORIGINAL JACKET	DIVISION FILE	Reviewer: C.Liang	CSO:	Branch Chief H. Patel

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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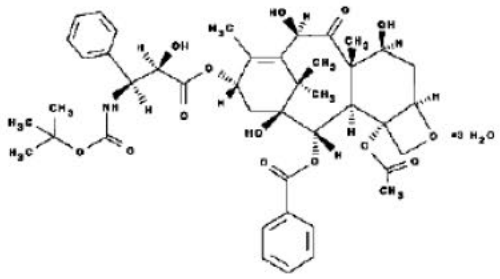
/s/

CHENG YI LIANG
01/14/2010

LIANG ZHOU
01/14/2010
Acting for Dr. H. Patel and requested by OND CSO due today afternoon

CHEMIST'S REVIEW #2	1. ORGANIZATION ONDQA/HFD-150	2. NDA NUMBER 20-449	
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Sanofi-Aventis U. S. LLC 200 Crossing Boulevard Bridgewater, NJ 08807		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG Taxotere Injection Concentrate	7. NONPROPRIETARY NAME Docetaxel	SCF 054	12/22/2008
8. SUPPLEMENT PROVIDES FOR: a new one-vial formulation DP to replace the approved two-vial DP.		9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Antineoplastic	11. HOW DISPENSED RX √ OTC	12. RELATED IND/NDA/DMF None	
13. DOSAGE FORM(S) Injection	14. POTENCY 20 mg and 80 mg/vial		

15. CHEMICAL NAME AND STRUCTURE



(2*R*,3*S*)-*N*-Carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β ,20-epoxy-1,2α,4α,7β,10β,8,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.
Molecular formula: $C_{43}H_{53}NO_{14}$. $3H_2O$. Molecular weight: 861.93

16. RECORDS AND REPORTS

CURRENT YES √ NO

REVIEWED YES √ NO

17. COMMENTS

The original supplement was approved pending DMEPA consult (b) (4)

The final labeling review was completed by DEMEPA and found the revised DP name Taxotere (docetaxel) Injection Concentrate, Intravenous Infusion (IV) to be acceptable. In addition, the section of How Supplied in PI is also acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval is recommended based on the adequate CMC information and DMEPA consult.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.		1-14-2010

DISTRIBUTION	ORIGINAL JACKET	DIVISION FILE	Reviewer: C.Liang	CSO:	Branch Chief H. Patel

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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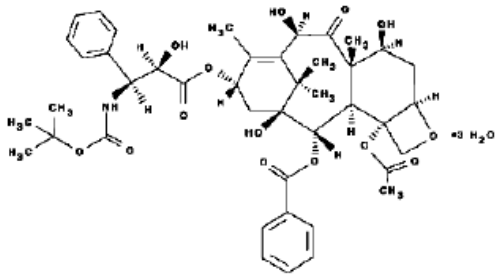
/s/

CHENG YI LIANG
01/14/2010

LIANG ZHOU
01/14/2010
sign for Dr. H. Patel

CHEMIST'S REVIEW #1	1. ORGANIZATION ONDQA/HFD-150	2. NDA NUMBER 20-449	
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Sanofi-Aventis U. S. LLC 200 Crossing Boulevard Bridgewater, NJ 08807		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG Taxotere Injection Concentrate	7. NONPROPRIETARY NAME Docetaxel	SCF 054	12/22/2008
8. SUPPLEMENT PROVIDES FOR: a new one-vial formulation DP to replace the approved two-vial DP.		9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Antineoplastic	11. HOW DISPENSED RX √ OTC	12. RELATED IND/NDA/DMF None	
13. DOSAGE FORM(S) Injection	14. POTENCY 20 mg and 80 mg/vial		
15. CHEMICAL NAME AND STRUCTURE  (2*R*,3*S*)-*N*-Carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β ,20-epoxy-1,2α,4α,7β,10β,8,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Molecular formula: $C_{43}H_{53}NO_{14}$. $3H_2O$. Molecular weight: 861.93		16. RECORDS AND REPORTS CURRENT YES √ NO REVIEWED YES √ NO	

17. COMMENTS

See review notes.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval is recommended based on the adequate CMC information Pending DMEPA consult.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.		6-19-2009

DISTRIBUTION	ORIGINAL JACKET	DIVISION FILE	Reviewer: C.Liang	CSO:	Branch Chief H. Patel

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/s/

Chengyi Liang
6/19/2009 08:35:39 AM
CHEMIST

Hasmukh Patel
6/19/2009 12:53:46 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449/S054

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**20,449**
eCTD SEQUENCE NUMBER:	**0001**
DATE RECEIVED BY CENTER:	**January 6, 2009**
PRODUCT:	**Docetaxel**
INTENDED CLINICAL POPULATION:	**Breast Cancer (BC), Non-Small Cell Lung Cancer (NSCLC), Hormone-Refractory Prostate Cancer (HRPC), Gastric Adenocarcionoma (GC), Squamous Cell Carcinoma of the Head and Neck (SCCHN)**
SPONSOR:	**Sanofi Aventis**
DOCUMENTS REVIEWED:	**Study Amendment**
REVIEW DIVISION:	**OODP/DDOP**
PHARM/TOX REVIEWER:	**Margaret E. Brower, Ph.D.**
PHARM/TOX SUPERVISOR:	**Haleh Saber, Ph.D.**
DIVISION DIRECTOR:	**Robert Justice, M.D.**
PROJECT MANAGER:	**Modupe Fagbami**

PHARMACOLOGY/TOXICOLOGY REVIEW

INTRODUCTION AND DRUG HISTORY

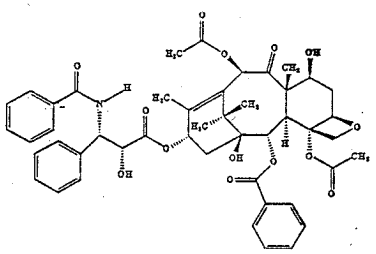
NDA number: 20,449
eCTD Sequence number/date/type of submission: 0001/January 6, 2009/Study amendment
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Sanofi Aventis, Vitry-sur-Seine, France

Reviewer name: Margaret Brower, Ph.D.
Division name: DDOP/OODP
Review completion date: April 2, 2009

