

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020449Orig1s079

Trade Name: Taxotere

Generic or Proper Name: docetaxel

Sponsor: sanofi-aventis U.S. LLC

Approval Date: October 05, 2018

Indication: 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
- Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unrespectable, locally advanced or metastatic untreated NSCLC
- Castration-Resistant Prostate Cancer (CRPC): with prednisone in metastatic castration-resistant 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

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APPROVAL LETTER



NDA 020449/S-079

SUPPLEMENT APPROVAL

sanofi-aventis U.S. LLC
Attention: Stefanie Doty
Director, Regulatory Affairs
55 Corporate Drive, Mail Stop: 55C-300
Bridgewater, NJ 08807

Dear Ms. Doty:

Please refer to your Supplemental New Drug Application (sNDA) dated April 11, 2018, received April 11, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Taxotere[®] (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL.

This Prior Approval supplemental new drug application provides for the addition of “Enterocolitis and Neutropenic Colitis” and for updates to “Hypersensitivity Reactions” in Section 5 “Warnings and Precautions” of the Prescribing Information (PI). Also, this Supplemental NDA provides for updates to Sections 6 “Adverse Reactions”, 6.2 “Postmarketing Experience”, and 17 “Patient Counseling” of the PI to reflect the above changes in Section 5 and to distinguish between risk of adverse events (AEs) during the TAX316 adjuvant breast cancer study and AEs persistent following completion of the trial, with a median follow-up time of 8 years, with regard to the following AEs: peripheral neuropathy, alopecia, amenorrhea, peripheral edema, lymphedema, asthenia, and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML).

APPROVAL & LABELING

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert and text for the patient package insert, with the addition of any labeling changes in pending “Changes Being

Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sakar Wahby, Regulatory Project Manager, at (240) 402-5364 or email me at sakar.wahby@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Supervisory Associate Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LALEH AMIRI KORDESTANI
10/05/2018

**CENTER FOR DRUG EVALUATION AND
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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, for intravenous use

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/m² (5.1)
- Should not be given if bilirubin > ULN, or if AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × 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/mm³. Obtain frequent blood counts to monitor for neutropenia (4, 5.3)
- 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 (5.5)
- Contraindicated if history of severe hypersensitivity reactions to TAXOTERE or to drugs formulated with polysorbate 80 (4)
- Severe fluid retention may occur despite dexamethasone (5.6)

RECENT MAJOR CHANGES

Warnings and Precautions (5.4, 5.5) 10/2018

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)
- **Castration-Resistant Prostate Cancer (CRPC):** with prednisone in metastatic castration-resistant 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. Use only a 21 gauge needle to withdraw TAXOTERE from the vial.

- BC locally advanced or metastatic: 60 mg/m² to 100 mg/m² single agent (2.1)
- BC adjuvant: 75 mg/m² administered 1 hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks for 6 cycles (2.1)
- NSCLC: after platinum therapy failure: 75 mg/m² single agent (2.2)

- NSCLC: chemotherapy naive: 75 mg/m² followed by cisplatin 75 mg/m² (2.2)
- HRPC: 75 mg/m² with 5 mg prednisone twice a day continuously (2.3)
- GC: 75 mg/m² followed by cisplatin 75 mg/m² (both on day 1 only) followed by fluorouracil 750 mg/m² per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion (2.4)
- SCCHN: 75 mg/m² followed by cisplatin 75 mg/m² IV (day 1), followed by fluorouracil 750 mg/m² per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion; for 4 cycles (2.5)
- SCCHN: 75 mg/m² followed by cisplatin 100 mg/m² IV (day 1), followed by fluorouracil 1000 mg/m² 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

- Injection: One-vial TAXOTERE: Single use vials 20 mg/mL and 80 mg/4 mL (3)

CONTRAINDICATIONS

- Hypersensitivity to docetaxel or polysorbate 80 (4)
- Neutrophil counts of <1500 cells/mm³ (4)

WARNINGS AND PRECAUTIONS

- Acute myeloid leukemia: In patients who received TAXOTERE, doxorubicin and cyclophosphamide, monitor for delayed myelodysplasia or myeloid leukemia. (5.7)
- Cutaneous reactions: Reactions including erythema of the extremities with edema followed by desquamation may occur. Severe skin toxicity may require dose adjustment. (5.8)
- Neurologic reactions: Reactions including paresthesia, dysesthesia, and pain may occur. Severe neurosensory symptoms require dose adjustment or discontinuation if persistent. (5.9)
- Eye disorders: Cystoid macular edema (CME) has been reported and requires treatment discontinuation. (5.10)
- Asthenia: Severe asthenia may occur and may require treatment discontinuation. (5.11)
- Alcohol content: The alcohol content in a dose of TAXOTERE Injection may affect the central nervous system. This may include impairment of a patient's ability to drive or use machines immediately after infusion. (5.12)
- 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. (5.13, 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, and 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: 10/2018

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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/m² [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 × ULN concomitant with alkaline phosphatase >2.5 × 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 × 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/mm³. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving TAXOTERE [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* (5.5)]. 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* (5.6)].

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 metastatic castration-resistant 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/m² to 100 mg/m² 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/m² administered 1 hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² 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/m² administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m² in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized controlled trials [*see Boxed Warning, 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/m² administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m² over 30-60 minutes every 3 weeks [*see Dosage and Administration (2.7)*].

2.3 Prostate Cancer

- For metastatic castration-resistant prostate cancer, the recommended dose of TAXOTERE is 75 mg/m² 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/m² as a 1 hour intravenous infusion, followed by cisplatin 75 mg/m², as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m² 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/m² as a 1 hour intravenous infusion followed by cisplatin 75 mg/m² intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m² 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/m² as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m² administered as a 30-minute to 3 hour infusion, followed by fluorouracil 1000 mg/m²/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 (5.5)*].

For metastatic castration-resistant 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 (5.5)*].

2.7 Dosage Adjustments During Treatment

Breast Cancer

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

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

Combination therapy with TAXOTERE for chemotherapy-naive NSCLC

For patients who are dosed initially at TAXOTERE 75 mg/m² in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm³, 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/m². In patients who require a further dose reduction, a dose of 50 mg/m² is recommended. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Prostate Cancer

Combination therapy with TAXOTERE for metastatic castration-resistant prostate cancer

TAXOTERE should be administered when the neutrophil count is $\geq 1,500$ cells/mm³. Patients who experience either febrile neutropenia, neutrophils < 500 cells/mm³ 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/m² to 60 mg/m². If subsequent episodes of complicated neutropenia occur the TAXOTERE dose should be reduced from 60 mg/m² to 45 mg/m². In case of grade 4 thrombocytopenia the TAXOTERE dose should be reduced from 75 mg/m² to 60 mg/m². Patients should not be retreated with subsequent cycles of TAXOTERE until neutrophils recover to a level $> 1,500$ cells/mm³ and platelets recover to a level $> 100,000$ cells/mm³. 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 $\leq 5 \times$ ULN and AP $\leq 2.5 \times$ ULN, or AST/ALT > 1.5 to $\leq 5 \times$ ULN and AP > 2.5 to $\leq 5 \times$ ULN, TAXOTERE should be reduced by 20%.

In case of AST/ALT $> 5 \times$ ULN and/or AP $> 5 \times$ 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 \geq grade 2 ($>1.5 \times$ 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 \geq 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 reinstated 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 coadministration 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 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 initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the TAXOTERE 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)

TAXOTERE Injection 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 and diluent) with the one-vial formulation.

One-vial TAXOTERE (Injection)

TAXOTERE Injection (20 mg/mL) requires NO prior dilution with a diluent and is ready to add to the infusion solution. Use only a 21 gauge needle to withdraw TAXOTERE from the vial because larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and rubber particulates.

1. TAXOTERE vials should be stored between 2°C and 25°C (36°F and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection vials to stand at room temperature for approximately 5 minutes before use.
2. Using **only** a 21 gauge needle, aseptically withdraw the required amount of TAXOTERE injection (20 mg docetaxel/mL) with a calibrated syringe and inject via a single injection (one shot) 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.
5. TAXOTERE infusion solution is supersaturated, therefore may crystallize over time. If crystals appear, the solution must no longer be used and shall 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 6 hours. TAXOTERE final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 6 hours (including the 1 hour intravenous administration).

In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2°C and 8°C (36°F and 46°F).

3 DOSAGE FORMS AND STRENGTHS

One-vial TAXOTERE (Injection)

TAXOTERE 20 mg/mL

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

TAXOTERE 80 mg/4 mL

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

4 CONTRAINDICATIONS

TAXOTERE is contraindicated in patients with:

- neutrophil counts of <1500 cells/mm³ [*see Warnings and Precautions (5.3)*].
- 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 (5.5)*].

5 WARNINGS AND PRECAUTIONS

5.1 Toxic Deaths

Breast Cancer

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

Non-Small Cell Lung Cancer

TAXOTERE administered at a dose of 100 mg/m² in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m² dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m² dose level, 3 of 5 patients had 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/mm³ and platelets recover to a level >100,000 cells/mm³.

A 25% reduction in the dose of TAXOTERE is recommended during subsequent cycles following severe neutropenia (<500 cells/mm³) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a TAXOTERE cycle [see *Dosage and Administration (2.7)*].

Neutropenia (<2000 neutrophils/mm³) occurs in virtually all patients given 60 mg/m² to 100 mg/m² of TAXOTERE and grade 4 neutropenia (<500 cells/mm³) occurs in 85% of patients given 100 mg/m² and 75% of patients given 60 mg/m². Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. TAXOTERE should not be administered to patients with neutrophils <1500 cells/mm³.

