

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

### WARNING

See full prescribing information for complete boxed warning

- Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with NSCLC and prior platinum-based therapy receiving TAXOTERE at 100 mg/m<sup>2</sup> ( 5.1)
- Should not be given if bilirubin > ULN, or if SGOT and/or SGPT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. LFT elevations increase risk of severe or life-threatening complications. Obtain LFTs before each treatment cycle ( 8.6)
- Should not be given if neutrophil counts are < 1500 cells/mm<sup>3</sup>. Obtain frequent blood counts to monitor for neutropenia ( 4)
- Severe hypersensitivity, including very rare fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of TAXOTERE and administration of appropriate therapy ( 5.3)
- Contraindicated if history of severe hypersensitivity reactions to TAXOTERE or to drugs formulated with polysorbate 80 ( 4)
- Severe fluid retention may occur despite dexamethasone ( 5.10)

### RECENT MAJOR CHANGES

Indications and usage ( 1), dosage and administration ( 2), warnings and precautions ( 5), adverse reactions( 6), 09/28/07

### INDICATIONS AND USAGE

Taxotere is a microtubule inhibitor used for:

**Breast Cancer (BC):** single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC ( 1.1)

**Non-Small Cell Lung Cancer (NSCLC):** single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC ( 1.2)

**Hormone Refractory Prostate Cancer (HRPC):** with prednisone in androgen independent (hormone refractory) metastatic prostate cancer ( 1.3)

**Gastric Adenocarcinoma (GC):** with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction ( 1.4)

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

### DOSAGE AND ADMINISTRATION

Administer under supervision of qualified physicians experienced in using antineoplastic agents. Facilities to manage possible complications must be available.

Administer IV over 1 hr every 3 weeks. PVC equipment is not recommended.

- BC: locally advanced or metastatic: 60-100 mg/m<sup>2</sup> single agent ( 2.1)
- BC adjuvant: 75 mg/m<sup>2</sup> administered 1 hour after doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> every 3 weeks for 6 cycles ( 2.1)

- NSCLC: after platinum therapy failure: 75 mg/m<sup>2</sup> single agent ( 2.2)
- NSCLC: chemotherapy-naive: 75 mg/m<sup>2</sup> followed by cisplatin 75 mg/m<sup>2</sup> ( 2.2)
- HRPC: 75 mg/m<sup>2</sup> with 5 mg prednisone twice a day continuously ( 2.3)
- GC: 75 mg/m<sup>2</sup> followed by cisplatin 75 mg/m<sup>2</sup> (both on day 1 only) followed by fluorouracil 750 mg/m<sup>2</sup> per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion ( 2.4)
- SCCHN: 75 mg/m<sup>2</sup> followed by cisplatin 75 mg/m<sup>2</sup> IV (day 1), followed by fluorouracil 750 mg/m<sup>2</sup> per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion; for 4 cycles ( 2.5)
- SCCHN: 75 mg/m<sup>2</sup> followed by cisplatin 100 mg/m<sup>2</sup> IV (day 1), followed by fluorouracil 1000 mg/m<sup>2</sup> per day as a 24-hr IV (days 1-4); for 3 cycles ( 2.5)

### Premedication Regimen ( 2.6)

- Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice a day) for 3 days starting 1 day before administration
- HRPC: oral dexamethasone 8 mg, at 12, 3, and 1 hrs before treatment

**Dosage adjustments during treatment** see full prescribing information ( 2.7)

### DOSAGE FORMS AND STRENGTHS

- Single dose vial 80 mg/2 mL and diluent, 20 mg/0.5 mL and diluent ( 3)

### CONTRAINDICATIONS

- Hypersensitivity to Taxotere or polysorbate 80 ( 4)
- Neutrophil counts of < 1500 cells/mm<sup>3</sup> ( 4)

### WARNINGS AND PRECAUTIONS

- Acute myeloid leukemia ( 5.6)
- Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant when taking TAXOTERE ( 5.7)
- Asthenia ( 5.12)

### ADVERSE REACTIONS

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

Other adverse reactions, including serious adverse reactions have been reported ( 6)

**To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-663-1610 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

### DRUG INTERACTIONS

- Compounds that induce, inhibit, or are metabolized by P450-3A4 ( 7)

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

**Revised: 09/28/07**

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**FULL PRESCRIBING INFORMATION**

**WARNING**

The incidence of treatment-related mortality associated with TAXOTERE therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive TAXOTERE as a single agent at a dose of 100 mg/m<sup>2</sup> [see *Warnings and Precautions (5.1)*].

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

TAXOTERE therapy should not be given to patients with neutrophil counts of <1500 cells/mm<sup>3</sup>. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving TAXOTERE.

Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the TAXOTERE infusion and administration of appropriate therapy [see *Warnings and Precautions (5.2)*]. 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 (5.10)*].

1 **1. INDICATIONS AND USAGE**  
2

3 **1.1 Breast Cancer**

- 4 • TAXOTERE is indicated for the treatment of patients with locally advanced or  
5 metastatic breast cancer after failure of prior chemotherapy.  
6 • TAXOTERE in combination with doxorubicin and cyclophosphamide is indicated for  
7 the adjuvant treatment of patients with operable node-positive breast cancer.  
8

9 **1.2 Non-Small Cell Lung Cancer**

- 10 • TAXOTERE as a single agent is indicated for the treatment of patients with locally  
11 advanced or metastatic non-small cell lung cancer after failure of prior platinum-  
12 based chemotherapy.  
13 • TAXOTERE in combination with cisplatin is indicated for the treatment of patients  
14 with unresectable, locally advanced or metastatic non-small cell lung cancer who  
15 have not previously received chemotherapy for this condition.  
16

17 **1.3 Prostate Cancer**

- 18 • TAXOTERE in combination with prednisone is indicated for the treatment of patients  
19 with androgen independent (hormone refractory) metastatic prostate cancer.  
20

21 **1.4 Gastric Adenocarcinoma**

- 22 • TAXOTERE in combination with cisplatin and fluorouracil is indicated for the  
23 treatment of patients with advanced gastric adenocarcinoma, including  
24 adenocarcinoma of the gastroesophageal junction, who have not received prior  
25 chemotherapy for advanced disease.  
26

27 **1.5 Head and Neck Cancer**

- 28 • TAXOTERE in combination with cisplatin and fluorouracil is indicated for the  
29 induction treatment of patients with locally advanced squamous cell carcinoma of the  
30 head and neck (SCCHN).  
31

32 **2. DOSAGE AND ADMINISTRATION**  
33

34 TAXOTERE (docetaxel) Injection Concentrate should be administered under the supervision of  
35 a qualified physician experienced in the use of antineoplastic agents. Appropriate management  
36 of complications is possible only when adequate diagnostic and treatment facilities are readily  
37 available.  
38

39 **2.1 Breast Cancer**

- 40 • The recommended dose of TAXOTERE is 60-100 mg/m<sup>2</sup> administered intravenously  
41 over 1 hour every 3 weeks.  
42 • In the adjuvant treatment of operable node-positive breast cancer, the recommended  
43 TAXOTERE dose is 75 mg/m<sup>2</sup> administered 1-hour after doxorubicin 50 mg/m<sup>2</sup> and  
44 cyclophosphamide 500 mg/m<sup>2</sup> every 3 weeks for 6 courses. Prophylactic G-CSF may

1 be used to mitigate the risk of hematological toxicities [*see Dosage Adjustments*  
2 *During Treatment (2.7)*].