Drug:

Generic Name: Docetaxel
Trade Name: Taxotere
Chemical Name: 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Structure:



Related INDs/NDAs/DMFs: IND 35555
Drug Class: Cytotoxic Antineoplastic Agent

Clinical formulation: **Current submission:** One-vial formulation (preparation of infusion solution simplified) with increased ethanol concentration (b) (4)

Marketed formulation: 2-vial formulation is concentrated solution requiring dilution prior to patient administration

Route of administration: iv

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

Study #	Study
DSE2003-0325	5-Day mouse toxicity study comparing currently marketed formulation ((b) (4) to formulation with increased ethanol (b) (4)
DSE 2003-0838	Comparative *in vitro* hemolysis in human blood
DSE-2003-0494	Local tolerance in rabbits

Studies not reviewed within this submission: none

Study title: 5-Day mouse toxicity study comparing currently marketed formulation (b) (4) to formulation with increased ethanol (b) (4)

Key study findings:
- Mortality at low-dose (LD) with (b) (4)
- Clinical findings of neurotoxicity with (b) (4) (not observed with (b) (4))
- Increased incidence of histopathological findings of neurotoxicity with (b) (4)

Note: The single LD death with the (b) (4) formulation may be procedure related. Additional clinical observations of neurotoxicity with the (b) (4) formulation, even though of low incidence, were due to the change in formulation (see below).

Note: Impurities reported for both formulations appear to be equal.

Study no: DSE2003-0325
Conducting laboratory and location: Sanofi Aventis, France
GLP compliance: Y

Dosing:

Species/strain: CD2F1/CrlBR mice
Age: 6-7w
# of animals/group: 12/sex

Methods: Mice from (b) (4) formulation (2-vial) group were administered solution of (b) (4)

Finding	(b) (4)		(b) (4)	
	6mg/m2	30mg/m2	6mg/m2	30mg/m2
Mortality		1/24 M(d8)	1/24 M(d1)[a]	
Clinical observations				1/24:↓motor activity (D2)[a] 2/24: unable to grasp w/ hindpaw (D18/22)[a]
Reticulocyte count (M/F) d12[b]		↓45/34		↓67/36
Organ weights(abs)[a] Brain (M) Heart (M) Liver (M)			 ↓8 ↓13	 ↓8 ↓27 ↓14

[a] Sponsor claims not compound related finding or does not recognize finding
[b] Percent compared to concurrent controls; partial rebound following recovery (D26)
M: males; F: females

Findings were not observed with both formulations. Males appeared to be more sensitive

Histopathology

Organ/finding /D12	(b) (4) 30mg/m2	(b) (4) 30mg/m2
Spinal cord/vacuolation /min-mild	5/6 (M) 4/6 (F)	5/6 (M) 5/6 (F) [a]
Lumbar nerve root/nerve fiber degeneration-axonal disruption/min-moderate	4/5 (M) 3/6 (F)	5/6 (M) 2/5 (F) [b]
Sciatic n/nerve fiber Degeneration/ min-moderate	6/6 (M) 6/6 (F)	6/6 (M) 6/6 (F)
Liver/extramedullary hematopoiesis (Gr 1)	3/6(F)	4/6(F)[a]
Spleen/extramed. Hematop (Gr3)	1/6(F)	2/6(F)[a]
Organ/finding/D26		
Spinal cord/vacuolation /min-mild	4/4 (M) 5/6 (F)	5/6 (M) 5/6 (F)[a]
Lumbar nerve root/nerve fiber degeneration-axonal disruption/min-moderate	4/5 (M) 6/6 (F)	6/6 (M) 6/6 (F)[a]
Sciatic n/nerve fiber Degeneration/ min-moderate	5/5(M) 6/6 (F)	6/6 (M) 6/6 (F)[b]

[a] increased incidence
[b] difficult to determine due to # animals, possibly equivocal
min: minimal

Study name: Comparative *in vitro* hemolysis /human blood

Key study findings: Hemolysis moderately increased with (b) (4)
Study no: DSE 2003-0838

Study name: Local tolerance in rabbits

Key study findings: Minimal to moderate erythema with both docetaxel formulations or vehicles.
Study no: DSE-2003-0494

Overall Conclusions and Recommendations:

Results from the comparative bridging study in mice indicated that the one-vial Taxotere formulation (b) (4) with the (b) (4) increase in ethanol concentration exhibited a slight increase in neurotoxicity in mice (clinical observations and histopathology). However, considering the history of neurotoxicity observed with the drug, the increase in neurotoxicity is not a significant concern. Impurities with the 2 formulations were reported to be equal.

RECOMMENDATIONS:
The one-vial formulation is acceptable from a pharmacology/toxicology perspective.

Discussion with Medical Officer: none

External Recommendations (to sponsor): none

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/s/

Margaret Brower
4/23/2009 01:52:18 PM
PHARMACOLOGIST

Haleh Saber
4/23/2009 03:32:12 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449/S054

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

06 April 2009

NDA: **020-449/SCF-054**

Drug Product Name
Proprietary: Taxotere® Injection Concentrate
Non-proprietary: Docetaxel

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
22-DEC-2008	22-DEC-2008	01-APR-2009	01-APR-2009

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Sanofi-aventis Inc.
Address: 55 Corporate Drive
Bridgewater, N.J. 08807
Representative: Linda Gustavson
Telephone: (908) 304-6221

Name of Reviewer: Denise Miller

Conclusion: Approve

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval

2. SUBMISSION PROVIDES FOR: Provides for a one-vial formulation (b) (4)

3. MANUFACTURING SITE:

Aventis Pharma Dagenham
Rainham Road South
DAGENHAM
Essex RM107XS
UNITED KINGDOM

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Liquid
- Intravenous Infusion
- 20mg/1 mL or 80mg/4mL (one vial formulation)
- (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Oncology

B. SUPPORTING/RELATED DOCUMENTS: N/A

C. REMARKS:

1) This was an electronic submission in CTD format.

filename: N020449S054R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend to approve from a quality microbiology standpoint

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Formulation change to add a one-vial configuration. (b) (4)