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

Enterocolitis and neutropenic colitis (typhlitis) have occurred in patients treated with TAXOTERE alone and in combination with other chemotherapeutic agents, despite the co-administration of G-CSF. Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Enterocolitis and neutropenic enterocolitis may develop at any time, and could lead to death as early as the first day of symptom onset. Monitor patients closely from onset of any symptoms of gastrointestinal toxicity. Inform patients to contact their healthcare provider with new, or worsening symptoms of gastrointestinal toxicity [*see Dosage and Administration (2), Warnings and Precautions (5.3), Adverse Reactions (6.2)].*

5.5 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 pre-medicated 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.

Patients who have previously experienced a hypersensitivity reaction to paclitaxel may develop a hypersensitivity reaction to docetaxel that may include severe or fatal reactions such as anaphylaxis. Monitor patients with a previous history of hypersensitivity to paclitaxel closely during initiation of TAXOTERE therapy. 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)].*

5.6 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/m². 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/m². Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the last infusion of TAXOTERE to resolution (range: 0 to 42+ weeks). Patients developing peripheral edema may be treated with standard measures, *e.g.*, salt restriction, oral diuretic(s).

5.7 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.

5.8 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.

5.9 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).

5.10 Eye Disorders

Cystoid macular edema (CME) has been reported in patients treated with TAXOTERE. Patients with impaired vision should undergo a prompt and comprehensive ophthalmologic examination. If CME is diagnosed, TAXOTERE treatment should be discontinued and appropriate treatment initiated. Alternative non-taxane cancer treatment should be considered.

5.11 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.

5.12 Alcohol Content

Cases of intoxication have been reported with some formulations of docetaxel due to the alcohol content. The alcohol content in a dose of TAXOTERE Injection may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in TAXOTERE Injection on the ability to drive or use machines immediately after the infusion. Each administration of TAXOTERE Injection at 100 mg/m² delivers 2.0 g/m² of ethanol. For a patient with a BSA of 2.0 m², this would deliver 4.0 grams of ethanol [see *Description (11)*]. Other docetaxel products may have a different amount of alcohol.

5.13 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, Warnings and Precautions (5.1)*]
- Hepatic Impairment [see *Boxed Warning, Warnings and Precautions (5.2)*]
- Hematologic Effects [see *Boxed Warning, Warnings and Precautions (5.3)*]
- Enterocolitis and Neutropenic Colitis [see *Warnings and Precautions (5.4)*]
- Hypersensitivity Reactions [see *Boxed Warning, Warnings and Precautions (5.5)*]
- Fluid Retention [see *Boxed Warning, Warnings and Precautions (5.6)*]
- Acute Myeloid Leukemia [see *Warnings and Precautions (5.7)*]
- Cutaneous Reactions [see *Warnings and Precautions (5.8)*]
- Neurologic Reactions [see *Warnings and Precautions (5.9)*]
- Eye Disorders [see *Warnings and Precautions (5.10)*]
- Asthenia [see *Warnings and Precautions (5.11)*]
- Alcohol Content [see *Warnings and Precautions (5.12)*]

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 Trials Experience

Breast Cancer

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

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

Table 3: Summary of Adverse Reactions in Patients Receiving TAXOTERE at 100 mg/m²

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
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			

Adverse Reaction	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
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 $> 38^{\circ}\text{C}$ 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/mm³) was 7 days. Among 2045 patients with solid tumors and normal baseline LFTs, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles.

Febrile neutropenia (< 500 cells/mm³ with fever $> 38^{\circ}\text{C}$ 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/mm³) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity reactions

Severe hypersensitivity reactions have been reported [see *Boxed Warning, Warnings and Precautions (5.5)*]. 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 (5.6)*].

Cutaneous reactions

Severe skin toxicity is discussed elsewhere in the label [see *Warnings and Precautions (5.8)*]. 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 (5.9)*].

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/m² in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF by $\geq 10\%$ 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/m² in the randomized and single arm studies of metastatic breast cancer after failure of previous chemotherapy; 18 patients in these studies who had abnormal baseline LFTs (defined as 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/m² 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/m² with Normal or Elevated Liver Function Tests or 60 mg/m² 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/m², ANC grade 4 and fever $> 38^{\circ}\text{C}$ with intravenous antibiotics and/or hospitalization; for 60 mg/m², ANC grade 3/4 and fever $> 38.1^{\circ}\text{C}$

Table 5: Non-Hematologic Adverse Reactions in Breast Cancer Patients Previously Treated with Chemotherapy Treated at TAXOTERE 100 mg/m² with Normal or Elevated Liver Function Tests or 60 mg/m² with Normal Liver Function Tests

Adverse 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/m² dose

NA = not available

In the three-arm monotherapy trial, TAX313, which compared TAXOTERE 60 mg/m², 75 mg/m² and 100 mg/m² in advanced breast cancer, grade 3/4 or severe adverse reactions occurred in 49.0% of patients treated with TAXOTERE 60 mg/m² compared to 55.3% and 65.9% treated with 75 mg/m² and 100 mg/m² respectively. Discontinuation due to adverse reactions was reported in 5.3% of patients treated with 60 mg/m² versus 6.9% and 16.5% for patients treated at 75 and 100 mg/m², respectively. Deaths within 30 days of last treatment occurred in 4.0% of patients treated with 60 mg/m² compared to 5.3% and 1.6% for patients treated at 75 mg/m² and 100 mg/m², respectively.

The following adverse reactions were associated with increasing docetaxel doses: fluid retention (26%, 38%, and 46% at 60 mg/m², 75 mg/m², and 100 mg/m² 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).

Adverse Reaction	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 %	
	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

	TAXOTERE 75 mg/m² + Doxorubicin 50 mg/m² + Cyclophosphamide 500 mg/m² (TAC) n=744 %		Fluorouracil 500 mg/m² + Doxorubicin 50 mg/m² + Cyclophosphamide 500 mg/m² (FAC) n=736 %	
Adverse Reaction	Any	Grade 3/4	Any	Grade 3/4
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
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

During the treatment period, 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 during the treatment period.

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 versus one patient in the FAC arm. Five of the 7 TAC-treated patients required treatment discontinuation; no deaths due to these events occurred during the treatment period.

Cardiovascular reactions

More cardiovascular reactions were reported in the TAC arm versus the FAC arm during the treatment period: arrhythmias, all grades (6.2% vs 4.9%), and hypotension, all grades (1.9% vs 0.8%). Twenty-six (26) patients (3.5%) in the TAC arm and 17 patients (2.3%) in the FAC arm developed CHF during the study period. All except one patient in each arm were diagnosed with CHF during the follow-up period. Two (2) patients in TAC arm and 4 patients in FAC arm died due to CHF. The risk of CHF was higher in the TAC arm in the first year, and then was similar in both treatment arms.

Adverse reactions during the follow-up period (median follow-up time of 8 years)

In study TAX316, the most common adverse reactions that started during the treatment period and persisted into the follow-up period in TAC and FAC patients are described below (median follow-up time of 8 years).

Nervous system disorders

In study TAX316, peripheral sensory neuropathy started during the treatment period and persisted into the follow-up period in 84 patients (11.3%) in TAC arm and 15 patients (2%) in FAC arm. At the end of the follow-up period (median follow-up time of 8 years), peripheral sensory neuropathy was observed to be ongoing in 10 patients (1.3%) in TAC arm, and in 2 patients (0.3%) in FAC arm.

Skin and subcutaneous tissue disorders

In study TAX316, alopecia persisting into the follow-up period after the end of chemotherapy was reported in 687 of 744 TAC patients (92.3%) and 645 of 736 FAC patients (87.6%). At the end of the follow-up period (actual median follow-up time of 8 years), alopecia was observed to be ongoing in 29 TAC patients (3.9%) and 16 FAC patients (2.2%).

Reproductive system and breast disorders

In study TAX316, amenorrhea that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 202 of 744 TAC patients

(27.2%) and 125 of 736 FAC patients (17.0%). Amenorrhea was observed to be ongoing at the end of the follow-up period (median follow-up time of 8 years) in 121 of 744 TAC patients (16.3%) and 86 FAC patients (11.7%).

General disorders and administration site conditions

In study TAX316, peripheral edema that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was observed in 119 of 744 TAC patients (16.0%) and 23 of 736 FAC patients (3.1%). At the end of the follow-up period (actual median follow-up time of 8 years), peripheral edema was ongoing in 19 TAC patients (2.6%) and 4 FAC patients (0.5%).

In study TAX316, lymphedema that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 11 of 744 TAC patients (1.5%) and 1 of 736 FAC patients (0.1%). At the end of the follow-up period (actual median follow-up time of 8 years), lymphedema was observed to be ongoing in 6 TAC patients (0.8%) and 1 FAC patient (0.1%).

In study TAX316, asthenia that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 236 of 744 TAC patients (31.7%) and 180 of 736 FAC patients (24.5%). At the end of the follow-up period (actual median follow-up time of 8 years), asthenia was observed to be ongoing in 29 TAC patients (3.9%) and 16 FAC patients (2.2%).

Acute myeloid leukemia (AML)/myelodysplastic syndrome

AML occurred in the adjuvant breast cancer trial (TAX316). The cumulative risk of developing treatment-related AML at median follow-up time of 8 years in TAX316 was 0.4% for TAC-treated patients and 0.1% for FAC-treated patients. One TAC patient (0.1%) and 1 FAC patient (0.1%) died due to AML during the follow-up period (median follow-up time of 8 years). Myelodysplastic syndrome occurred in 2 of 744 (0.3%) patients who received TAC and in 1 of 736 (0.1%) patients who received FAC. AML occurs at a higher frequency when these agents are given in combination with radiation therapy.