## 3 4 **2.2 Non-Small Cell Lung Cancer**

- 5 • For treatment after failure of prior platinum-based chemotherapy, TAXOTERE was  
6 evaluated as monotherapy, and the recommended dose is 75 mg/m<sup>2</sup> administered  
7 intravenously over 1 hour every 3 weeks. A dose of 100 mg/m<sup>2</sup> in patients previously  
8 treated with chemotherapy was associated with increased hematologic toxicity,  
9 infection, and treatment-related mortality in randomized, controlled trials [*see Boxed*  
10 *Warning, Dosage Adjustments During Treatment (2.7), Warnings and Precautions*  
11 *(5), Clinical Studies (14)*].
- 12 • For chemotherapy-naïve patients, TAXOTERE was evaluated in combination with  
13 cisplatin. The recommended dose of TAXOTERE is 75 mg/m<sup>2</sup> administered  
14 intravenously over 1 hour immediately followed by cisplatin 75 mg/m<sup>2</sup> over  
15 30-60 minutes every 3 weeks [*see Dosage Adjustments During Treatment (2.7)*].

## 16 17 **2.3 Prostate cancer**

- 18 • For hormone-refractory metastatic prostate cancer, the recommended dose of  
19 TAXOTERE is 75 mg/m<sup>2</sup> every 3 weeks as a 1 hour intravenous infusion.  
20 Prednisone 5 mg orally twice daily is administered continuously [*see Dosage*  
21 *Adjustments During Treatment (2.7)*].

## 22 23 **2.4 Gastric adenocarcinoma**

- 24 • For gastric adenocarcinoma, the recommended dose of TAXOTERE is 75 mg/m<sup>2</sup> as a  
25 1 hour intravenous infusion, followed by cisplatin 75 mg/m<sup>2</sup>, as a 1 to 3 hour  
26 intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m<sup>2</sup> per  
27 day given as a 24-hour continuous intravenous infusion for 5 days, starting at the end  
28 of the cisplatin infusion. Treatment is repeated every three weeks. Patients must  
29 receive premedication with antiemetics and appropriate hydration for cisplatin  
30 administration [*see Dosage Adjustments During Treatment (2.7)*].

## 31 32 **2.5 Head and Neck Cancer**

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

- 37  
38 • Induction chemotherapy followed by radiotherapy (TAX323)  
39 For the induction treatment of locally advanced inoperable SCCHN, the  
40 recommended dose of TAXOTERE is 75 mg/m<sup>2</sup> as a 1 hour intravenous infusion  
41 followed by cisplatin 75 mg/m<sup>2</sup> intravenously over 1 hour, on day one, followed by  
42 fluorouracil as a continuous intravenous infusion at 750 mg/m<sup>2</sup> per day for five days.  
43 This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy,  
44 patients should receive radiotherapy. [*see Dosage Adjustments During Treatment*  
45 *(2.7)*].

- 1  
2
- Induction chemotherapy followed by chemoradiotherapy (TAX324)

3 For the induction treatment of patients with locally advanced (unresectable, low  
4 surgical cure, or organ preservation) SCCHN, the recommended dose of TAXOTERE  
5 is 75 mg/m<sup>2</sup> as a 1 hour intravenous infusion on day 1, followed by cisplatin  
6 100 mg/m<sup>2</sup> administered as a 30-minute to 3 hour infusion, followed by fluorouracil  
7 1000 mg/m<sup>2</sup>/day as a continuous infusion from day 1 to day 4. This regimen is  
8 administered every 3 weeks for 3 cycles. Following chemotherapy, patients should  
9 receive chemoradiotherapy [*see Dosage Adjustments During Treatment (2.7)*].

10  
11 **2.6 Premedication Regimen**

- 12
- All patients should be premedicated with oral corticosteroids (see below for prostate  
13 cancer) such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting  
14 1 day prior to TAXOTERE administration in order to reduce the incidence and  
15 severity of fluid retention as well as the severity of hypersensitivity reactions [*see*  
16 ***Boxed Warning, Warnings and Precautions (5)***].
  - For hormone-refractory metastatic prostate cancer, given the concurrent use of  
17 prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, at  
18 12 hours, 3 hours and 1 hour before the TAXOTERE infusion [*see Warnings and*  
19 ***Precautions (5)***].  
20

21  
22 **2.7 Dosage Adjustments During Treatment**

- 23
- **Breast Cancer**

24 Patients who are dosed initially at 100 mg/m<sup>2</sup> and who experience either febrile neutropenia,  
25 neutrophils <500 cells/mm<sup>3</sup> for more than 1 week, or severe or cumulative cutaneous reactions  
26 during TAXOTERE therapy should have the dosage adjusted from 100 mg/m<sup>2</sup> to 75 mg/m<sup>2</sup>. If  
27 the patient continues to experience these reactions, the dosage should either be decreased from  
28 75 mg/m<sup>2</sup> to 55 mg/m<sup>2</sup> or the treatment should be discontinued. Conversely, patients who are  
29 dosed initially at 60 mg/m<sup>2</sup> and who do not experience febrile neutropenia, neutrophils  
30 <500 cells/mm<sup>3</sup> for more than 1 week, severe or cumulative cutaneous reactions, or severe  
31 peripheral neuropathy during TAXOTERE therapy may tolerate higher doses. Patients who  
32 develop ≥grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued  
33 entirely.  
34

- 35
- **Combination Therapy with TAXOTERE in the Adjuvant Treatment of Breast  
36 Cancer**

37 TAXOTERE in combination with doxorubicin and cyclophosphamide should be administered  
38 when the neutrophil count is ≥1,500 cells/mm<sup>3</sup>. Patients who experience febrile neutropenia  
39 should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction  
40 should remain on G-CSF and have their TAXOTERE dose reduced to 60 mg/m<sup>2</sup>. Patients who  
41 experience Grade 3 or 4 stomatitis should have their TAXOTERE dose decreased to 60 mg/m<sup>2</sup>.  
42 Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory  
43 signs and/or symptoms during TAXOTERE therapy should have their dosage of TAXOTERE  
44

1 reduced from 75 to 60 mg/m<sup>2</sup>. If the patient continues to experience these reactions at 60 mg/m<sup>2</sup>,  
2 treatment should be discontinued.

3  
4 • **Non-Small Cell Lung Cancer**

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

7 Patients who are dosed initially at 75 mg/m<sup>2</sup> and who experience either febrile neutropenia,  
8 neutrophils <500 cells/mm<sup>3</sup> for more than one week, severe or cumulative cutaneous reactions,  
9 or other grade 3/4 non-hematological toxicities during TAXOTERE treatment should have  
10 treatment withheld until resolution of the toxicity and then resumed at 55 mg/m<sup>2</sup>. Patients who  
11 develop ≥grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued  
12 entirely.

13 *Combination therapy with TAXOTERE for chemotherapy-naïve NSCLC*

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

20  
21 • **Prostate Cancer**

22 *Combination therapy with TAXOTERE for hormone-refractory metastatic prostate*  
23 *cancer*

24 TAXOTERE should be administered when the neutrophil count is ≥1,500 cells/mm<sup>3</sup>. Patients  
25 who experience either febrile neutropenia, neutrophils <500 cells/mm<sup>3</sup> for more than one week,  
26 severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms  
27 during TAXOTERE therapy should have the dosage of TAXOTERE reduced from 75 to  
28 60 mg/m<sup>2</sup>. If the patient continues to experience these reactions at 60 mg/m<sup>2</sup>, the treatment  
29 should be discontinued.