B. Brief Description of Microbiology Deficiencies - none

C. Assessment of Risk Due to Microbiology Deficiencies - N/A

III. Administrative

A. Reviewer's Signature _____
Denise Miller, Microbiologist

B. Endorsement Block _____
Bryan S. Riley, Ph.D.

C. CC Block
N/A

5 pages immediately following withheld - Trade Secret/Confidential
b(4)

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/s/

Denise Miller
4/8/2009 08:21:09 AM
MICROBIOLOGIST

Bryan Riley
4/8/2009 09:22:04 AM
MICROBIOLOGIST
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449/S054

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 14, 2010
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Denise P. Toyer, Pharm.D, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Taxotere (Docetaxel Injection) Concentrate 20 mg/mL and 80 mg/4 mL (20 mg/mL) vials
Application Type/Number:	NDA #20449/SCF-054
Applicant/sponsor:	Sanofi Aventis
OSE RCM #:	2009-122

1 INTRODUCTION

This review is written in response to a request from the Division of Drug Oncology Products for assessment of the revised container labels, carton and insert labeling for Taxotere (Docetaxel Injection) Concentrate one-vial configuration (NDA #20449/SCF-054).

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) to evaluate the insert labeling for the one-vial only configuration submitted by the Applicant on May 13, 2009 and the revised insert labeling submitted by the Applicant via e-mail on January 13, 2010. We also evaluated the container labels and carton labeling submitted on January 8, 2010.

3 RECOMMENDATIONS

The Applicant has addressed all of DMEPA's previous comments for the container labels and carton labeling in the January 8, 2010 submission. At the request of DDOP, our comments pertaining to the insert labeling were forward to the Division in an e-mail dated January 13, 2010. These comments are also contained in Appendix A. Subsequent to the DMEPA e-mail, the Applicant revised the insert labeling and we find the revisions acceptable.

Thus, we have no further label and labeling comments for this supplement.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact, Sarah Simon, OSE Regulatory Project Manager, at 301-796-5205.

APPENDICES

Appendix A Insert Labeling Recommendations

1. Section 2.8 Administration Precautions.
   Revise the second paragraph that begins "If Taxotere Injection Concentrate..." to read: "If Taxotere Injection Concentrate or the dilution for intravenous infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If Taxotere Injection Concentrate or the dilution for intravenous infusion should come into contact with mucosa, immediately and thoroughly wash with water."

2. Section 2.9 Preparation and Administration, Step 4.
   Revise the sentence that begins "If the Taxotere dilution..." to read: "If the Taxotere dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded."

3. Section 2.10 Stability
   The abbreviation "i.v." is used in the paragraph. Replace the abbreviation "i.v." with the completely spelled out word "intravenous".

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

LORETTA HOLMES
01/14/2010

DENISE P TOYER
01/14/2010

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	June 19, 2009
To:	Robert Justice, MD Director, Division of Drug Oncology Products
Through:	Kristina Arnwine, Pharm.D, RPh, Team Leader Denise P. Toyer, Pharm.D, Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, PharmD., Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name:	Taxotere (Docetaxel Injection) Concentrate 20 mg/mL and 80 mg/4 mL (20 mg/mL) vials
Application Type/Number:	NDA #20-449/SCF-054
Applicant:	Sanofi Aventis
OSE RCM #:	2009-122

EXECUTIVE SUMMARY

The Applicant proposes to market a Taxotere 1-vial formulation. The Applicant currently markets a Taxotere 2-vial formulation that has undergone numerous label/labeling changes, in addition to educational interventions, to address medication errors resulting from confusion with the unusual two step dilution. (b) (4)

(b) (4)

1 INTRODUCTION

This review is in response to a January 15, 2009 request from the Division of Drug Oncology Products to evaluate the Taxotere 1-vial formulation labels and labeling submitted by the Applicant in the CMC supplement (NDA 20-449/SCF-054) submitted on December 22, 2008.

2 REGULATORY HISTORY

After our preliminary evaluation of the supplement, DMEPA identified safety concerns with the proposed labels and labeling and met with the Division on April 3, 2009 to discuss our concerns. (b) (4)

On April 17, 2009, the Applicant submitted a FMEA proposal and revised labels and labeling and requested comments from DMEPA concerning the FMEA proposal (which also contained information on a market research study sponsored by the Applicant). Based on the new information provided, a two month extension was granted. On June 4, 2009, during the process of setting up a telecon to discuss the FMEA proposal, DMEPA was informed that the Applicant had already completed the FMEA and it had been submitted on May 13, 2009 along with further revised labels and labeling. After reviewing the completed FMEA and revised labels and labeling, we discussed our evaluation of the completed FMEA, market research study, and label/labeling revisions in a telecon with the Applicant on June 18, 2009.

3 MATERIAL REVIEWED

We evaluated the container labels, carton and insert labeling submitted by the Applicant on December 22, 2008, April 17, 2009, and May 13, 2009. (b) (4)

4 DISCUSSION

Our analysis of the market research study noted that although the study was conducted using the appropriate participants, the details of the methodology used were not provided so we are unable to evaluate the validity of the results obtained from the study. The study consisted of 37 participants (pharmacists, pharmacy technicians, and oncology infusion nurses in both the community and academic settings with experience mixing Taxotere in its current 2-vial form). However, it is not stated which labels and labeling were reviewed, the setting in which they were reviewed, exactly what questions were asked and the individual responses, or how questions and responses were obtained. Subsequent to concluding this market research, the Applicant revised the labels and labeling and incorporated the DMEPA April 3, 2009 comments. However, the revised labels and lableing (submitted on April 17, 2009) were not retested to determine if the problematic areas were addressed or if the changes created new problematic areas that needed to be addressed.

Our analysis noted that the completed FMEA was not conducted using the appropriate participants. The FMEA team consisted of 6 Drug Safety Institute staff including three medication safety/patient safety experts, a lawyer/pharmacist, an English major/registered nurse, and a pharmacist. The DSI staff is not representative of the recommended make-up of a FMEA team which should include practicing health professionals of varying clinical backgrounds, disciplines, and experience who would be procuring, prescribing, dispensing, and administering the product under evaluation. We acknowledge the FMEA team included three participants with expertise in the field of medication errors and/or patient safety. However, based on the inadequacy of the team we do not have confidence in the validity of the results obtained and the resultant label and labeling revisions.