Lung Cancer

Monotherapy with TAXOTERE for unresectable, locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy

TAXOTERE 75 mg/m²: 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/m² 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
Gastrointestinal			
Nausea			
Any	34	31	31

Adverse Reaction	TAXOTERE 75 mg/m² n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Grade 3/4 Vomiting	5	4	8
Any	22	27	22
Grade 3/4 Diarrhea	3	2	6
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 $>38^{\circ}\text{C}$ with intravenous antibiotics and/or hospitalization

***COSTART term and grading system

†Not Applicable

†† Not Done

Combination therapy with TAXOTERE in chemotherapy-naive 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-Naive Advanced Non-Small Cell Lung Cancer Patients Receiving TAXOTERE in Combination with Cisplatin

Adverse Reaction	TAXOTERE 75 mg/m² + Cisplatin 75 mg/m² n=406 %	Vinorelbine 25 mg/m² + Cisplatin 100 mg/m² 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
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		

Adverse Reaction	TAXOTERE 75 mg/m² + Cisplatin 75 mg/m² n=406 %	Vinorelbine 25 mg/m² + Cisplatin 100 mg/m² n=396 %
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)

Adverse Reaction	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 %	
	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
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

	TAXOTERE 75 mg/m² every 3 weeks + prednisone 5 mg twice daily n=332 %		Mitoxantrone 12 mg/m² every 3 weeks + prednisone 5 mg twice daily n=335 %	
Adverse Reaction	Any	Grade 3/4	Any	Grade 3/4
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/m² 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/m² + cisplatin 75 mg/m² + fluorouracil 750 mg/m² n=221		Cisplatin 100 mg/m² + fluorouracil 1000 mg/m² 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
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

Adverse Reaction	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	
	Any %	Grade 3/4 %	Any %	Grade 3/4 %
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/odyn ophagia	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/m² 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)

Adverse Reaction (by Body System)	TAX323 (n=355)				TAX324 (n=494)			
	TAXOTERE arm (n=174)		Comparator arm (n=181)		TAXOTERE arm (n=251)		Comparator arm (n=243)	
	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

	TAX323 (n=355)				TAX324 (n=494)			
	TAXOTERE arm (n=174)		Comparator arm (n=181)		TAXOTERE arm (n=251)		Comparator arm (n=243)	
	Any %	Grade 3/4 %	Any %	Grade 3/4 %	Any %	Grade 3/4 %	Any %	Grade 3/4 %
Adverse Reaction (by Body System)								
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
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

	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 %
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 Postmarketing Experience

The following adverse reactions have been identified from clinical trials and/or postmarketing 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, injection site recall reaction (recurrence of skin reaction at a site of previous extravasation following administration of docetaxel at a different site) at the site of previous extravasation.

Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction. Ventricular arrhythmia including ventricular tachycardia has been reported in patients treated with docetaxel in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide, and may be associated with fatal outcome.

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. Cases of permanent alopecia have been reported.

Gastrointestinal: enterocolitis, including colitis, ischemic colitis, and neutropenic enterocolitis, has been reported with a potential fatal outcome. Abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, intestinal obstruction, ileus, 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 myelodysplastic 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. Hypersensitivity reactions with potential fatal outcome have been reported with docetaxel in patients who previously experienced hypersensitivity reactions to paclitaxel.

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. Cases of cystoid macular edema (CME) have been reported in patients treated with TAXOTERE.

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/pneumonitis, interstitial lung disease, interstitial pneumonia, respiratory failure, and pulmonary fibrosis have rarely been reported and may be associated with fatal outcome. 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.

Metabolism and nutrition disorders: electrolyte imbalance, including cases of hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia has been reported.

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 (5.13)*]

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 [see *Warnings and Precautions (5.13)*].

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 [see *Warnings and Precautions (5.13)*].

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 alcohol content of TAXOTERE Injection should be taken into account when given to pediatric patients [see *Warnings and Precautions (5.12)*].

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-fluorouracil (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 $125 \text{ mg}/\text{m}^2$ 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 ($75 \text{ mg}/\text{m}^2$) in combination with cisplatin ($75 \text{ mg}/\text{m}^2$) and 5-fluorouracil ($750 \text{ mg}/\text{m}^2$) (TCF) or to cisplatin ($80 \text{ mg}/\text{m}^2$) and 5-fluorouracil ($1000 \text{ mg}/\text{m}^2/\text{day}$) (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/m² to 235 mg/m² 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/m².

Docetaxel was administered in combination with cisplatin and 5-fluorouracil (TCF), at dose levels of 75 mg/m² 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/m², 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-naive 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-naive, 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 $\geq 10\%$ 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 $>1.5 \times ULN$ concomitant with alkaline phosphatase $>2.5 \times ULN$ should not receive TAXOTERE [see *Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)*].

The alcohol content of TAXOTERE Injection should be taken into account when given to patients with hepatic impairment [see *Warnings and Precautions (5.12)*].

10 OVERDOSAGE

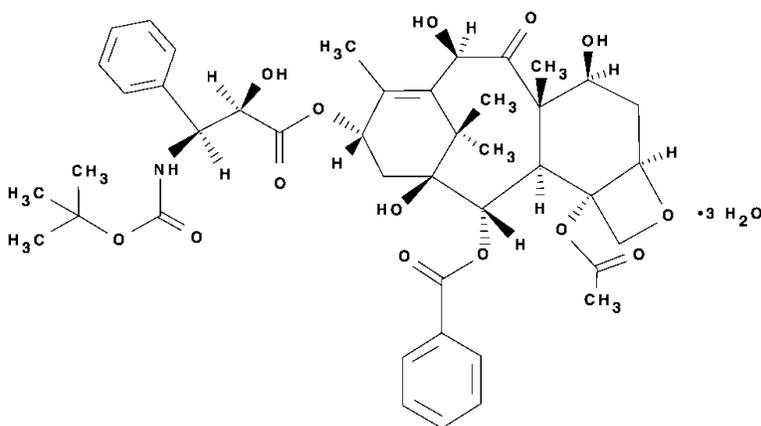
There is no known antidote for TAXOTERE overdose. In case of overdose, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdose include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive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

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

In mice, lethality was observed following single intravenous doses that were ≥ 154 mg/kg (about 4.5 times the human dose of 100 mg/m² on a mg/m² 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/m² basis). In male and female rats, lethality was observed at a dose of 20 mg/kg (comparable to the human dose of 100 mg/m² on a mg/m² 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 5 β -20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of C₄₃H₅₃NO₁₄•3H₂O, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

One-vial TAXOTERE (Injection)

TAXOTERE (docetaxel) Injection 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 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 Pharmacokinetics

Absorption

The pharmacokinetics of docetaxel has been evaluated in cancer patients after administration of 20 mg/m² to 115 mg/m² in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m² to 115 mg/m² with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α , β , and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m².

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

Specific Populations

Effect of Age: A population pharmacokinetic analysis was carried out after TAXOTERE treatment of 535 patients dosed at 100 mg/m². Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel was 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/m² to 90 mg/m² was similar to that of European/American populations dosed at 100 mg/m², suggesting no significant difference in the elimination of docetaxel in the two populations.

Drug Interaction Studies

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 coadministered with ketoconazole [*see Dosage and Administration (2.7) and 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 metastatic castration-resistant 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-K₁ cells and in the *in vivo* micronucleus test in mice administered doses of 0.39 to 1.56 mg/kg (about 1/60th to 1/15th the recommended human dose on a mg/m² 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 1/50th the recommended human dose on a mg/m² basis), but decreased testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at intravenous doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/3rd and 1/15th the recommended human dose on a mg/m² 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/m² every 3 weeks) or the combination of mitomycin (12 mg/m² every 6 weeks) and vinblastine (6 mg/m² 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	p=0.01 Log Rank
Risk Ratio*, Mortality (Docetaxel: Control)	0.73		
95% CI (Risk Ratio)	0.58-0.93		
Median Time to	4.3 months	2.5 months	

Efficacy Parameter	Docetaxel (n=203)	Mitomycin/ Vinblastine (n=189)	p-value
Progression			p=0.01 Log Rank
Risk Ratio*, Progression (Docetaxel: Control)	0.75		
95% CI (Risk Ratio)	0.61-0.94		
Overall Response Rate	28.1%	9.5%	p<0.0001 Chi Square
Complete Response Rate	3.4%	1.6%	

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

In a second randomized trial, patients previously treated with an alkylating-containing regimen were assigned to treatment with TAXOTERE (100 mg/m²) or doxorubicin (75 mg/m²) 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	p=0.39 Log Rank
Risk Ratio*, Mortality (Docetaxel: Control)	0.89		
95% CI (Risk Ratio)	0.68-1.16		
Median Time to Progression	6.5 months	5.3 months	p=0.45 Log Rank
Risk Ratio*, Progression (Docetaxel: Control)	0.93		
95% CI (Risk Ratio)	0.71-1.16		
Overall Response Rate	45.3%	29.7%	p=0.004 Chi Square
Complete Response Rate	6.8%	4.2%	

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

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/m² (n=151), 75 mg/m² (n=188) or 100 mg/m² (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/m² group compared to

22.3% for the 75 mg/m² and 29.8% for the 100 mg/m² group; pair-wise comparison between the 60 mg/m² and 100 mg/m² groups was statistically significant (p=0.037).