30  
31 • **Gastric or Head and Neck Cancer**

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

34 Patients treated with TAXOTERE in combination with cisplatin and fluorouracil must receive  
35 antiemetics and appropriate hydration according to current institutional guidelines. In both  
36 studies, G-CSF was recommended during the second and/or subsequent cycles in case of febrile  
37 neutropenia, or documented infection with neutropenia, or neutropenia lasting more than 7 days.  
38 If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs  
39 despite G-CSF use, the TAXOTERE dose should be reduced from 75 to 60 mg/m<sup>2</sup>. If  
40 subsequent episodes of complicated neutropenia occur the TAXOTERE dose should be reduced  
41 from 60 to 45 mg/m<sup>2</sup>. In case of Grade 4 thrombocytopenia the TAXOTERE dose should be  
42 reduced from 75 to 60 mg/m<sup>2</sup>. Patients should not be retreated with subsequent cycles of  
43 TAXOTERE until neutrophils recover to a level >1,500 cells/mm<sup>3</sup> and platelets recover to a  
44 level >100,000 cells/mm<sup>3</sup>. Discontinue treatment if these toxicities persist. [*see Warnings and*  
45 *Precautions (5)*].

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

3  
4 **Table 1 - Recommended Dose Modifications for Toxicities in Patients Treated with**  
5 **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%.

6  
7 Liver dysfunction:

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

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

11  
12 The dose modifications for cisplatin and fluorouracil in the gastric cancer study are provided  
13 below:

14 Cisplatin dose modifications and delays

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

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

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

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

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

1

**Table 2 – Dose Reductions for Evaluation of Creatinine Clearance**

<b>Creatinine clearance result before next cycle</b>	<b>Cisplatin dose next cycle</b>
CrCl ≥60 mL/min	Full dose of cisplatin was given. CrCl was to be repeated before each treatment cycle.
CrCl between 40 and 59 mL/min	Dose of cisplatin was reduced by 50% at subsequent cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was 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 <u>that treatment cycle only</u> .  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.

2 CrCl = Creatinine clearance

3

4 Fluorouracil dose modifications and treatment delays

5 For diarrhea and stomatitis, see Table 1.

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

8 For other greater than grade 3 toxicities, except alopecia and anemia, chemotherapy should be  
9 delayed (for a maximum of 2 weeks from the planned date of infusion) until resolution to grade  
10 ≤1 and then recommenced, if medically appropriate.

11 For other fluorouracil dosage adjustments, also refer to the manufacturers’ prescribing  
12 information.

13

14 **2.8 Administration Precautions**

15 TAXOTERE is a cytotoxic anticancer drug and, as with other potentially toxic compounds,  
16 caution should be exercised when handling and preparing TAXOTERE solutions. The use of  
17 gloves is recommended. Please refer to *Handling and Disposal (16.3)*.

18 If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for intravenous  
19 infusion should come into contact with the skin, immediately and thoroughly wash with soap and  
20 water. If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for  
21 intravenous infusion should come into contact with mucosa, immediately and thoroughly wash  
22 with water.

23 Contact of the TAXOTERE concentrate with plasticized PVC equipment or devices used to  
24 prepare solutions for infusion is not recommended. In order to minimize patient exposure to the



1 plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or  
2 sets, the final TAXOTERE dilution for infusion should be stored in bottles (glass,  
3 polypropylene) or plastic bags (polypropylene, polyolefin) and administered through  
4 polyethylene-lined administration sets.

5 TAXOTERE Injection Concentrate requires two dilutions prior to administration. Please follow  
6 the preparation instructions provided below. **Note:** Both the TAXOTERE Injection Concentrate  
7 and the diluent vials contain an overfill to compensate for liquid loss during preparation. This  
8 overfill ensures that after dilution with the **entire** contents of the accompanying diluent, there is  
9 an initial diluted solution containing 10 mg/mL docetaxel.

10 The table below provides the fill range of the diluent, the approximate extractable volume of  
11 diluent when the entire contents of the diluent vial are withdrawn, and the concentration of the  
12 initial diluted solution for TAXOTERE 20 mg and TAXOTERE 80 mg (see Table 3).  
13  
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**Table 3 – Initial Dilution of TAXOTERE Injection Concentrate**

Product	Diluent 13% (w/w) ethanol in water for injection Fill Range (mL)	Approximate extractable volume of diluent when entire contents are withdrawn (mL)	Concentration of the initial diluted solution (mg/mL docetaxel)
Taxotere® 20 mg/0.5 mL	1.88 – 2.08 mL	1.8 mL	10 mg/mL
Taxotere® 80 mg/2 mL	6.96 – 7.70 mL	7.1 mL	10 mg/mL

## 2.9 Preparation and Administration

### A. Initial Diluted Solution

1. TAXOTERE vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection Concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes.
2. Aseptically withdraw the entire contents of the appropriate diluent vial (approximately 1.8 mL for TAXOTERE 20 mg and approximately 7.1 mL for TAXOTERE 80 mg) into a syringe by partially inverting the vial, and transfer it to the appropriate vial of TAXOTERE Injection Concentrate. **If the procedure is followed as described, an initial diluted solution of 10 mg docetaxel/mL will result.**
3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4. The initial diluted TAXOTERE solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

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

1 **B. Final Dilution for Infusion**

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

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

8 2. Thoroughly mix the infusion by manual rotation.

9 3. As with all parenteral products, TAXOTERE should be inspected visually for particulate  
10 matter or discoloration prior to administration whenever the solution and container permit. If  
11 the TAXOTERE initial diluted solution or final dilution for intravenous infusion is not clear or  
12 appears to have precipitation, these should be discarded.

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

15  
16 **2.10 Stability**

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

20  
21 **3. DOSAGE FORMS AND STRENGTHS**

22 **TAXOTERE 80 mg/2 mL**

23 TAXOTERE (docetaxel) Injection Concentrate 80 mg/2 mL: 80 mg docetaxel in 2 mL  
24 polysorbate 80 and Diluent for TAXOTERE 80 mg (13% (w/w) ethanol in water for injection).  
25 Both items are in a blister pack in one carton.

26 **TAXOTERE 20 mg/0.5 mL**

27 TAXOTERE (docetaxel) Injection Concentrate 20 mg/0.5 mL: 20 mg docetaxel in 0.5 mL  
28 polysorbate 80 and Diluent for TAXOTERE 20 mg (13% (w/w) ethanol in water for injection).  
29 Both items are in a blister pack in one carton.

30  
31 **4. CONTRAINDICATIONS**

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

34 TAXOTERE should not be used in patients with neutrophil counts of  $<1500$  cells/mm<sup>3</sup>.

35  
36 **5. WARNINGS AND PRECAUTIONS**

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

40  
41 **5.1 Toxic Deaths**

42 • **Breast Cancer**

43 TAXOTERE administered at 100 mg/m<sup>2</sup> was associated with deaths considered possibly or  
44 probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both  
45 previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of

1 patients with various tumor types who had abnormal baseline liver function (SGOT and/or SGPT  
2 >1.5 times ULN together with AP >2.5 times ULN). Among patients dosed at 60 mg/m<sup>2</sup>,  
3 mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function,  
4 and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred  
5 during the first cycle. Sepsis accounted for the majority of the deaths.