Subsequent to completing the FMEA, DSI revised the Applicant's April 17, 2009 version of the labels and labeling. We note that some of DSI's revisions were modifications to information on the container label and carton labeling that the practicing healthcare practitioners in the market research study thought would (b) (4) We are concerned that DSI made these revisions despite the recommendations from the practicing healthcare practitioners. Furthermore, we note that DSI did not retest the revised labels and labeling to determine unanticipated use-related failures; demonstrate that the identified use-related failures had been addressed and validate whether the intended users could safely and effectively use the 1-vial formulation.

5 CONCLUSIONS

Our analysis of the data submitted by the Applicant in support of the approval of the Taxotere Injection Concentrate (1-vial formulation) (b) (4)

We would be willing to meet with the Division for further discussion, if needed. Also, please copy the Division of Medication Error Prevention and Analysis on any correspondence to the sponsor pertaining to this consult. If you have any questions or need clarification, contact Sandra Griffith, OSE Project Manager, at 301-796-2445.

6 RECOMMENDATIONS

We request the following recommendations in section 6.1 be communicated to the Applicant.

6.1 COMMENTS TO THE APPLICANT

We have completed our analysis of the market research study and the Failure Mode and Effects Analysis submitted in support of the label design for the proposed 1-vial Taxotere. We have determined that these data are insufficient to support the use of the proposed Taxotere 1-vial labels and labeling to minimize anticipated medication errors between the 1-vial formulation and the currently marketed 2-vial formulation.

Detailed information on the market research methodology was not provided. Therefore, we are unable to assess the validity of the proposed label and labeling revisions made based on this market research. With respect to the FMEA, the composition of the FMEA team was inadequate. The team should include a representative sample of practicing health professionals of varying clinical backgrounds, disciplines, and experience who would be procuring, prescribing, dispensing, and administering the product under evaluation. The FMEA team should include health professionals with experience in actual-use settings and members with expertise in the field of medication error prevention. Because the composition of the FMEA team did not include practicing healthcare professionals and this is a critical step in the process, we don't have confidence that all use-related failures were adequately identified and addressed. In both the market research study and the FMEA, neither revisions were further tested. To demonstrate that the use-related failures identified in your market research study and FMEA were addressed we recommend the following:

- Conduct usability studies on the revised container labels, carton and insert labeling with appropriate end-users, such as those used in your market research study in a realistic or simulated environment of use. If further revisions are required based on the results of these studies, then these revisions should also be tested to identify any unanticipated use-related failures; clarify suspected or known problems; demonstrate that the use-related failures identified in the market research study and FMEA have been addressed; and validate safe and effective use by intended users. The validity of usability testing depends on the extent to which realistic or simulated environments are used during the testing.

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/s/

Loretta Holmes
6/19/2009 04:48:17 PM
DRUG SAFETY OFFICE REVIEWER

Kristina Arnwine
6/19/2009 04:51:05 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/19/2009 04:52:14 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 8, 2009
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Kristina C. Arnwine, PharmD, Team Leader Kellie Taylor, PharmD, MPH, Associate Director Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Taxotere (Docetaxel Injection) Concentrate 20 mg/mL and 80 mg/4 mL (20 mg/mL) vials
Application Type/Number:	NDA #20449/SCF-054
Applicant/sponsor:	Sanofi Aventis
OSE RCM #:	2009-122

1 EXECUTIVE SUMMARY

Taxotere was approved May 14, 1996 as a two-vial configuration consisting of one vial of active drug and one vial of diluent that must be mixed before being added to the infusion solution. The currently marketed Taxotere two-vial configuration has undergone numerous label and labeling changes, in addition to educational interventions, to address medication errors that resulted from confusion with the unusual two-step dilution. (b) (4) generic formulations of the two-vial configuration will be available indefinitely which could lead to medication errors (b) (4)

Subsequently, the Applicant submitted the Taxotere 1-vial Usability Study which DMEPA evaluated in this review. Our analysis of the protocol and the results identified flaws in the methodology, deficiencies in the manner in which data was collected and documented, and a failure to identify and address any potentially problematic areas in the labels and labeling. Despite these deficiencies, we have determined that a new study is not warranted because the clarity ratings of the labels and labeling in most of the measured areas were above seven, indicating that healthcare practitioners had an adequate understanding of how this product is meant to be used. Additionally, we were able to extract from the data some useful comments concerning improvements that could be made to improve the clarity of the labels and labeling. We find the proposed labels and labeling are adequate pending some minor revisions based on our analysis of the data submitted and our review of the proposed labels and labeling.

2 INTRODUCTION

This review is written in response to a January 15, 2009 request from the Division of Drug Oncology Products to evaluate the Taxotere one-vial configuration labels and labeling submitted by the Applicant in the CMC supplement (NDA 20449/SCF-054) submitted on December 22, 2008.

3 REGULATORY HISTORY

After our preliminary evaluation of the supplement, DMEPA identified safety concerns with the proposed labels and labeling and met with the Division on April 3, 2009 to discuss our concerns. DMEPA indicated the Applicant should conduct a Failure Mode and Effects Analysis (FMEA) on the proposed labels and labeling. The Applicant was informed of DMEPA's concerns and we provided guidance in an e-mail dated April 3, 2009.

On April 17, 2009, the Applicant submitted a FMEA proposal and revised labels and labeling and requested comments from DMEPA concerning the FMEA proposal (which also contained information on a market research study sponsored by the Applicant). Based on the new information submitted, a two month extension was granted. On June 4, 2009, during the process of setting up a telecon to discuss the FMEA proposal, DMEPA was informed that the Applicant had already completed the FMEA and it had been submitted on May 13, 2009 along with further revised labels and labeling. After reviewing the completed FMEA and revised labels and labeling, we discussed our evaluation of the completed FMEA, market research study, and label/labeling revisions in a telecon with the Applicant on June 18, 2009. We determined the

FMEA did not adequately evaluate the risks associated with the revised labels and labeling and recommended the Applicant conduct a usability study in order to further evaluate the proposed revised labels and labeling. The Applicant submitted a Taxotere 1-vial Usability Study on September 14, 2009. After reviewing the usability study, DMEPA had additional questions about the study which were answered by the Applicant in a telecon held on November 23, 2009.