Single Arm Studies

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

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

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/m² administered 1-hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² (TAC arm), or doxorubicin 50 mg/m² followed by fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m² (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

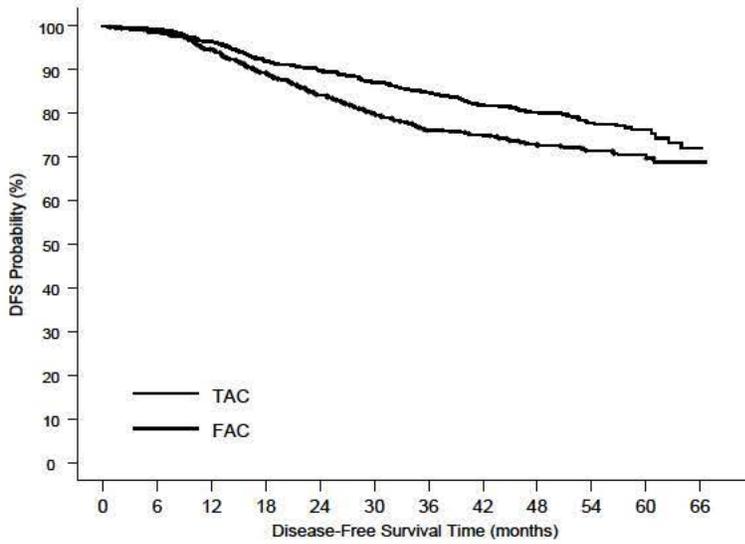
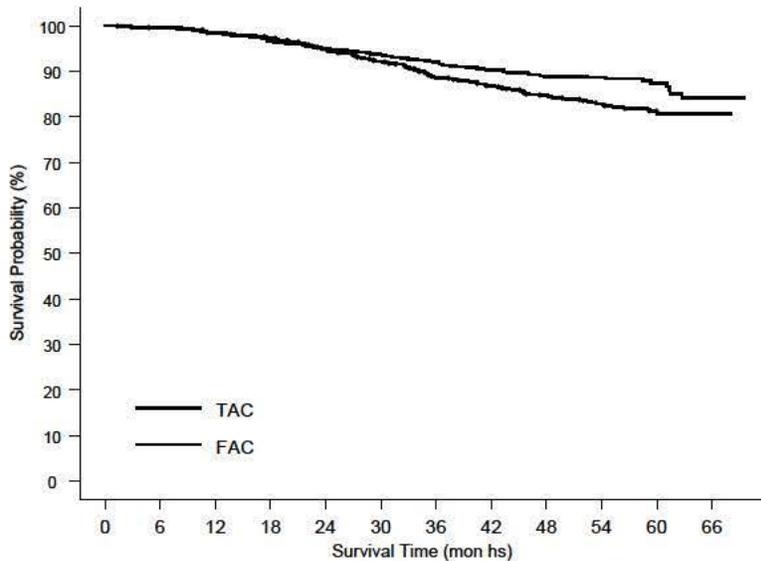


Figure 2: TAX316 Overall Survival K-M Curve



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

Table 14: Subset Analyses-Adjuvant Breast Cancer Study

Patient subset	Number of patients	Disease Free Survival		Overall Survival	
		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 naive.

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

Two randomized, controlled trials established that a TAXOTERE dose of 75 mg/m² was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy (see below). TAXOTERE at a dose of 100 mg/m², however, was associated with unacceptable hematologic toxicity, infections, and treatment-related mortality and this dose should not be used [see *Boxed Warning, 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/m² or best supportive care, but early toxic deaths at this dose led to a dose reduction to TAXOTERE 75 mg/m². A total of 104 patients were randomized in this amended study to either TAXOTERE 75 mg/m² or best supportive care.

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

Figure 3: TAX317 Survival K-M Curves - TAXOTERE 75 mg/m² Versus Best Supportive Care

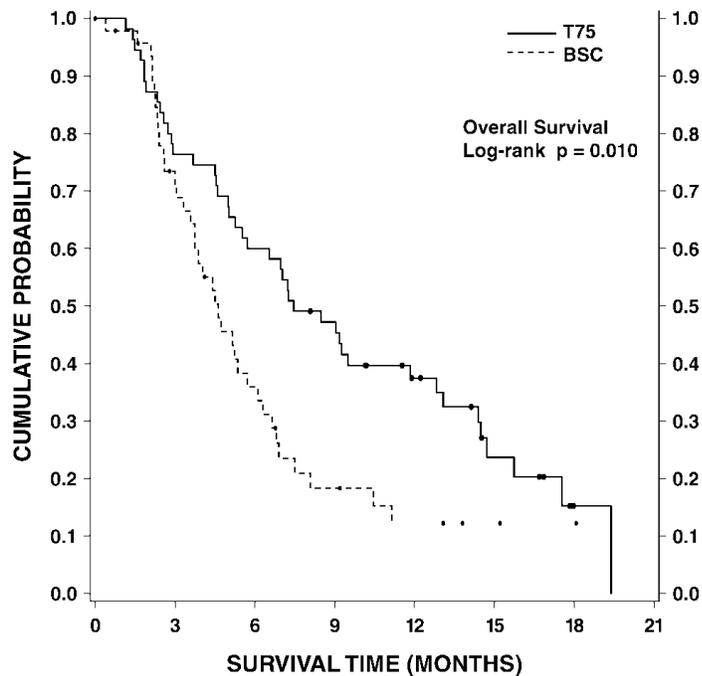
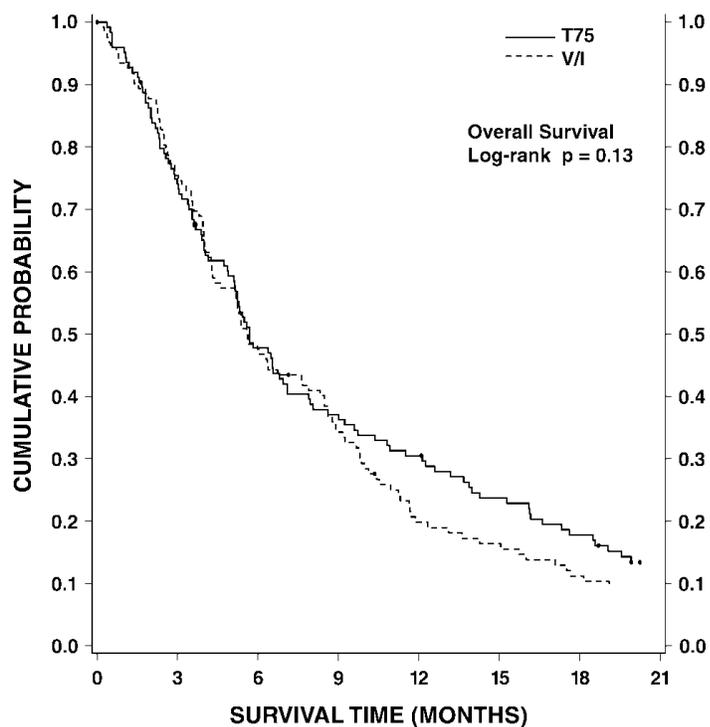


Figure 4: TAX320 Survival K-M Curves - TAXOTERE 75 mg/m² Versus Vinorelbine or Ifosfamide Control



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

Combination Therapy with TAXOTERE for Chemotherapy-Naive 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/m² as a 1 hour infusion immediately followed by cisplatin 75 mg/m² over 30 to 60 minutes every 3 weeks; vinorelbine 25 mg/m² administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100 mg/m² 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-Naive 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)	

^aFrom the superiority test (stratified log rank) comparing TAXOTERE+cisplatin to vinorelbine+cisplatin

^bHazard ratio of TAXOTERE+cisplatin versus vinorelbine+cisplatin. A hazard ratio of less than 1 indicates that TAXOTERE+cisplatin is associated with a longer survival.

^cAdjusted 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-Naive NSCLC

Endpoint	TAXOTERE + Cisplatin	Vinorelbine + Cisplatin	p-value
Objective Response Rate (95% CI) ^a	31.6% (26.5%, 36.8%)	24.4% (19.8%, 29.2%)	Not Significant
Median Time to Progression ^b (95% CI) ^a	21.4 weeks (19.3, 24.6)	22.1 weeks (18.1, 25.6)	Not Significant

^aAdjusted for multiple comparisons.

^bKaplan-Meier estimates.

14.4 Castration-Resistant Prostate Cancer

The safety and efficacy of TAXOTERE in combination with prednisone in patients with metastatic castration-resistant 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/m² every 3 weeks for 10 cycles.
- TAXOTERE 30 mg/m² administered weekly for the first 5 weeks in a 6-week cycle for 5 cycles.
- Mitoxantrone 12 mg/m² every 3 weeks for 10 cycles.

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

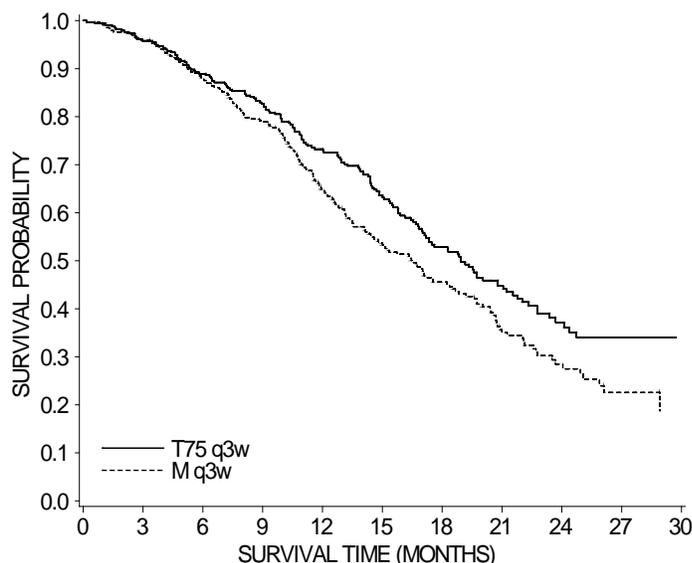
In the TAXOTERE every three week arm, a statistically significant overall survival advantage was demonstrated compared to mitoxantrone. In the TAXOTERE weekly arm, no overall survival advantage was demonstrated compared to the mitoxantrone control arm. Efficacy results for the TAXOTERE every 3 week arm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