6  
7 • **Non-Small Cell Lung Cancer**

8 TAXOTERE administered at a dose of 100 mg/m<sup>2</sup> in patients with locally advanced or metastatic  
9 non-small cell lung cancer who had a history of prior platinum-based chemotherapy was  
10 associated with increased treatment-related mortality (14% and 5% in two randomized,  
11 controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at  
12 the 75 mg/m<sup>2</sup> dose in the randomized trials. Among patients who experienced treatment-related  
13 mortality at the 75 mg/m<sup>2</sup> dose level, 3 of 5 patients had a PS of 2 at study entry [*see Boxed*  
14 *Warning, Clinical Studies (14), and Dosage and Administration (2.2)*].

15  
16 **5.2 Premedication Regimen**

17 All patients should be premedicated with oral corticosteroids (see below for prostate cancer)  
18 such as dexamethasone 16 mg per day (*e.g.*, 8 mg BID) for 3 days starting 1 day prior to  
19 TAXOTERE to reduce the severity of fluid retention and hypersensitivity reactions [*see Dosage*  
20 *and Administration (2.6)*]. This regimen was evaluated in 92 patients with metastatic breast  
21 cancer previously treated with chemotherapy given TAXOTERE at a dose of 100 mg/m<sup>2</sup> every  
22 3 weeks.

23 The pretreatment regimen for hormone-refractory metastatic prostate cancer is oral  
24 dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the TAXOTERE infusion [*see*  
25 *Dosage and Administration (2.6)*].

26  
27 **5.3 Hypersensitivity Reactions**

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

34  
35 Hypersensitivity reactions may occur within a few minutes following initiation of a TAXOTERE  
36 infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of  
37 therapy is not required. All patients should be premedicated with an oral corticosteroid prior to  
38 the initiation of the infusion of TAXOTERE [*see Boxed Warning, Premedication Regimen*  
39 *(2.6)*].

40  
41 **5.4 Hematologic Effects**

42 Neutropenia (<2000 neutrophils/mm<sup>3</sup>) occurs in virtually all patients given 60-100 mg/m<sup>2</sup> of  
43 TAXOTERE and grade 4 neutropenia (<500 cells/mm<sup>3</sup>) occurs in 85% of patients given  
44 100 mg/m<sup>2</sup> and 75% of patients given 60 mg/m<sup>2</sup>. Frequent monitoring of blood counts is,  
45 therefore, essential so that dose can be adjusted. TAXOTERE should not be administered to  
46 patients with neutrophils <1500 cells/mm<sup>3</sup>.

1 Febrile neutropenia occurred in about 12% of patients given 100 mg/m<sup>2</sup> but was very uncommon  
2 in patients given 60 mg/m<sup>2</sup>. Hematologic responses, febrile reactions and infections, and rates of  
3 septic death for different regimens are dose related and are described in *Clinical Studies (14)*.

4  
5 Three breast cancer patients with severe liver impairment (bilirubin >1.7 times ULN) developed  
6 fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia. In gastric  
7 cancer patients treated with TAXOTERE in combination with cisplatin and fluorouracil (TCF),  
8 febrile neutropenia and/or neutropenic infection occurred in 12% of patients receiving G-CSF  
9 compared to 28% who did not. Patients receiving TCF should be closely monitored during the  
10 first and subsequent cycles for febrile neutropenia and neutropenic infection [*see Adverse*  
11 *Reactions (6.0) and Dosage Adjustments (2.7)*].

12 In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral  
13 blood cell counts be performed on all patients receiving TAXOTERE. Patients should not be  
14 retreated with subsequent cycles of TAXOTERE until neutrophils recover to a level  
15 >1500 cells/mm<sup>3</sup> and platelets recover to a level > 100,000 cells/mm<sup>3</sup>.

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

## 19 20 **5.5 Hepatic Impairment**

21 [*see Boxed Warning, Use in Specific Populations (8.6)*].

## 22 23 **5.6 Acute Myeloid Leukemia**

24 Treatment-related acute myeloid leukemia (AML) or myelodysplasia has occurred in patients  
25 given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast  
26 cancer. In the adjuvant breast cancer trial [(TAX316), *see Clinical Studies (14)*] AML occurred  
27 in 3 of 744 patients who received TAXOTERE, doxorubicin and cyclophosphamide and in 1 of  
28 736 patients who received fluorouracil, doxorubicin and cyclophosphamide. In the  
29 TAXOTERE, doxorubicin and cyclophosphamide (TAC) treated patients, the risk of delayed  
30 myelodysplasia or myeloid leukemia requires hematological follow-up [*see Adverse Reactions*  
31 *(6)*].

## 32 33 **5.7 Pregnancy**

34 Pregnancy Category D

35  
36 TAXOTERE can cause fetal harm when administered to pregnant women. Studies in both rats  
37 and rabbits at doses ≥0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily  
38 maximum recommended human dose on a mg/m<sup>2</sup> basis), administered during the period of  
39 organogenesis, have shown that TAXOTERE is embryotoxic and fetotoxic (characterized by  
40 intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay).  
41 The doses indicated above also caused maternal toxicity.

42 There are no adequate and well-controlled studies in pregnant women using TAXOTERE. If  
43 TAXOTERE is used during pregnancy, or if the patient becomes pregnant while receiving this  
44 drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss  
45 of the pregnancy. Women of childbearing potential should be advised to avoid becoming  
46 pregnant during therapy with TAXOTERE [*see Use In Specific Populations (8.1)*].

1  
2 **5.8 General**

3 Responding patients may not experience an improvement in performance status on therapy and  
4 may experience worsening. The relationship between changes in performance status, response to  
5 therapy, and treatment-related side effects has not been established.  
6

7 **5.9 Cutaneous**

8 Localized erythema of the extremities with edema followed by desquamation has been observed.  
9 In case of severe skin toxicity, an adjustment in dosage is recommended [*see Dose Adjustments*  
10 *During Treatment (2.7)*]. The discontinuation rate due to skin toxicity was 1.6% (15/965) for  
11 metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day  
12 corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued  
13 TAXOTERE due to skin toxicity.  
14

15 **5.10 Fluid Retention**

16 Severe fluid retention has been reported following TAXOTERE therapy [*see Boxed Warning,*  
17 *Premedication Regimen (2.6)*]. Patients should be premedicated with oral corticosteroids prior  
18 to each TAXOTERE administration to reduce the incidence and severity of fluid retention [*see*  
19 *Premedication Regimen (2.6)*]. Patients with pre-existing effusions should be closely monitored  
20 from the first dose for the possible exacerbation of the effusions.  
21

22 When fluid retention occurs, peripheral edema usually starts in the lower extremities and may  
23 become generalized with a median weight gain of 2 kg.  
24

25 Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid  
26 retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to  
27 onset of moderate or severe fluid retention was 819 mg/m<sup>2</sup>. 9.8% (9/92) of patients discontinued  
28 treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the  
29 remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment  
30 discontinuation due to fluid retention was 1021 mg/m<sup>2</sup>. Fluid retention was completely, but  
31 sometimes slowly, reversible with a median of 16 weeks from the last infusion of TAXOTERE  
32 to resolution (range: 0 to 42+ weeks). Patients developing peripheral edema may be treated with  
33 standard measures, *e.g.*, salt restriction, oral diuretic(s).  
34

35 **5.11 Neurologic**

36 Severe neurosensory symptoms (paresthesia, dysesthesia, pain) were observed in 5.5% (53/965)  
37 of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When  
38 these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be  
39 discontinued [*see Dose Adjustments During Treatment (2.7)*]. Patients who experienced  
40 neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of  
41 the event was available had spontaneous reversal of symptoms with a median of 9 weeks from  
42 onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal  
43 extremity weakness occurred in 4.4% (42/965).  
44

## 5.12 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.

## 6. ADVERSE REACTIONS

Adverse reactions are described for TAXOTERE according to indication.