4 METHODS AND MATERIALS

DMEPA evaluated the revised container labels, carton labeling, and insert labeling submitted by the Applicant on May 13, 2009 (see Appendix A). Additionally, we evaluated the Taxotere 1-vial Usability Study submitted on September 14, 2009 and the supporting raw data submitted on November 19, 2009 and December 1, 2009. The study evaluated a total of 31 measures related to labeling and packaging, concentration, and package content designed to reduce the risk of medication errors. Due to the number of measures evaluated, DMEPA focused on those measures we considered to be most critical to the safe use of the product and for which qualitative data was provided (see Appendix B).

5 RESULTS

The Taxotere 1-vial Usability Study used the appropriate number and representative professional sample of participants [49 participants (pharmacists, pharmacy technicians, and oncology nurses with experience mixing Taxotere in the current two-vial configuration in both the community and academic settings)]. Of the 49 participants, 23 participated in the market research study conducted in March 2009. The usability study was conducted in five cities across the continental US representing different areas of the country. Respondents were randomly assigned to one of two groups for the exercise of filling a Taxotere prescription with products placed on a simulated chemo shelf. (b) (4) the results obtained from this portion of the study.

Participants were then asked to review the one-vial Taxotere container and carton and provide feedback on 31 measures related to labeling and packaging, concentration, and package content. The moderator captured whether the respondent noticed the measures unaided or only after being aided by the moderator. We noted that not all critical elements were noticed unaided. The respondents were also asked to rate the clarity of the measures from 1 to 10 ("1" being not clear at all and "10" being very clear). The average clarity rating for most of the measure areas was above seven. They were then asked, "What does this information mean to you?"; "Reasons for rating 7 or lower"; and "Suggestions for improvement". Our analysis noted the study did not adequately capture responses to the aforementioned questions from all respondents with regard to all measures. As a result, the study may not have adequately identified all potential failure modes because this information was not consistently documented. However, we were able to gather and evaluate qualitative responses to 11 critical labeling and packaging measures (see Appendix B). Based on the information gathered from the responses and what we considered to be the critical label and packaging measures, we have made label and labeling recommendations in section 7.

(b) (4)

(b) (4)

6 DISCUSSION

The Applicant submitted the Taxotere 1-vial Usability Study which DMEPA evaluated in this review. Our analysis of the protocol and the results identified flaws in the methodology, deficiencies in the manner in which data was collected and documented, and a failure to identify and address any potentially problematic areas in the labels and labeling. Despite these deficiencies, we have determined that a new study is not warranted because the clarity ratings of the labels and labeling in most of the measured areas were above seven, indicating that healthcare practitioners had an adequate understanding of how this product is meant to be used. Additionally, through our review of the raw data, we were able to identify some areas where improvements can be made to the proposed labels and labeling without introducing new failures. We noted several comments from participants suggesting that certain statements on the container and carton be placed in bold font. If implemented, this would amount to minor revisions what would highlight these statements that are already on the labels and labeling. We believe these minor revisions may improve the readability of the highlighted information and thus improve how the information is communicated to health care professionals. Additionally, our review of the labels and labeling identified areas where information such as the presentation of the established name and a net quantity statement can be modified or added in order to provide clarity. We have restricted our recommendations since the labels and labeling have already been tested and we want to prevent the introduction of new failures that were not captured in the usability study.

These revisions, along with the Applicant's communication strategy (b) (4) to launch Taxotere one-vial, may help to ensure the safe use of the product when introduced into the marketplace. However, we acknowledge that given the history of medication errors with the use of the two-vial configuration, we may not be able to fully mitigate the risks for medication errors with the use of this product.

7 CONCLUSION

DMEPA analyzed the Taxotere 1-vial Usability Study, supporting raw data, proposed container labels, carton and insert labeling submitted by the Applicant. Although we identified deficiencies in the study, we believe that the proposed container labels and carton labeling are adequate providing minor revisions are made to improve the readability and clarity of certain statements in order to help minimize the risk for medication errors with the use of the product.

(b) (4)

8 RECOMMENDATIONS

Our review of the labels and labeling identified areas where information such as the presentation of the established name and a usual dosage statement can be modified or added in order to help prevent confusion with the use of the product.

We provide comments on the insert labeling in Section 8.1 *Comments to the Division* for discussion by the review team. Section 8.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 8.1 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Sarah Simon, at 301-796-5205.

8.1 COMMENTS TO THE DIVISION

DMEPA notes that the Taxotere 1-vial Usability Study evaluated the clarity of a package insert (b) (4)

Additionally, we acknowledge that given the history of medication errors with the use of the two-vial configuration, we may not be able to fully mitigate the risks for medication errors with the use of this product once it is introduced into the marketplace. Thus, DMEPA will monitor for medication errors with the use of this product and may periodically request updates from the Applicant post approval to facilitate such monitoring.

8.2 COMMENTS TO THE APPLICANT

A. General Comments

1. Ensure that the established name is at least ½ the size of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)].

(b) (4)

B. (b) (4)

(b) (4)

(b) (4)

(b) (4)

4 pages immediately following withheld - Draft Labelng b(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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

/s/

LORETTA HOLMES
01/08/2010

KRISTINA C ARNWINE
01/08/2010

CAROL A HOLQUIST
01/08/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449/S054

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
sanofi-aventis U.S. Inc. on behalf of sanofi-aventis U.S. LLC	08/13/2010

TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
908-981-5000	877-332-5512

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
55 Corporate Drive Bridgewater, NJ 08807	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*: 020449

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
docetaxel	Taxotere® Injection Concentrate

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
(2R, 3S)-N-Carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5b-20-epoxy-1, 2a, 4, 7b, 10b, 13	XRP6976

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Concentrate for Infusion	20 mg and 80 mg	Intravenous infusion

(PROPOSED) INDICATION(S) FOR USE: Treatment of Cancer (see Addendum to Form FDA 356h)

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*: ☑ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE: ☑ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug: _____ Holder of Approved Application: _____

TYPE OF SUBMISSION *(check one)*: ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☑ OTHER Structured Product Labeling

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY: ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION: Structured Product Labeling

PROPOSED MARKETING STATUS *(check one)*: ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: eCTD _____ THIS APPLICATION IS: ☐ PAPER ☐ PAPER AND ELECTRONIC ☑ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Establishment Information, Module 1.1.2

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 035555

This application contains the following items: *(Check all that apply)*

☑	1. Index
☑	2. Labeling *(check one)* ☐ Draft Labeling ☑ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Linda M. Gustavson	Linda Gustavson, PhD, RAC, Director, Regulatory Affairs	08/13/2010

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
200 Crossing Boulevard P.O. Box 6890, Mailstop: BX2-712B Bridgewater, NJ 08807	908-304-6221

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

APPLICANT INFORMATION This section should include the name, street address, telephone and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. applicant should be entered in the indicated area. Only one person should sign the form.