Table 18: Efficacy of TAXOTERE in the Treatment of Patients with Metastatic Castration-Resistant 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/m² on day 1) in combination with cisplatin (C) (75 mg/m² on day 1) and fluorouracil (F) (750 mg/m² per day for 5 days) or cisplatin (100 mg/m² on day 1) and fluorouracil (1000 mg/m² 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) (95%CI)	5.6 (4.86-5.91)	3.7 (3.45-4.47)
Hazard ratio [†] (95%CI) *p-value	0.68 (0.55-0.84) 0.0004	
Median survival (months) (95%CI)	9.2 (8.38-10.58)	8.6 (7.16-9.46)
Hazard ratio [†] (95%CI) *p-value	0.77 (0.62-0.96) 0.0201	
Overall Response Rate (CR+PR) (%) p-value	36.7	25.4
	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

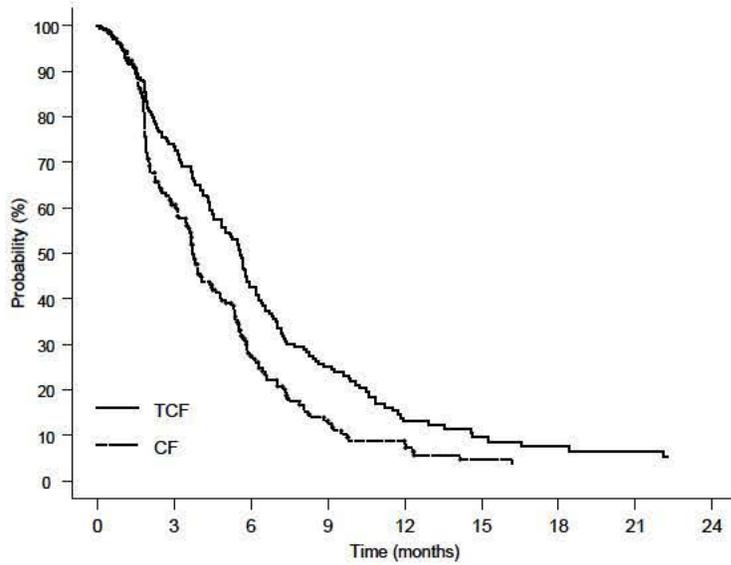
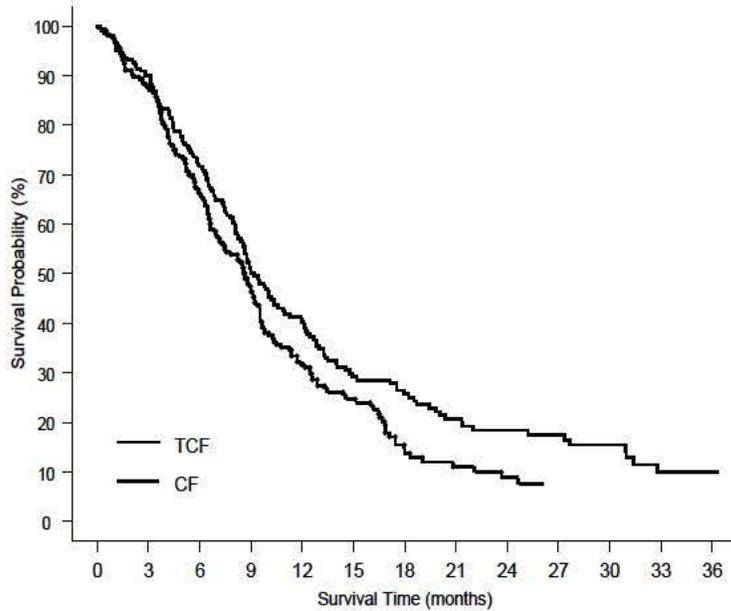


Figure 7: Gastric Cancer Study (TAX325) Survival K-M Curve



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/m² followed by cisplatin (P) 75 mg/m² on Day 1, followed by fluorouracil (F) 750 mg/m² 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/m² on Day 1, followed by fluorouracil (F) 1000 mg/m²/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)	0.71 (0.56-0.91)	
*p-value	0.0077	
Median survival (months) (95% CI)	18.6 (15.7-24.0)	14.2 (11.5-18.7)
Hazard ratio (95% CI)	0.71 (0.56-0.90)	
**p-value	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

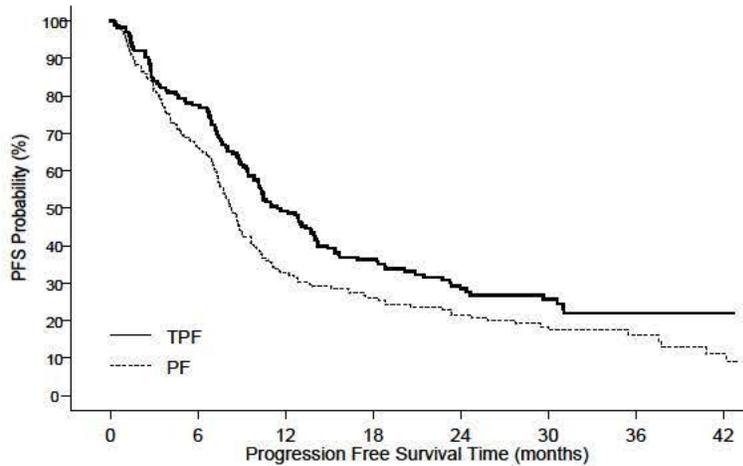
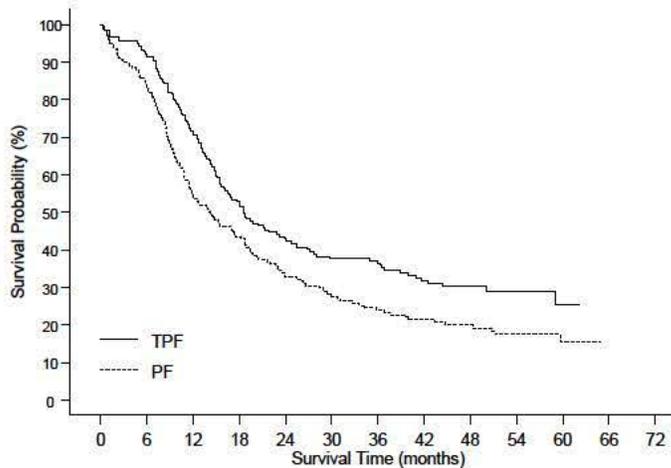


Figure 9: TAX323 Overall Survival K-M Curve



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 vs 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)

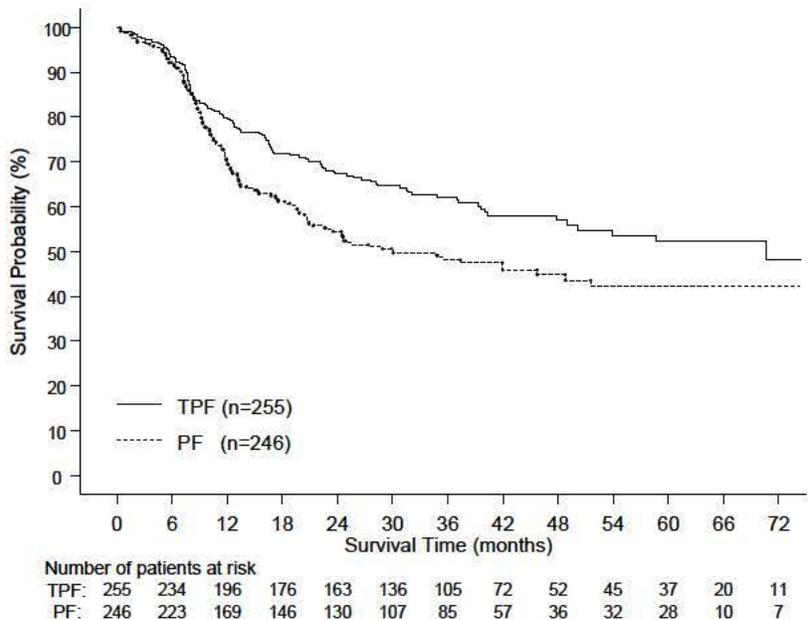
ENDPOINT	TAXOTERE + Cisplatin + Fluorouracil n=255	Cisplatin + Fluorouracil n=246
Median overall survival (months) (95% CI)	70.6 (49.0-NE)	30.1 (20.9-51.5)
Hazard ratio: (95% CI) *p-value	0.70 (0.54-0.90) 0.0058	

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

<http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

One-vial TAXOTERE (Injection)

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

TAXOTERE 20 mg/mL (NDC 0075-8003-01)

TAXOTERE (docetaxel) Injection 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.

TAXOTERE 80 mg/4 mL (NDC 0075-8004-04)

TAXOTERE (docetaxel) Injection 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.

16.2 Storage

Store between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect from 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

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Bone Marrow Suppression

Explain the significance of routine blood cell counts. Thus, it is important that periodic assessment of their blood count be performed to detect the development of neutropenia, thrombocytopenia and/ or anemia [*see Contraindications (4) and Warnings and Precautions (5.3)*]. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever.

Gastrointestinal Events, Eye Disorders

Explain to patients that side effects such as nausea, vomiting, diarrhea, constipation, excessive tearing and/or vision disturbances are associated with docetaxel administration [*see Adverse Reactions (6)*]. Tell patients to immediately report abdominal pain or tenderness, and/or diarrhea, with or without fever [*see Warnings and Precautions (5.4)*], any vision changes [*see Warnings and Precautions (5.10)*].

Hypersensitivity Reactions

Obtain detailed allergy information from the patient prior to TAXOTERE administration. Instruct patients to immediately report signs of a hypersensitivity reaction. Ask patients whether they have previously received paclitaxel therapy, and if they have experienced a hypersensitivity reaction to paclitaxel [*see Contraindications (4) and Warnings and Precautions (5.5)*].