### 6.1 Clinical Trial Experience

- Breast Cancer

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

TAXOTERE 100 mg/m<sup>2</sup>: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received TAXOTERE administered at 100 mg/m<sup>2</sup> 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 4).

**Table 4 - Summary of Adverse Reactions in Patients Receiving TAXOTERE at 100 mg/m<sup>2</sup>**

<b>Adverse Reaction</b>	<b>All Tumor Types Normal LFTs* n=2045 %</b>	<b>All Tumor Types Elevated LFTs** n=61 %</b>	<b>Breast Cancer Normal LFTs* n=965 %</b>
<b>Hematologic</b>			
Neutropenia <2000 cells/mm <sup>3</sup>	95.5	96.4	98.5
<500 cells/mm <sup>3</sup>	75.4	87.5	85.9
Leukopenia <4000 cells/mm <sup>3</sup>	95.6	98.3	98.6
<1000 cells/mm <sup>3</sup>	31.6	46.6	43.7
Thrombocytopenia <100,000 cells/mm <sup>3</sup>	8.0	24.6	9.2
Anemia <11 g/dL	90.4	91.8	93.6
<8 g/dL	8.8	31.1	7.7

<b>Adverse Reaction</b>	<b>All Tumor Types Normal LFTs* n=2045 %</b>	<b>All Tumor Types Elevated LFTs** n=61 %</b>	<b>Breast Cancer Normal LFTs* n=965 %</b>
Febrile Neutropenia***	11.0	26.2	12.3
<b>Septic Death</b>	1.6	4.9	1.4
<b>Non-Septic Death</b>	0.6	6.6	0.6
<b>Infections</b>			
Any	21.6	32.8	22.2
Severe	6.1	16.4	6.4
<b>Fever in Absence of Infection</b>			
Any	31.2	41.0	35.1
Severe	2.1	8.2	2.2
<b>Hypersensitivity Reactions Regardless of Premedication</b>			
Any	21.0	19.7	17.6
Severe	4.2	9.8	2.6
<b>With 3-day Premedication</b>	n=92	n=3	n=92
Any	15.2	33.3	15.2
Severe	2.2	0	2.2
<b>Fluid Retention Regardless of Premedication</b>			
Any	47.0	39.3	59.7
Severe	6.9	8.2	8.9
<b>With 3-day Premedication</b>	n=92	n=3	n=92
Any	64.1	66.7	64.1
Severe	6.5	33.3	6.5
<b>Neurosensory</b>			
Any	49.3	34.4	58.3
Severe	4.3	0	5.5
<b>Cutaneous</b>			
Any	47.6	54.1	47.0
Severe	4.8	9.8	5.2
<b>Nail Changes</b>			
Any	30.6	23.0	40.5
Severe	2.5	4.9	3.7
<b>Gastrointestinal</b>			
Nausea	38.8	37.7	42.1
Vomiting	22.3	23.0	23.4

<b>Adverse Reaction</b>	<b>All Tumor Types Normal LFTs* n=2045 %</b>	<b>All Tumor Types Elevated LFTs** n=61 %</b>	<b>Breast Cancer Normal LFTs* n=965 %</b>
Diarrhea	38.7	32.8	42.6
Severe	4.7	4.9	5.5
<b>Stomatitis</b>			
Any	41.7	49.2	51.7
Severe	5.5	13.0	7.4
<b>Alopecia</b>	75.8	62.3	74.2
<b>Asthenia</b>			
Any	61.8	52.5	66.3
Severe	12.8	24.6	14.9
<b>Myalgia</b>			
Any	18.9	16.4	21.1
Severe	1.5	1.6	1.8
<b>Arthralgia</b>	9.2	6.6	8.2
<b>Infusion Site Reactions</b>	4.4	3.3	4.0

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

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

5 \*\*\*Febrile Neutropenia: ANC grade 4 with fever  $> 38^{\circ}\text{C}$  with IV antibiotics and/or hospitalization  
6

### 7 **Hematologic [see Warnings and Precautions (5.4)].**

8 Reversible marrow suppression was the major dose-limiting toxicity of TAXOTERE. The  
9 median time to nadir was 7 days, while the median duration of severe neutropenia  
10 ( $< 500$  cells/ $\text{mm}^3$ ) was 7 days. Among 2045 patients with solid tumors and normal baseline LFTs,  
11 severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles.

12 Febrile neutropenia ( $< 500$  cells/ $\text{mm}^3$  with fever  $> 38^{\circ}\text{C}$  with IV antibiotics and/or hospitalization)  
13 occurred in 11% of patients with solid tumors, in 12.3% of patients with metastatic breast cancer,  
14 and in 9.8% of 92 breast cancer patients premedicated with 3-day corticosteroids.

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

18 Thrombocytopenia ( $< 100,000$  cells/ $\text{mm}^3$ ) associated with fatal gastrointestinal hemorrhage has  
19 been reported.  
20

### 21 **Hypersensitivity Reactions**

22 Severe hypersensitivity reactions are discussed in the *Boxed Warning, Warnings and*  
23 *Precautions (5.3)* sections. Minor events, including flushing, rash with or without pruritus, chest  
24 tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after  
25 discontinuing the infusion and appropriate therapy.



1  
2 **Fluid Retention** [see *Boxed Warning, Warnings and Precautions (5.10), Premedication*  
3 *Regimen (2.6)*].

4  
5 **Cutaneous**

6 Severe skin toxicity is discussed in *Warnings and Precautions (5.9)*. Reversible cutaneous  
7 reactions characterized by a rash including localized eruptions, mainly on the feet and/or hands,  
8 but also on the arms, face, or thorax, usually associated with pruritus, have been observed.  
9 Eruptions generally occurred within 1 week after TAXOTERE infusion, recovered before the  
10 next infusion, and were not disabling.

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

13  
14 **Neurologic** [see *Warnings and Precautions (5.11)*].

15  
16 **Gastrointestinal**

17 Gastrointestinal reactions (nausea and/or vomiting and/or diarrhea) were generally mild to  
18 moderate. Severe reactions occurred in 3-5% of patients with solid tumors and to a similar extent  
19 among metastatic breast cancer patients. The incidence of severe reactions was 1% or less for the  
20 92 breast cancer patients premedicated with 3-day corticosteroids.

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

24  
25 **Cardiovascular**

26 Hypotension occurred in 2.8% of patients with solid tumors; 1.2% required treatment. Clinically  
27 meaningful events such as heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable  
28 angina, pulmonary edema, and hypertension occurred rarely. 8.1% (7/86) of metastatic breast  
29 cancer patients receiving TAXOTERE 100 mg/m<sup>2</sup> in a randomized trial and who had serial left  
30 ventricular ejection fractions assessed developed deterioration of LVEF by ≥10% associated with  
31 a drop below the institutional lower limit of normal.

32  
33 **Infusion Site Reactions**

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

36  
37 **Hepatic**

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

**Hematologic and Other Toxicity: Relation to dose and baseline liver chemistry abnormalities**

Hematologic and other toxicity is increased at higher doses and in patients with elevated baseline liver function tests (LFTs). In the following tables, adverse drug reactions are compared for three populations: 730 patients with normal LFTs given TAXOTERE at 100 mg/m<sup>2</sup> in the randomized and single arm studies of metastatic breast cancer after failure of previous chemotherapy; 18 patients in these studies who had abnormal baseline LFTs (defined as SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN); and 174 patients in Japanese studies given TAXOTERE at 60 mg/m<sup>2</sup> who had normal LFTs (see Tables 5 and 6).