PRODUCT DESCRIPTION This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications, the proposed indication should be given. For supplements to an approved application, please give the approved indications for use.

APPLICATION INFORMATION If this submission is an ANDA or 505(b)(2), this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

TYPE OF SUBMISSION should be indicated by checking the appropriate box:

Original Application = a complete new application that has never before been submitted;

Amendment to a Pending Application = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

Resubmission = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

Presubmission = information submitted prior to the submission of a complete new application;

Annual Report = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

Establishment Description Supplement = supplements to the information contained in the Establishment Description section (#15) for biological products;

Efficacy Supplement = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g., prescription to Over-The-Counter switch;

Labeling Supplement = all label change supplements required under 21 CFR 314.70 and 21 CFR 601.12 that do not qualify as efficacy supplements;

Chemistry, Manufacturing, and Controls Supplement = manufacturing change supplement submissions as provided in 21 CFR 314.70, 21 CFR 314.71, 21 CFR 314.72 and 21 CFR 601.12;

Other = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

Submission of Partial Application Letter date of agreement to partial submission should be provided. Also, provide copy of scheduled plan.

CBE "Supplement-Changes Being Effected" supplement submission for certain moderate changes for which distribution can occur when FDA receives the supplement as provided in 21 CFR 314.70 and 21 CFR 601.12.

CBE-30 "Supplement-Changes Being Effected in 30 Days" supplement submission for certain moderate changes for which FDA receives at least 30 days before the distribution of the product made using the change as provided in 21 CFR 314.70 and 21 CFR 601.12.

Prior Approval (PA) "Prior Approval Supplements" supplement submission for a major change for which distribution of the product made using the change cannot occur prior to FDA approval as provided in 21 CFR 314.70 and 21 CFR 601.12.

REASON FOR SUBMISSION This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request Letter of 1/9/97" or "Pediatric exclusivity determination request" or "to satisfy a subpart H postmarketing commitment".

NUMBER OF VOLUMES SUBMITTED Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

This application is
☐ Paper ☐ Paper and Electronic ☐ Electronic
Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

ESTABLISHMENT INFORMATION This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used, please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File (DMF) number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

CROSS REFERENCES This section should contain a list of all License Applications, Investigational New Drug Applications (INDs), NDAs, Premarket Approval Applications (PMAs), Premarket Notifications (510(k)s), Investigational Device Exemptions (IDEs), Biological Master Files (BMFs) and DMFs that are referenced in the current application.

Items 1 through 20 on the reverse side of the form constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follows the Form FDA 356h and, if applicable, the User Fee Cover Sheet (Form FDA 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

Signature The form must be signed and dated. Ordinarily only one person should sign the form, i.e., the applicant, or the applicant's attorney, agent, or other authorized official. However, if the person signing the application does not reside or have a place of business within the United States, the application should be countersigned by an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

From: Fagbami, Modupe
Sent: Tuesday, July 20, 2010 10:08 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cross Jr, Frank H
Subject: Recent Major Changes
Importance: High

Hi Linda,

Reference our telephone discussion yesterday, (Linda, Frank and Modupe) on the sections that come under Recent Major Changes in a labeling.

Please find FDA the confirmation below.:

Recent Major Changes cover 5 sections of the label: Boxed Warnings, Indications & Usage, Dosage & Administration, Contraindications, and Warnings & Precautions.

Any changes to any of those 5 sections within the last 12 months must be listed, including those in a supplement upon approval.

Please update your latest labeling of 6-25-2010 as indicated above

Kindly let me know if you have any questions.

Thank you.

Modupe O. Fagbami
RPM
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 2108
Silver Spring, Maryland 20993
Phone: 301-796-1348
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

MODUPE O FAGBAMI
07/22/2010

From: Fagbami, Modupe
Sent: Wednesday, April 28, 2010 11:29 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cross Jr, Frank H
Subject: NDA 020449 S-054 DMEPA Recommendations
Importance: High

Hi Linda,

We refer you to your submission of April 26, 2010 for NDA 020449 S-054.

FDA has accepted all your updates, however, the following are recommended for you for update in the latest label of April 26, 2010.

They are:

(b) (4)

(b) (4)

(b) (4)

Please send the updated label back to me by COB, Thursday, April 29, 2010

Kindly let me know if you have any questions.

Thank you.

Modupe O. Fagbami

RPM
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 2108
Silver Spring, Maryland 20993
Phone: 301-796-1348
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

MODUPE O FAGBAMI
04/28/2010

From: Fagbami, Modupe
Sent: Monday, July 19, 2010 2:10 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cross Jr, Frank H
Subject: NDA 20449 S-054 Minor Updates Required

Hi Linda,

We are requesting that you make the following updates indicated in red to your labeling of June 25, 2010 in the **HIGHLIGHTS OF PRESCRIBING INFORMATION**

Recent Major Changes
Dosage and administration (2.8, 2.9) 05/2010
Drug interactions (7) 04/2010

Revised: 07/2010

Please let me know if you have any questions.

Thanks

Modupe O. Fagbami
RPM
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 2108
Silver Spring, Maryland 20993
Phone: 301-796-1348
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

MODUPE O FAGBAMI
07/22/2010

From: Fagbami, Modupe
Sent: Friday, April 23, 2010 4:56 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cross Jr, Frank H
Subject: NDA 020449 S-054 DMEPA Recommendations
Importance: High

Hi Linda,

Kindly make the following updates to your NDA 020449 S-054 label of April 6, 2010 and send back to me on or before 12:00 noon on Tuesday, April 27, 2010.