Fluid Retention

Tell patients to watch for signs of fluid retention such as peripheral edema in the lower extremities, weight gain and dyspnea and instruct patients to immediately report them [*see Warnings and Precautions (5.6)*].

Myalgia, Cutaneous Reactions, Neurologic Reactions, Local Site Reactions, Fatigue, Alopecia

Instruct patients to report myalgia [*see Adverse Reactions (6)*], cutaneous reactions [*see Warnings and Precautions (5.8)*], neurologic reactions [*see Warnings and Precautions (5.9)*], or infusion site reactions [*see Adverse Reactions (6)*]. Explain to patients that side effects such as fatigue and hair loss (cases of permanent hair loss have been reported) are associated with docetaxel administration [*see Adverse Reactions (6)*].

Cardiac disorders

Tell patients to report any irregular and/or rapid heartbeat, severe shortness of breath, dizziness, and/or fainting [*see Adverse Reactions (6)*].

Importance of Corticosteroids

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 [*see Dosage and Administration (2.6)*].

Alcohol Content in TAXOTERE Injection

Explain to patients the possible effects of the alcohol content in TAXOTERE Injection, including possible effects on the central nervous system [*see Warnings and Precautions (5.12)*].

Ability to Drive or Operate Machines

Explain to patients that TAXOTERE Injection may impair their ability to drive or operate machines due to its side effects [*see Adverse Reactions (6)*] or due to the alcohol content of TAXOTERE Injection [*see Warnings and Precautions (5.12)*]. Advise them not to drive or use machines if they experience these side effects during treatment.

Drug Interactions

Inform patients about the risk of drug interactions and the importance of providing a list of prescription and non-prescription drugs to their healthcare provider [*see Drug Interactions (7)*].

Embryo-Fetal Toxicity

TAXOTERE may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Advise female patients of childbearing potential to use effective contraceptives during treatment [*see Warnings and Precautions (5.13) and Use in Specific Populations (8.1)*].

Patient Information
TAXOTERE (TAX-O-TEER)
(docetaxel) injection
for intravenous use

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 healthcare provider 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.

- **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
- **TAXOTERE can affect your blood cells.** Your healthcare provider 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 healthcare provider may not treat you with TAXOTERE until you have enough white blood cells. People with low white blood cell counts can develop life-threatening infections. The earliest sign of infection may be fever. Follow your healthcare provider's instructions for how often to take your temperature during treatment with TAXOTERE. Call your healthcare provider right away if you have a fever.
- **Swelling (inflammation) of the small intestine and colon.** This can happen at any time and could lead to death as early as the first day you get symptoms. Tell your healthcare provider right away if you develop new or worse symptoms of intestinal problems, including stomach (abdominal) pain or tenderness, diarrhea, or fever.
- **Severe allergic reactions** are medical emergencies that can happen in people who receive TAXOTERE and can lead to death. You may be at higher risk of developing a severe allergic reaction to TAXOTERE if you are allergic to paclitaxel. Your healthcare provider will monitor you closely for allergic reactions during your TAXOTERE infusion. Tell your healthcare provider right away if you have any of these signs of a severe 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
- **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 healthcare provider tells you. Tell your healthcare provider or nurse before your TAXOTERE treatment if you forgot to take your corticosteroid dose or do not take it as your healthcare provider tells you. Tell your healthcare provider right away if you have swelling in your legs or feet, weight gain or shortness of breath.

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

It is not known if TAXOTERE is effective in children.

Do not receive TAXOTERE if you:

- have a low white blood cell count.
 - have had a severe allergic reaction to:
 - docetaxel, the active ingredient in TAXOTERE, or
 - any other medicines that contain polysorbate 80. Ask your healthcare provider 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.
- See the end of this Patient Information for a complete list of the ingredients in TAXOTERE.

Before you receive TAXOTERE, tell your healthcare provider about all of your medical conditions, including if you:

- are allergic to any medicines, including paclitaxel. See "**Do not receive TAXOTERE if you**".
- have liver problems
- are pregnant or plan to become pregnant. TAXOTERE can harm your unborn baby. You should not become pregnant during treatment with TAXOTERE. Females who are able to become pregnant should use effective birth control

(contraception) during treatment with TAXOTERE. Talk to your healthcare provider if you have questions about birth control options that are right for you.

- are breastfeeding or plan to breastfeed. It is not known if TAXOTERE passes into your breast milk. You and your healthcare provider should decide if you will receive TAXOTERE or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter 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 to show your healthcare provider 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 healthcare provider will decide how long you will receive treatment with TAXOTERE.
- Your healthcare provider will check your blood cell counts and other blood tests during your treatment with TAXOTERE to check for side effects of TAXOTERE.
- Your healthcare provider may stop your treatment, change the timing of your treatment, or change the dose of your treatment if you have certain side effects while receiving 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 receive TAXOTERE along with certain other medicines.
- **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. Tell your healthcare provider if you are having a skin reaction.
- **Neurologic problems.** Neurologic symptoms are common in people who receive TAXOTERE but can be severe. Tell your healthcare provider if you have numbness, tingling, or burning in your hands or feet (peripheral neuropathy) or weakness of your legs, feet, arms, or hands (motor weakness).
- **Vision problems** including blurred vision or loss of vision. Tell your healthcare provider right away if you have any vision changes.
- **TAXOTERE injection contains alcohol.** The alcohol content in TAXOTERE injection may impair your ability to drive or use machinery right after receiving TAXOTERE injection. Consider whether you should drive, operate machinery or do other dangerous activities right after you receive TAXOTERE injection treatment.
- You may experience side effects of this medicine that may impair your ability to drive, use tools, or operate machines. If this happens, do not drive or use any tools or machines before discussing with your healthcare provider.

The most common side effects of TAXOTERE include:

- infections
- low white blood cells (help fight infections), low red blood cells (anemia) and low platelets (help blood to clot)
- allergic reactions (See “**What is the most important information I should know about TAXOTERE?**”)
- changes in your sense of taste
- shortness 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 lip sores
- hair loss: in some people, permanent hair loss has been reported
- 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 healthcare provider if you have a fast or irregular heartbeat, severe shortness of breath, dizziness or fainting during your infusion. If any of these events occurs after your infusion, get medical help right away.

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

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

General information about the safe and effective use of TAXOTERE.

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information. You can ask your

pharmacist or healthcare provider for information about TAXOTERE that is written for health professionals.

What are the ingredients in TAXOTERE?

Active ingredient: docetaxel

Inactive ingredients: polysorbate 80 and dehydrated alcohol solution

sanofi-aventis U.S. LLC

Bridgewater, NJ 08807

A SANOFI COMPANY

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For more information, call 1-800-633-1610 or go to www.sanofi-aventis.com.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 10/2018

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 healthcare provider 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 healthcare provider tells you.

Oral corticosteroid dosing:

Date: _____ Time: _____

Date: _____ Time: _____

(TAXOTERE Treatment Day)

Time: _____

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020449Orig1s079

OTHER REVIEW(S)

Division of Oncology Products 1

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 020449/SLR-079

Name of Drug: Taxotere® (docetaxel) Injection Concentrate

Applicant: sanofi-aventis U.S. LLC

Labeling Reviewed

Submission Date: April 11, 2018

Receipt Date: April 11, 2018

Background and Summary Description: NDA 020449 is approved for the treatment of patients with Breast Cancer, Non-Small Cell Lung Cancer, Hormone Refractory Prostate Cancer, Gastric Adenocarcinoma, Squamous Cell Carcinoma of the Head and Neck Cancer.

SLR-079 (PAS) provides for the addition of “Enterocolitis and Neutropenic Colitis” and for updates to “Hypersensitivity Reactions” in section 5 “Warnings and Precautions” of the Prescribing Information (PI). Also provides for updates to sections 6 “Adverse Reactions”, 6.2 “Postmarketing Experience”, and 17 “Patient Counseling” of the PI to reflect the above changes in section 5 and to distinguish between risk of adverse events (AEs) during the TAX316 adjuvant breast cancer study and AEs persistent following completion of the trial, with a median follow-up time of 8 years, with regard to the following AEs: peripheral neuropathy, alopecia, amenorrhea, peripheral edema, lymphedema, asthenia, and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML).

We held two internal meetings, on August 9, 2018, and August 16, 2018, which included division management. See Clinical review dated October 3, 2018; Patient Labeling Review dated August 30, 2018; and Office of Prescription Drug Promotion review dated August 29, 2018.

Review

The submitted draft package was compared to the currently approved package insert. Attached is the proposed package insert with “Review Comments”.

Recommendations

SLR-079 can be approved.

Sakar Wahby, PharmD

Regulatory Project Manager

Alice Kacuba, RN, MSN, GWCPM, RAC

Chief, Project Management Staff

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SAKAR M WAHBY
10/04/2018

ALICE KACUBA
10/05/2018

NDA: 020449

Supplement: S-079

eCTD #: 0148

Drug: Docetaxel (Taxotere)

Sponsor: Sanofi-Aventis

Submission Date: 04/11/2018

PDUFA Date: 10/11/2018

Review Completed: 10/02/2018

Clinical Reviewer: Tatiana Prowell, MD

Clinical Team Leader: Laleh Amiri, MD

RPM: Sakah Wahby

This is a prior approval supplement (PAS) labeling update submitted by Sanofi Aventis for NDA020449 for docetaxel (Taxotere). The principal purpose of this supplement was to provide for [REDACTED] (b) (4)

[REDACTED] The proposed labeling changes and FDA assessment of these changes is described below.

With this supplement, the Sponsor has proposed addition of the following new listing to Warnings & Precautions:

5.4 [REDACTED] (b) (4)

Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Enterocolitis [REDACTED] (b) (4) develop at any time, and could lead to death as early as on the first day of onset. [REDACTED] (b) (4)

[REDACTED] [see Dosage and Administration (2), Warnings and Precautions (5.3), Adverse Reactions (6.2)].