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

Adverse Reaction	TAXOTERE 100 mg/m <sup>2</sup>		TAXOTERE 60 mg/m <sup>2</sup>
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
<b>Neutropenia</b>			
Any <2000 cells/mm <sup>3</sup>	98.4	100	95.4
Grade 4 <500 cells/mm <sup>3</sup>	84.4	93.8	74.9
<b>Thrombocytopenia</b>			
Any <100,000 cells/mm <sup>3</sup>	10.8	44.4	14.4
Grade 4 <20,000 cells/mm <sup>3</sup>	0.6	16.7	1.1
<b>Anemia</b> <11 g/dL	94.6	94.4	64.9
<b>Infection***</b>			
Any	22.5	38.9	1.1
Grade 3 and 4	7.1	33.3	0
<b>Febrile Neutropenia****</b>			
By Patient	11.8	33.3	0
By Course	2.4	8.6	0
<b>Septic Death</b>	1.5	5.6	1.1
<b>Non-Septic Death</b>	1.1	11.1	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: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN

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

\*\*\*\*Febrile Neutropenia: For 100 mg/m<sup>2</sup>, ANC grade 4 and fever >38°C with IV antibiotics and/or hospitalization; for 60 mg/m<sup>2</sup>, ANC grade 3/4 and fever >38.1°C

1 **Table 6 - Non-Hematologic Adverse Reactions in Breast Cancer Patients Previously**  
2 **Treated with Chemotherapy Treated at TAXOTERE 100 mg/m<sup>2</sup> with Normal or Elevated**  
3 **Liver Function Tests or 60 mg/m<sup>2</sup> with Normal Liver Function Tests**

Adverse Reaction	TAXOTERE 100 mg/m <sup>2</sup>		TAXOTERE 60 mg/m <sup>2</sup>
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
<b>Acute Hypersensitivity Reaction Regardless of Premedication</b>			
Any	13.0	5.6	0.6
Severe	1.2	0	0
<b>Fluid Retention*** Regardless of Premedication</b>			
Any	56.2	61.1	12.6
Severe	7.9	16.7	0
<b>Neurosensory</b>			
Any	56.8	50	19.5
Severe	5.8	0	0
<b>Myalgia</b>	22.7	33.3	3.4
<b>Cutaneous</b>			
Any	44.8	61.1	30.5
Severe	4.8	16.7	0
<b>Asthenia</b>			
Any	65.2	44.4	65.5
Severe	16.6	22.2	0
<b>Diarrhea</b>			
Any	42.2	27.8	NA
Severe	6.3	11.1	
<b>Stomatitis</b>			
Any	53.3	66.7	19.0
Severe	7.8	38.9	0.6

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

6 \*\* Elevated Baseline Liver Function: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase  
7 >2.5 times ULN

8 \*\*\*Fluid Retention includes (by COSTART): edema (peripheral, localized, generalized, lymphedema, pulmonary  
9 edema, and edema otherwise not specified) and effusion (pleural, pericardial, and ascites); no premedication given  
10 with the 60 mg/m<sup>2</sup> dose

11 NA = not available

In the three-arm monotherapy trial, TAX313, which compared TAXOTERE 60, 75 and 100 mg/m<sup>2</sup> in advanced breast cancer, the overall safety profile was consistent with the safety profile observed in previous TAXOTERE trials. Grade 3/4 or severe adverse reactions occurred in 49.0% of patients treated with TAXOTERE 60 mg/m<sup>2</sup> compared to 55.3% and 65.9% treated with 75 and 100 mg/m<sup>2</sup> respectively. Discontinuation due to adverse reactions was reported in 5.3% of patients treated with 60 mg/m<sup>2</sup> vs. 6.9% and 16.5% for patients treated at 75 and 100 mg/m<sup>2</sup> respectively. Deaths within 30 days of last treatment occurred in 4.0% of patients treated with 60 mg/m<sup>2</sup> compared to 5.3% and 1.6% for patients treated at 75 and 100 mg/m<sup>2</sup> respectively.

The following adverse reactions were associated with increasing docetaxel doses: fluid retention (26%, 38%, and 46% at 60, 75, and 100 mg/m<sup>2</sup> 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 (TEAEs) observed in 744 patients, who were treated with TAXOTERE 75 mg/m<sup>2</sup> every 3 weeks in combination with doxorubicin and cyclophosphamide (see Table 7).

**Table 7 - 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 <sup>2</sup> + Doxorubicin 50 mg/m <sup>2</sup> + Cyclophosphamide 500 mg/m <sup>2</sup> (TAC) n=744 %		Fluorouracil 500 mg/m <sup>2</sup> + Doxorubicin 50 mg/m <sup>2</sup> + Cyclophosphamide 500 mg/m <sup>2</sup> (FAC) n=736 %	
	Any	G 3/4	Any	G 3/4
Anemia	91.5	4.3	71.7	1.6
Neutropenia	71.4	65.5	82.0	49.3
Fever in absence of infection	46.5	1.3	17.1	0.0
Infection	39.4	3.9	36.3	2.2
Thrombocytopenia	39.4	2.0	27.7	1.2
Febrile neutropenia	24.7	N/A	2.5	N/A
Neutropenic infection	12.1	N/A	6.3	N/A
Hypersensitivity reactions	13.4	1.3	3.7	0.1
Lymphedema	4.4	0.0	1.2	0.0
Fluid Retention*	35.1	0.9	14.7	0.1
Peripheral edema	26.9	0.4	7.3	0.0
Weight gain	12.9	0.3	8.6	0.3
Neuropathy sensory	25.5	0.0	10.2	0.0

	<b>TAXOTERE 75 mg/m<sup>2</sup>+ Doxorubicin 50 mg/m<sup>2</sup>+ Cyclophosphamide 500 mg/m<sup>2</sup> (TAC) n=744 %</b>		<b>Fluorouracil 500 mg/m<sup>2</sup>+ Doxorubicin 50 mg/m<sup>2</sup>+ Cyclophosphamide 500 mg/m<sup>2</sup> (FAC) n=736 %</b>	
<b>Adverse Reaction</b>	<b>Any</b>	<b>G 3/4</b>	<b>Any</b>	<b>G 3/4</b>
<b>Neuro-cortical</b>	5.1	0.5	6.4	0.7
<b>Neuropathy motor</b>	3.8	0.1	2.2	0.0
<b>Neuro-cerebellar</b>	2.4	0.1	2.0	0.0
<b>Syncope</b>	1.6	0.5	1.2	0.3
<b>Alopecia</b>	97.8	N/A	97.1	N/A
<b>Skin toxicity</b>	26.5	0.8	17.7	0.4
<b>Nail disorders</b>	18.5	0.4	14.4	0.1
<b>Nausea</b>	80.5	5.1	88.0	9.5
<b>Stomatitis</b>	69.4	7.1	52.9	2.0
<b>Vomiting</b>	44.5	4.3	59.2	7.3
<b>Diarrhea</b>	35.2	3.8	27.9	1.8
<b>Constipation</b>	33.9	1.1	31.8	1.4
<b>Taste perversion</b>	27.8	0.7	15.1	0.0
<b>Anorexia</b>	21.6	2.2	17.7	1.2
<b>Abdominal Pain</b>	10.9	0.7	5.3	0.0
<b>Amenorrhea</b>	61.7	N/A	52.4	N/A
<b>Cough</b>	13.7	0.0	9.8	0.1
<b>Cardiac dysrhythmias</b>	7.9	0.3	6.0	0.3
<b>Vasodilatation</b>	27.0	1.1	21.2	0.5
<b>Hypotension</b>	2.6	0.0	1.1	0.1
<b>Phlebitis</b>	1.2	0.0	0.8	0.0
<b>Asthenia</b>	80.8	11.2	71.2	5.6
<b>Myalgia</b>	26.7	0.8	9.9	0.0
<b>Arthralgia</b>	19.4	0.5	9.0	0.3
<b>Lacrimation disorder</b>	11.3	0.1	7.1	0.0
<b>Conjunctivitis</b>	5.1	0.3	6.9	0.1