They are:

- (b) (4) Also, Section 16.1 *How Supplied* has "single dose vial", however, it should state "single use vial"
- In Section 2.6, (b) (4), the abbreviation "BID" is used. The abbreviation should be deleted and replaced with either "twice a day" or "twice daily".
- (b) (4)
- (b) (4)

Please let me know if you have any questions.

Thank you.

Modupe O. Fagbami
RPM
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 2108
Silver Spring, Maryland 20993
Phone: 301-796-1348
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

MODUPE O FAGBAMI
04/27/2010

Cross Jr, Frank H

From: Vidra, James D
Sent: Thursday, January 14, 2010 5:05 PM
To: Cross Jr, Frank H
Subject: FW: revised annotatedpi-1vial-13Jan10 - RPM.doc

Attachments: revised annotatedpi-1vial-13Jan10 - RPM.doc

Frank,

(b) (4)

Jim Vidra

James D. Vidra, Ph.D.
Branch Chief
Branch VII, Division of Postmarketing Evaluation
Office of New Drug Quality Assessment
Center of Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Telephone No. 301-796-1767
Fax No. 301-796-9749
Email Address: james.vidra@fda.hhs.gov

From: Cross Jr, Frank H
Sent: Thursday, January 14, 2010 5:01 PM
To: Vidra, James D
Subject: revised annotatedpi-1vial-13Jan10 - RPM.doc

Please let me know if this final draft is acceptable.

revised
notatedpi-1vial-13Ja

61 pages immediately following withheld - Draft Labeling b(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

FRANK H Cross
01/14/2010

JAMES D VIDRA
01/15/2010

From: Fagbami, Modupe [mailto:Modupe.Fagbami@fda.hhs.gov]
Sent: Wednesday, January 13, 2010 3:10 PM
To: Gustavson, Linda R&D/US
Cc: Cross Jr, Frank H
Subject: NDA 02449/S-054 DMEPA Comment to proposed one- vial Label
Importance: High

Hi Linda,

Please find below the following DMEPA's comments concerning the insert labeling that contains information for the one-vial configuration only:

1. Section 2.8 Administration Precautions.
Revise the second paragraph that begins "If Taxotere Injection Concentrate..." to read:
"If Taxotere Injection Concentrate or the dilution for intravenous infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If Taxotere Injection Concentrate or the dilution for intravenous infusion should come into contact with mucosa, immediately and thoroughly wash with water."

2. Section 2.9 Preparation and Administration, Step 4.
Revise the sentence that begins "If the Taxotere dilution..." to read: "If the Taxotere dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded."

3. Section 2.10 Stability
The abbreviation "i.v." is used in the paragraph. Replace the abbreviation "i.v." with the completely spelled out word "intravenous"

Please send your response on or before 5:00 pm EST today, January 13, 2010

Please let me know if you have any questions

Thank you

Modupe O. Fagbami
RPM
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 2108
Silver Spring, Maryland 20993
Phone: 301-796-1348
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

MODUPE O FAGBAMI
03/02/2010

From: Holmes, Loretta

Sent: Monday, January 11, 2010 4:30 PM

To: Fagbami, Modupe; Simon, Sarah

Cc: Cross Jr, Frank H; Arnwine, Kristina

Subject: RE: Successfully Processed eCTD: nda020449 in DARRTS

Hi Modupe,

We find the revised container labels and carton labeling acceptable. We acknowl edge the comment from the Sponsor that due to insufficient space on the containe r labels they were not able to relocate the established name to below the propri etary name. However, from a safety perspective, we find this is acceptable.

Thanks,

Loretta

-----Original Message-----

From: Fagbami, Modupe

Sent: Monday, January 11, 2010 2:53 PM

To: Simon, Sarah

Cc: Holmes, Loretta; Cross Jr, Frank H

Subject: FW: Successfully Processed eCTD: nda020449 in DARRTS

Importance: High

Hi Sarah,

Please let me know OSE decision on the response from Sponsor, this is especially relating to the second page of the cover letter- insufficient space to relocate established name below proprietary name.

Thanks

Modupe O. Fagbami

RPM

Division of Drug Oncology Products

Office of Oncology Drug Products

CDER, FDA

10903 New Hampshire Avenue

WO-22, Room 2108

Silver Spring, Maryland 20993

Phone: 301-796-1348

Fax: 301-796-9845

-----Original Message-----

From: asr-dontreply@fda.hhs.gov [mailto:asr-dontreply@fda.hhs.gov]

Sent: Friday, January 08, 2010 2:57 PM

To: Fagbami, Modupe; CDER-OND-DDOP-EDRNOTIFY; CDER-EDR_ASR_Document_Coordinators ; CDER-EDRSTAFF; CDER-EDRADMIN; CDER ESUB; Khalsa, Gurminders J; Elnigoumi, Fatima

Subject: Successfully Processed eCTD: nda020449 in DARRTS

Successfully Processed eCTD: nda020449 in DARRTS. Details below:

EDR Location: \\CDSESUB1\EVSPROD\NDA020449\020449.enx

For Document Room Staff Use:

Application Type/Number: nda020449

Incoming Document Category/Sub Category: Electronic_Gateway

Incoming Document Category/Sub Category Number: 0381

Letter Date: 01/08/2010

Stamp Date: 1/8/2010

Receipt Date/Time from Notification: 01-08-2010, 14:44:26

Origination Date/Time from Notification: 01-08-2010, 14:43:20

DOCUMENT ID: 4259724

356H Form: NOT FOUND

Cover Letter: \\CDSESUB1\EVSPROD\NDA020449\0019\m1\us\cover.pdf

3397 Form: NOT FOUND

For EDR Staff Use:

The submission has already been processed. The following information is provided if verification is required. No additional action is required on your part

EDR Location: \\CDSESUB1\EVSPROD\NDA020449\0019

Submission Size: 2258639

Gateway Location: \\fdswa132\cderesub\inbound\ectd\ci1262979798837.89036@llnap03_te

Copy to EDR Status: Good-1

For CDER Project Manager Use:

The following submission received through the Electronic Submission Gateway has been processed using the following information. This information will be updated once Document Room personnel have been able to verify the content of the submission.