Reviewer Comment:

The Sponsor performed a search of the Sanofi global pharmacovigilance database to identify all cases of enterocolitis for which docetaxel was suspected to have contributed. A total of 1092 potential cases were identified, including 156 cases of neutropenic enterocolitis. In the majority of cases of neutropenic enterocolitis (100 out of 156), use of G-CSF was not reported. The outcome according to G-CSF use in either the prophylactic or therapeutic setting is shown in the Sponsor's table below:

Table 4 - Use of G-CSF

Use of G-CSF	Counts	Fatal outcome
Not reported*	100	22 (22.0%)
Not given**	1	0 (0.0%)
Prophylactic G-CSF was given	18	9 (50.0%)
Therapeutic G-CSF was given	35	4 (11.%)
Prophylactic G-CSF and Therapeutic G-CSF were given	2	0 (0.0%)
Total	156	35 (22.4%)

The time to onset of enterocolitis was widely variable. Fatalities were reported as early as the first day of symptom onset, despite co-administration of G-CSF. Enterocolitis has been reported in both neutropenic and non-neutropenic patients. As a result, the following revised language was proposed by DOP1 and accepted by the Sponsor:

5.4 Enterocolitis and Neutropenic Colitis

Enterocolitis and neutropenic colitis (typhlitis) have occurred in patients treated with TAXOTERE alone and in combination with other chemotherapeutic agents, despite the co-administration of G-CSF. Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Enterocolitis and neutropenic enterocolitis may develop at any time, and could lead to death as early as the first day of symptom onset. Monitor patients closely from onset of any symptoms of gastrointestinal toxicity. Inform patients to contact their healthcare provider with new, or worsening symptoms of gastrointestinal toxicity [see Dosage and Administration (2), Warnings and Precautions (5.3), Adverse Reactions (6.2)].

With this supplement, the Sponsor has proposed update of the existing listing in Warnings & Precautions to include a statement cautioning about risk of hypersensitivity reaction in patients with a history of previous hypersensitivity reaction to paclitaxel, as follows:

5.5 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. Patients who have previously experienced a hypersensitivity reaction to paclitaxel may develop a ^{(b) (4)} hypersensitivity reaction to docetaxel.

Reviewer Comment:

Hypersensitivity reaction to docetaxel is a known AE associated with docetaxel and is listed in the currently approved package insert. In response to a CHMP request to perform ongoing

monitoring for potential cross-reactivity between taxanes resulting in hypersensitivity reactions, the Sponsor conducted a search of the Sanofi global pharmacovigilance database to identify cases of hypersensitivity in which docetaxel was a potential causal agent. A total of 110 serious reports were identified, of which 71 were distinct cases with sufficient information for review. There were 38 cases of reaction to docetaxel following prior reaction to paclitaxel (of which 7 reported a more severe hypersensitivity reaction to docetaxel than had previously occurred with paclitaxel). Among the 38 cases of reaction to docetaxel following prior reaction to paclitaxel, there was one fatality due to Stevens Johnson Syndrome and another non-fatal case of toxic epidermal necrolysis. The Division therefore found the Sponsor's proposed addition to the existing W&P to be generally acceptable, however the clinical team felt that the proposed language did not provide adequate detail or direction for clinicians on these reactions. The revised language which was agreed upon between the Agency and the Sponsor is as follows:

5.5 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 pre-medicated 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. Patients who have previously experienced a hypersensitivity reaction to paclitaxel may develop a hypersensitivity reaction to docetaxel that may include severe or fatal reactions such as anaphylaxis. Monitor patients with a previous history of hypersensitivity to paclitaxel closely during initiation of TAXOTERE therapy. 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)].

With this supplement, the Sponsor has proposed (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer Comment:

Cardiology consultation was obtained from Division of Cardiovascular & Renal Products. There were 6 serious ventricular arrhythmia events reported, 3 of which were confounded by concomitant medications or underlying cardiopulmonary disease and 2 of which could not

establish temporality. There were 12 other cases of ventricular tachycardia, 7 other cases of ventricular fibrillation, and 6 other cases of ventricular extrasystole that were confounded by concomitant therapies; underlying disease (e.g., hypertension, cardiomyopathy, pulmonary disease; pneumonia/septic shock/hypokalemia); occurred in the context of hypersensitivity/anaphylactic shock (labeled); or did not appear to occur in a close temporal relationship to drug administration. The consultants noted that Section 6.1 of the approved labeling already includes language concerning cardiovascular reactions and arrhythmias, and that the limited number of cases, the majority of which were confounded or uninformative, reported over the long marketing period (~20 years), does not support the notion of causality. The consultant also advised against the recommendation for [REDACTED] (b) (4) as it was not clear how this assessment would guide management. As a result, the Sponsor's proposed [REDACTED] (b) (4) was rejected.

The Sponsor also proposed to update Section 6 and Section 6.2 of the label to reflect the above changes and to distinguish between between risk of adverse events (AEs) during the TAX316 adjuvant breast cancer study and AEs persistent following completion of the trial, with a median follow-up time of 8 years, with regard to the following AEs: peripheral neuropathy, alopecia, amenorrhea, peripheral edema, lymphedema, asthenia, and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML). This included addition of the words “during the treatment period” in several places in Section 6.1 and addition of a section describing persistent adverse events from TAX316 during a more prolonged follow-up period (median of 8 years of follow-up).

Reviewer Comment:

The Sponsor's proposed additions to the label were generally acceptable with some revisions of the Sponsor's proposed language. The language agreed upon between FDA and the Sponsor is as follows:

Adverse reactions during the follow-up period (median follow-up time of 8 years)

In study TAX316, the most common adverse reactions that started during the treatment period and persisted into the follow-up period in TAC and FAC patients are described below (median follow-up time of 8 years).

Nervous system disorders

In study TAX316, peripheral sensory neuropathy started during the treatment period and persisted into the follow-up period in 84 patients (11.3%) in TAC arm and 15 patients (2%) in FAC arm. At the end of the follow-up period (median follow-up time of 8 years), peripheral sensory neuropathy was observed to be ongoing in 10 patients (1.3%) in TAC arm, and in 2 patients (0.3%) in FAC arm.

Skin and subcutaneous tissue disorders

In study TAX316, alopecia persisting into the follow-up period after the end of chemotherapy was reported in 687 of 744 TAC patients (92.3%) and 645 of 736 FAC patients (87.6%). At the end of the follow-up period (actual median follow-up time of 8 years), alopecia was observed to be ongoing in 29 TAC patients (3.9%) and 16 FAC patients (2.2%).

Reproductive system and breast disorders

In study TAX316, amenorrhea that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 202 of 744 TAC patients (27.2%) and 125 of 736 FAC patients (17.0%). Amenorrhea was observed to be ongoing at the end of the follow-up period (median follow-up time of 8 years) in 121 of 744 TAC patients (16.3%) and 86 FAC patients (11.7%).

General disorders and administration site conditions

In study TAX316, peripheral edema that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was observed in 119 of 744 TAC patients (16.0%) and 23 of 736 FAC patients (3.1%). At the end of the follow-up period (actual median follow-up time of 8 years), peripheral edema was ongoing in 19 TAC patients (2.6%) and 4 FAC patients (0.5%).

In study TAX316, lymphedema that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 11 of 744 TAC patients (1.5%) and 1 of 736 FAC patients (0.1%). At the end of the follow-up period (actual median follow-up time of 8 years), lymphedema was observed to be ongoing in 6 TAC patients (0.8%) and 1 FAC patient (0.1%).

In study TAX316, asthenia that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 236 of 744 TAC patients (31.7%) and 180 of 736 FAC patients (24.5%). At the end of the follow-up period (actual median follow-up time of 8 years), asthenia was observed to be ongoing in 29 TAC patients (3.9%) and 16 FAC patients (2.2%).

Acute myeloid leukemia (AML)/myelodysplastic syndrome

AML occurred in the adjuvant breast cancer trial (TAX316). The cumulative risk of developing treatment-related AML at median follow-up time of 8 years in TAX316 was 0.4% for TAC-treated patients and 0.1% for FAC-treated patients. One TAC patient (0.1%) and 1 FAC patient (0.1%) died due to AML during the follow-up period (median follow-up time of 8 years).

Myelodysplastic syndrome occurred in 2 of 744 (0.3%) patients who received TAC and in 1 of 736 (0.1%) patients who received FAC. AML occurs at a higher frequency when these agents are given in combination with radiation therapy.

The Sponsor also proposes to update Section 17 and PPI to convey the above changes to the labeling in patient-friendly language and to warn patients that they may experience side effects that impair ability to drive, use tools, or operate machines related to alcohol content. These changes have been reviewed by DMPP/OPDP (see separate reviews in DARRTS), and the final package insert reflects their recommendations.

The labeling update also provides for numerous formatting/editorial changes and updates the term “hormone refractory prostate cancer” to the currently accepted term, “castration-resistant prostate cancer” throughout the label.

Recommended Regulatory Action:

The agreed-upon revised docetaxel labeling is acceptable from a clinical standpoint. Approval is recommended.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TANYA M PROWELL
10/02/2018

LALEH AMIRI KORDESTANI
10/03/2018

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: August 30, 2018

To: Julia Beaver, MD
Director
Division of Oncology Products 1 (DOP 1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Ruth Lidoshore, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TAXOTERE (docetaxel)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: NDA 020449

Supplement Number: S-079

Applicant: sanofi-aventis U.S. LLC

1 INTRODUCTION

On April 11, 2018, sanofi-aventis U.S. LLC submitted for the Agency's review a Prior Approval Supplement (PAS) – Labeling to their approved New Drug Application (NDA) 020449/079 for TAXOTERE (docetaxel) injection. With this submission, the Applicant proposes to [REDACTED] (b) (4)

[REDACTED] to section 5 “WARNINGS AND PRECAUTIONS” and section 6 “ADVERSE REACTIONS” of the Prescribing Information (PI). The Applicant also proposes to update information regarding injection site recall and hypersensitivity reactions in the PI.