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

1  
2  
3 Of the 744 patients treated with TAC, 36.3% experienced severe TEAEs compared to 26.6% of  
4 the 736 patients treated with FAC. Dose reductions due to hematologic toxicity occurred in 1%  
5 of cycles in the TAC arm versus 0.1% of cycles in the FAC arm. Six percent of patients treated  
6 with TAC discontinued treatment due to adverse reactions, compared to 1.1% treated with FAC;  
7 fever in the absence of infection and allergy being the most common reasons for withdrawal

1 among TAC-treated patients. Two patients died in each arm within 30 days of their last study  
2 treatment; 1 death per arm was attributed to study drugs.

### 3 4 **Fever and Infection**

5 Fever in the absence of infection was seen in 46.5% of TAC-treated patients and in 17.1% of  
6 FAC-treated patients. Grade 3/4 fever in the absence of infection was seen in 1.3% and 0% of  
7 TAC- and FAC-treated patients respectively. Infection was seen in 39.4% of TAC-treated  
8 patients compared to 36.3% of FAC-treated patients. Grade 3/4 infection was seen in 3.9% and  
9 2.2% of TAC-treated and FAC-treated patients respectively. There were no septic deaths in  
10 either treatment arm.

### 11 12 **Gastrointestinal events**

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

### 17 18 **Cardiovascular events**

19 More cardiovascular events were reported in the TAC arm vs. the FAC arm; dysrhythmias, all  
20 grades (7.9% vs. 6.0%), hypotension, all grades (2.6% vs. 1.1%) and CHF (2.3% vs. 0.9%, at  
21 70 months median follow-up). One patient in each arm died due to heart failure.

### 22 23 **Acute Myeloid Leukemia (AML)**

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

- 32
- 33 • Lung Cancer
- 34

### 35 *Monotherapy with TAXOTERE for unresectable, locally advanced or metastatic NSCLC* 36 *previously treated with platinum-based chemotherapy*

37 TAXOTERE 75 mg/m<sup>2</sup>: Treatment emergent adverse drug reactions are shown in Table 8.  
38 Included in this table are safety data for a total of 176 patients with non-small cell lung  
39 carcinoma and a history of prior treatment with platinum-based chemotherapy who were treated  
40 in two randomized, controlled trials. These reactions were described using NCI Common  
41 Toxicity Criteria regardless of relationship to study treatment, except for the hematologic  
42 toxicities or where otherwise noted.

1 **Table 8 - Treatment Emergent Adverse Reactions Regardless of Relationship to Treatment**  
2 **in Patients Receiving TAXOTERE as Monotherapy for Non-Small Cell Lung Cancer**  
3 **Previously Treated with Platinum-Based Chemotherapy\***

<b>Adverse Reaction</b>	<b>TAXOTERE 75 mg/m<sup>2</sup> n=176 %</b>	<b>Best Supportive Care n=49 %</b>	<b>Vinorelbine/ Ifosfamide n=119 %</b>
<b>Neutropenia</b>			
Any	84.1	14.3	83.2
Grade 3/4	65.3	12.2	57.1
<b>Leukopenia</b>			
Any	83.5	6.1	89.1
Grade 3/4	49.4	0	42.9
<b>Thrombocytopenia</b>			
Any	8.0	0	7.6
Grade 3/4	2.8	0	1.7
<b>Anemia</b>			
Any	91.0	55.1	90.8
Grade 3/4	9.1	12.2	14.3
<b>Febrile Neutropenia**</b>	6.3	NA <sup>†</sup>	0.8
<b>Infection</b>			
Any	33.5	28.6	30.3
Grade 3/4	10.2	6.1	9.2
<b>Treatment Related Mortality</b>	2.8	NA <sup>†</sup>	3.4
<b>Hypersensitivity Reactions</b>			
Any	5.7	0	0.8
Grade 3/4	2.8	0	0
<b>Fluid Retention</b>			
Any	33.5	ND <sup>††</sup>	22.7
Severe	2.8		3.4
<b>Neurosensory</b>			
Any	23.3	14.3	28.6
Grade 3/4	1.7	6.1	5.0
<b>Neuromotor</b>			
Any	15.9	8.2	10.1
Grade 3/4	4.5	6.1	3.4
<b>Skin</b>			
Any	19.9	6.1	16.8
Grade 3/4	0.6	2.0	0.8

<b>Adverse Reaction</b>	<b>TAXOTERE 75 mg/m<sup>2</sup> n=176 %</b>	<b>Best Supportive Care n=49 %</b>	<b>Vinorelbine/ Ifosfamide n=119 %</b>
<b>Gastrointestinal</b>			
Nausea			
Any	33.5	30.6	31.1
Grade 3/4	5.1	4.1	7.6
Vomiting			
Any	21.6	26.5	21.8
Grade 3/4	2.8	2.0	5.9
Diarrhea			
Any	22.7	6.1	11.8
Grade 3/4	2.8	0	4.2
<b>Alopecia</b>	56.3	34.7	49.6
<b>Asthenia</b>			
Any	52.8	57.1	53.8
Severe***	18.2	38.8	22.7
<b>Stomatitis</b>			
Any	26.1	6.1	7.6
Grade 3/4	1.7	0	0.8
<b>Pulmonary</b>			
Any	40.9	49.0	45.4
Grade 3/4	21.0	28.6	18.5
<b>Nail Disorder</b>			
Any	11.4	0	1.7
Severe***	1.1	0	0
<b>Myalgia</b>			
Any	6.3	0	2.5
Severe***	0	0	0
<b>Arthralgia</b>			
Any	3.4	2.0	1.7
Severe***	0	0	0.8
<b>Taste Perversion</b>			
Any	5.7	0	0
Severe***	0.6	0	0

- 1 \*Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated
- 2 elevations of transaminases or alkaline phosphatase up to 5 times ULN
- 3 \*\*Febrile Neutropenia: ANC grade 4 with fever >38°C with IV antibiotics and/or hospitalization
- 4 \*\*\*COSTART term and grading system
- 5 †Not Applicable; †† Not Done



1  
2 *Combination therapy with TAXOTERE in chemotherapy-naïve advanced unresectable*  
3 *or metastatic NSCLC*  
4 Table 9 presents safety data from two arms of an open label, randomized controlled trial  
5 (TAX326) that enrolled patients with unresectable stage IIIB or IV non-small cell lung cancer  
6 and no history of prior chemotherapy. Adverse reactions were described using the NCI Common  
7 Toxicity Criteria except where otherwise noted.  
8