Application Type/Number: nda020449

Incoming Document Category/Sub Category: Electronic_Gateway

Incoming Document Category/Sub Category Number: 0381

Letter Date: 01/08/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

LORETTA HOLMES
01/12/2010

From: Fagbami, Modupe
Sent: Thursday, January 07, 2010 3:48 PM
To: Linda.Gustavson@sanofi-aventis.com
Cc: Cross Jr, Frank H; Simon, Sarah
Subject: NDA 020449 SCF-054 Taxotere (Docetaxel Injection) DMEPA Information Request
Importance: High

Dear Linda,

Please find the following comments from DMEPA for your urgent response on or before 4:00 pm on Friday, January 8, 2010.

They are:

A. General Comments

1. Ensure that the established name is at least ½ the size of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)].

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

.

Kindly copy Frank Cross and Sarah Simon with your response.

Please let me know if you have any questions.

Thank you very much.

Modupe O. Fagbami
RPM
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 2108
Silver Spring, Maryland 20993
Phone: 301-796-1348
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-54	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

MODUPE O FAGBAMI
01/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-449/S-054

COMPLETE RESPONSE

sanofi-aventis US Inc.
Attention: Linda Gustavson, Ph.D., RAC
Director, Regulatory Development
U.S. Assoc. Therapeutic Axis Head, Oncology
Corporate Regulatory Affairs
Mail code: BX4-212C
200 Crossing Blvd.
Bridgewater, NJ 08890-0890

Dear Dr. Gustavson:

Please refer to your supplemental new drug application (sNDA) dated December 22, 2008, received December 22, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taxotere ® (docetaxel) Injection Concentrate, 20mg and 80mg.

We acknowledge receipt of your amendments dated January 6, April 17, and May 14, 2009.

This supplemental new drug application proposes a new one-vial formulation (b) (4)

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

The Office of Surveillance and Epidemiology has completed the analysis of the market research study and the Failure Mode and Effects Analysis (FMEA) submitted in support of the label design for the proposed 1-vial Taxotere. It has been determined that these data are insufficient to support the use of the proposed Taxotere 1-vial labels (b) (4)

Detailed information on the market research methodology was not provided. Therefore, we are unable to assess the validity of the proposed label and labeling revisions made based on this market research. In addition, the composition of the FMEA team was inadequate. The team should include a representative sample of practicing health professionals of varying clinical backgrounds, disciplines, and experience who would be procuring, prescribing, dispensing, and administering the product under evaluation. The FMEA team should include health professionals with experience in actual-use settings and members with expertise in the field of medication error prevention. The composition of the FMEA team did not include practicing healthcare

professionals, a critical step towards adequately identifying and addressing all use-related failures. In both the market research study and the FMEA, neither revisions were further tested. To demonstrate that the use-related failures identified in your market research study and FMEA are addressed, we recommend the following:

> Conduct usability studies on the revised container labels, carton and insert labeling with appropriate end-users, such as those used in your market research study in a realistic or simulated environment of use. If further revisions are required based on the results of these studies, then these revisions should also be tested to identify any unanticipated use-related failures; clarify suspected or known problems; demonstrate that the use-related failures identified in the market research study and FMEA have been addressed; and validate safe and effective use by intended users. The validity of usability testing depends on the extent to which realistic or simulated environments are used during the testing.

We reserve further comments on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With APPLICANTs and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Amna Ibrahim
6/22/2009 05:24:43 PM
For Dr Robert Justice

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PDUFA GOAL DATE EXTENSION

NDA 20-449/S-054

Linda Gustavson, Ph.D., RAC
Director, Regulatory Development
U.S. Assoc. Therapeutic Axis Head, Oncology
Corporate Regulatory Affairs
sanofi-aventis US Inc.
Mail code: BX4-212C
200 Crossing Blvd, Bridgewater, NJ 08890-0890

Dear Dr. Gustavson:

Please refer to your December 22, 2008, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taxotere Injection Concentrate (XRP6976).

On April 15, 2009, we received your April 15, 2009, major amendment to this application. The receipt date is within two months of the user fee goal date. Therefore, we are extending the goal date by two months to provide time for a full review of the submission. The extended user fee goal date is June 22, 2009.

If you have questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Anthony Murgo
4/17/2009 06:03:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-449/S-054 **PRIOR APPROVAL SUPPLEMENT**

Linda Gustavson, Ph.D., RAC
Director, Regulatory Development
U.S. Assoc. Therapeutic Axis Head, Oncology
Corporate Regulatory Affairs
sanofi-aventis US Inc.
Mail code: BX4-212C
200 Crossing Blvd, Bridgewater, NJ 08890-0890

Dear Dr. Gustavson:

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

Name of Drug Product: TAXOTERE (docetaxel) Injection Concentrate, 20mg and 80mg.

NDA Number: 20-449

Supplement number: 054

Date of supplement: December 22, 2008

Date of receipt: December 22, 2008

This supplemental application proposes the following change:

A new one-vial formulation of Taxotere (docetaxel).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 20, 2009, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 22, 2009.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Frank H. Cross Jr.
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Frank Cross

4/12/2009 05:30:22 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Sylvia Gantt, HFD-003, 301-796-2123. WO51 Rm. 4195

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Tu-Van Lambert, ONDQA, Division of Post-Marketing Assessment, 301-796-4246, WO21 Rm. 2625

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 1, 2009		N 20-449	SCF-054	December 22, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Taxotere			ASAP

NAME OF FIRM: sanofi-aventis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☒ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Supplement provides for a new one-vial formulation (b) (4) .

Submission in EDR: \\FDSWA150\NONECTD\4061754

Please review as soon as possible since PDUFA goal date is April 22, 2009.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Tu-Van Lambert	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Tu-Van Lambert

4/1/2009 01:24:31 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Mail: OSE/DMEPA/Loretta Holmes

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Modupe Fagbami, PM, DDOP/OODP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/15/2009		20-449/SCF-054	CMC Supplement-New 1 vial formulation	12/22/2008 (Receipt date)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Taxotere	Standard (4 months)		4/22/2009 (PDUFA due date)

NAME OF FIRM: Sanofi Aventis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
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- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review this prior approval Chemistry Supplement from DMEPA perspective
EDR link already forwarded

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Modupe Fagbami, PM	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Modupe Fagbami

1/15/2009 05:12:31 PM