The Applicant submitted this labeling supplement [REDACTED] (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP 1) on April 30, 2018, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TAXOTERE (docetaxel) injection.

2 MATERIAL REVIEWED

- Draft TAXOTERE (docetaxel) injection PPI received on April 11, 2018, and received by DMPP and OPDP on August 17, 2018.
- Draft TAXOTERE (docetaxel) injection Prescribing Information (PI) received on April 11, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 17, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

RUTH I LIDOSHORE
08/30/2018

KEVIN WRIGHT
08/30/2018

LASHAWN M GRIFFITHS
08/30/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: August 29, 2018

To: Julia Beaver, M.D., Director
Division of Oncology Products 1 (DOP1)

Sakar Wahby, PharmD, Regulatory Project Manager, DOP1

William Pierce, PharmD, Associate Director for Labeling, DOP1

From: Kevin Wright, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for Taxotere[®] (docetaxel) injection, for intravenous use

NDA: 020449/Supplement 079

In response to Division of Oncology Products 1 consult request dated April 30, 2018, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI), for this supplemental NDA submission for Taxotere[®] (docetaxel) injection, for intravenous use (Taxotere). This supplement (S-079) proposes changes to the WARNINGS and PRECAUTIONS, ADVERSE REACTIONS section of the PI and “What is the most important information I should know about TAXOTERE?”, and “What are the possible side effects of TAXOTERE?” sections of the PPI.

OPDP’s comments on the proposed labeling are based on the draft PI and PPI/Medication Guide/IFU received by electronic mail from DOP1 (Kim Robertson) on August 16, 2018, and we do not have any comments.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

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/s/

KEVIN WRIGHT
08/29/2018

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020449Orig1s079

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Wahby, Sakar

From: Wahby, Sakar
Sent: Tuesday, October 2, 2018 3:18 PM
To: 'Stefanie.Doty@sanofi.com'
Subject: FDA Communication, NDA 20449 SLR-079/FDA Revised PPI
Attachments: 10-2-18 FDA revised PPI.docx

Importance: High

Dear Stefanie,

Attached please find the Taxotere PPI with a few minor edits for NDA 20449 SLR-079. Please let me know if you agree with these edits via email **by 12:00 pm EST., on Wednesday, October 3, 2018.** Feel free to contact me if you have any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

sakar.wahby@fda.hhs.gov

(P): 240-402-5364

(F): 301-796-9845

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SAKAR M WAHBY
10/03/2018

Wahby, Sakar

From: Wahby, Sakar
Sent: Wednesday, September 26, 2018 11:10 AM
To: 'Stefanie.Doty@sanofi.com'
Subject: FDA Communication, NDA 20449 SLR-079/FDA Revised PI & PPI
Attachments: 9-26-18 FDA revised PI.doc; 9-26-18 FDA revised PPI.doc

Importance: High

Dear Stefanie,

Attached please find the Taxotere PI & PPI for NDA 20449 SLR-079, with DOP1 comments and revisions. Please return your comments/revisions to us **by COB, on Friday, September 28, 2018.** Feel free to contact me if you have any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP1
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
(F): 301-796-9845

66 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SAKAR M WAHBY
09/26/2018

Wahby, Sakar

From: Wahby, Sakar
Sent: Thursday, September 6, 2018 6:57 AM
To: 'Stefanie.Doty@sanofi.com'
Subject: FDA Communication, NDA 20449 SLR-079/FDA Revised PI & PPI
Attachments: 9-5-18 FDA revised PI NDA 20449 SLR079.docx; 9-6-18 FDA Revised PPI NDA 20449 SLR079.docx

Importance: High

Dear Stefanie,

Attached please find the Taxotere PI & PPI for NDA 20449 SLR-079, with DOP1 comments and revisions. Please return your comments/revisions to us **by COB, on Wednesday, September 12, 2018.** Feel free to contact me if you have any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP1

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

sakar.wahby@fda.hhs.gov

(P): 240-402-5364

(F): 301-796-9845

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/s/

SAKAR M WAHBY
09/13/2018



NDA 020449/S-079

**ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT**

sanofi-aventis U.S. LLC
Attention: Stefanie Doty
Director, Regulatory Affairs
55 Corporate Drive, Mail Stop: 55C-300
Bridgewater, NJ 08807

Dear Ms. Doty:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 020449
SUPPLEMENT NUMBER: 079
PRODUCT NAME: Taxotere[®] (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL
DATE OF SUBMISSION: April 11, 2018
DATE OF RECEIPT: April 11, 2018

This supplemental application proposes to [REDACTED] (b) (4) to section 5 “WARNINGS AND PRECAUTIONS” and section 6 “ADVERSE REACTIONS” of the Prescribing Information (PI). Also, to update information regarding injection site recall reaction and hypersensitivity reactions in the PI.

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 June 10, 2018, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be October 11, 2018.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

SUBMISSION REQUIREMENTS

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 Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (240) 402-5364 or email me at sakar.wahby@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sakar Wahby, PharmD
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

SAKAR M WAHBY
05/14/2018

REQUEST FOR CONSULTATION

TO (Office/Division): ODE 1/Cardiovascular and Renal Products (DCRP)

FROM (Name, Office/Division, and Phone Number of Requestor):

Sakar Wahby, PharmD
Regulatory Project Manager
OND/OHOP/DOP1
Phone: 240-402-5364

DATE
April 30, 2018

IND NO.

NDA NO.
NDA 20449/
SLR-079

TYPE OF DOCUMENT
NEW Labeling Supplement
to NDA Application 20449
(Supplement 079)

DATE OF DOCUMENT
April 11, 2018

NAME OF DRUG
Taxotere (docetaxel)

PRIORITY CONSIDERATION
N/A

CLASSIFICATION OF DRUG
Oncology

DESIRED COMPLETION DATE
July 15, 2018

NAME OF FIRM: Sanofi-aventis

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- | | |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|--|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

DOP1/OHOP received a NEW labeling supplement under NDA 20449/SLR-079 Taxotere (docetaxel). This SLR provides for the addition of a subsection to the Prescribing Information (b) (4) adverse reactions being added to the "WARNINGS AND PRECAUTIONS" section of the PI. Also updates sections 6.2 and 17 to add these adverse reactions. (b) (4)

The link to the submission is as follows:

EDR Location: <\\CDSESUB1\evsprod\NDA020449\020449.enx>

Labeling Meetings: TBD

Goal Date: October 11, 2018

SIGNATURE OF REQUESTOR

Sakar Wahby

METHOD OF DELIVERY (Check all that apply)

DARRTS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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

/s/

SAKAR M WAHBY
04/30/2018

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

9
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-OPDP-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Sakar Wahby, PharmD Regulatory Project Manager OND/OHOP/DOP1 Phone: 240-402-5364
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REQUEST DATE: April 30, 2018	IND NO.	NDA/BLA NO. NDA 20449/ SLR-079	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) NEW Labeling Supplement to NDA Application 20449 (Supplement 079)
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NAME OF DRUG: Taxotere (docetaxel)	PRIORITY CONSIDERATION: N/A	CLASSIFICATION OF DRUG Oncology	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) July 15, 2018
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NAME OF FIRM: Sanofi-aventis	Goal Date: October 11, 2018
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TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION For OSE USE ONLY <input type="checkbox"/> REMS
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EDR link to submission:
 EDR Location: <\\CDSESUB1\evsprod\NDA020449\020449.enx>

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, “substantially complete” labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling Meetings: TBD

Goal Date: October 11, 2018

SIGNATURE OF REQUESTER

Sakar Wahby

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

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

/s/

SAKAR M WAHBY
04/30/2018

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

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO: CDER-DMPP-PatientLabelingTeam		FROM: (Name/Title, Office/Division/Phone number of requestor) Sakar Wahby, PharmD Regulatory Project Manager OND/OHOP/DOP1 Phone: 240-402-5364	
REQUEST DATE: April 30, 2018	NDA/BLA NO.: NDA 20449/ SLR-079	TYPE OF DOCUMENTS: NEW Labeling Supplement to NDA Application 20449 (Supplement 079)	
NAME OF DRUG: Taxotere (docetaxel)	PRIORITY CONSIDERATION: N/A	CLASSIFICATION OF DRUG: Oncology	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) July 15, 2018
SPONSOR: Sanofi-aventis		Goal Date: October 11, 2018	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply)	TYPE OF APPLICATION/SUBMISSION	REASON FOR LABELING CONSULT
<input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI)	<input type="checkbox"/> ORIGINAL NDA/BLA	<input type="checkbox"/> INITIAL PROPOSED LABELING
<input type="checkbox"/> MEDICATION GUIDE	<input type="checkbox"/> EFFICACY SUPPLEMENT	<input checked="" type="checkbox"/> LABELING REVISION
<input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<input type="checkbox"/> SAFETY SUPPLEMENT	
	<input checked="" type="checkbox"/> LABELING SUPPLEMENT	
	<input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT	
	<input type="checkbox"/> PLR CONVERSION	

EDR link to submission:

EDR Location: <\\CDSESUB1\evsprod\NDA020449\020449.enx>

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling Meetings: TBD

Goal Date: October 11, 2018

SIGNATURE OF REQUESTER Sakar Wahby (240)-402-5364	SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL (BLAs Only) <input type="checkbox"/> DARRTS <input type="checkbox"/>
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAKAR M WAHBY
04/30/2018