9 **Table 9 - Adverse Reactions Regardless of Relationship to Treatment in Chemotherapy-**  
10 **Naïve Advanced Non-Small Cell Lung Cancer Patients Receiving TAXOTERE in**  
11 **Combination with Cisplatin**

<b>Adverse Reaction</b>	<b>TAXOTERE 75 mg/m<sup>2</sup> + Cisplatin 75 mg/m<sup>2</sup> n=406 %</b>	<b>Vinorelbine 25 mg/m<sup>2</sup> + Cisplatin 100 mg/m<sup>2</sup> n=396 %</b>
<b>Neutropenia</b>		
Any	91	90
Grade 3/4	74	78
<b>Febrile Neutropenia</b>	5	5
<b>Thrombocytopenia</b>		
Any	15	15
Grade 3/4	3	4
<b>Anemia</b>		
Any	89	94
Grade 3/4	7	25
<b>Infection</b>		
Any	35	37
Grade 3/4	8	8
<b>Fever in absence of infection</b>		
Any	33	29
Grade 3/4	< 1	1
<b>Hypersensitivity Reaction*</b>		
Any	12	4
Grade 3/4	3	< 1
<b>Fluid Retention**</b>		
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

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

1 \* Replaces NCI term "Allergy"

2 \*\* COSTART term and grading system

3

1 Deaths within 30 days of last study treatment occurred in 31 patients (7.6%) in the  
 2 docetaxel+cisplatin arm and 37 patients (9.3%) in the vinorelbine+cisplatin arm. Deaths within  
 3 30 days of last study treatment attributed to study drug occurred in 9 patients (2.2%) in the  
 4 docetaxel+cisplatin arm and 8 patients (2.0%) in the vinorelbine+cisplatin arm.

5 The second comparison in the study, vinorelbine+cisplatin versus TAXOTERE+carboplatin  
 6 (which did not demonstrate a superior survival associated with TAXOTERE, [see *Clinical*  
 7 *Studies (14)*]) demonstrated a higher incidence of thrombocytopenia, diarrhea, fluid retention,  
 8 hypersensitivity reactions, skin toxicity, alopecia and nail changes on the  
 9 TAXOTERE+carboplatin arm, while a higher incidence of anemia, neurosensory toxicity,  
 10 nausea, vomiting, anorexia and asthenia was observed on the vinorelbine+cisplatin arm.

- 11 • Prostate Cancer

12  
 13  
 14 *Combination therapy with TAXOTERE in patients with prostate cancer*

15 The following data are based on the experience of 332 patients, who were treated with  
 16 TAXOTERE 75 mg/m<sup>2</sup> every 3 weeks in combination with prednisone 5 mg orally twice daily  
 17 (see Table 10).

18  
 19 **Table 10 - Clinically Important Treatment Emergent Adverse Reactions (Regardless of**  
 20 **Relationship) in Patients with Prostate Cancer who Received TAXOTERE in Combination**  
 21 **with Prednisone (TAX327)**

Adverse Reaction	TAXOTERE 75 mg/m <sup>2</sup> every 3 weeks + prednisone 5 mg twice daily n=332 %		Mitoxantrone 12 mg/m <sup>2</sup> every 3 weeks + prednisone 5 mg twice daily n=335 %	
	Any	G 3/4	Any	G 3/4
Anemia	66.5	4.9	57.8	1.8
Neutropenia	40.9	32.0	48.2	21.7
Thrombocytopenia	3.4	0.6	7.8	1.2
Febrile neutropenia	2.7	N/A	1.8	N/A
Infection	32.2	5.7	20.3	4.2
Epistaxis	5.7	0.3	1.8	0.0
Allergic Reactions	8.4	0.6	0.6	0.0
Fluid Retention*	24.4	0.6	4.5	0.3
Weight Gain*	7.5	0.3	3.0	0.0
Peripheral Edema*	18.1	0.3	1.5	0.0
Neuropathy Sensory	30.4	1.8	7.2	0.3
Neuropathy Motor	7.2	1.5	3.0	0.9
Rash/Desquamation	6.0	0.3	3.3	0.6
Alopecia	65.1	N/A	12.8	N/A

	<b>TAXOTERE 75 mg/m<sup>2</sup> every 3 weeks + prednisone 5 mg twice daily n=332 %</b>		<b>Mitoxantrone 12 mg/m<sup>2</sup> every 3 weeks + prednisone 5 mg twice daily n=335 %</b>	
<b>Adverse Reaction</b>	<b>Any</b>	<b>G 3/4</b>	<b>Any</b>	<b>G 3/4</b>
<b>Nail Changes</b>	29.5	0.0	7.5	0.0
<b>Nausea</b>	41.0	2.7	35.5	1.5
<b>Diarrhea</b>	31.6	2.1	9.6	1.2
<b>Stomatitis/Pharyngitis</b>	19.6	0.9	8.4	0.0
<b>Taste Disturbance</b>	18.4	0.0	6.6	0.0
<b>Vomiting</b>	16.9	1.5	14.0	1.5
<b>Anorexia</b>	16.6	1.2	14.3	0.3
<b>Cough</b>	12.3	0.0	7.8	0.0
<b>Dyspnea</b>	15.1	2.7	8.7	0.9
<b>Cardiac left ventricular function</b>	9.6	0.3	22.1	1.2
<b>Fatigue</b>	53.3	4.5	34.6	5.1
<b>Myalgia</b>	14.5	0.3	12.8	0.9
<b>Tearing</b>	9.9	0.6	1.5	0.0
<b>Arthralgia</b>	8.1	0.6	5.1	1.2

\*Related to treatment

- Gastric Cancer

#### *Combination therapy with TAXOTERE in gastric adenocarcinoma*

Data in the following table are based on the experience of 221 patients with advanced gastric adenocarcinoma and no history of prior chemotherapy for advanced disease, who were treated with TAXOTERE 75 mg/m<sup>2</sup> in combination with cisplatin and fluorouracil (see Table 11).

**Table 11 - Clinically Important Treatment Emergent Adverse Reactions Regardless of Relationship to Treatment in the Gastric Cancer Study**

	<b>TAXOTERE 75 mg/m<sup>2</sup> + cisplatin 75 mg/m<sup>2</sup> + fluorouracil 750 mg/m<sup>2</sup> n=221</b>		<b>Cisplatin 100 mg/m<sup>2</sup> + fluorouracil 1000 mg/m<sup>2</sup> n=224</b>	
<b>Adverse Reaction</b>	<b>Any %</b>	<b>G3/4 %</b>	<b>Any %</b>	<b>G3/4 %</b>
<b>Anemia</b>	96.8	18.2	93.3	25.6
<b>Neutropenia</b>	95.5	82.3	83.3	56.8

	<b>TAXOTERE 75 mg/m<sup>2</sup> + cisplatin 75 mg/m<sup>2</sup> + fluorouracil 750 mg/m<sup>2</sup> n=221</b>		<b>Cisplatin 100 mg/m<sup>2</sup> + fluorouracil 1000 mg/m<sup>2</sup> n=224</b>	
<b>Adverse Reaction</b>	<b>Any %</b>	<b>G3/4 %</b>	<b>Any %</b>	<b>G3/4 %</b>
<b>Fever in the absence of infection</b>	35.7	1.8	22.8	1.3
<b>Thrombocytopenia</b>	25.5	7.7	39.0	13.5
<b>Infection</b>	29.4	16.3	22.8	10.3
<b>Febrile neutropenia</b>	16.4	N/A	4.5	N/A
<b>Neutropenic infection</b>	15.9	N/A	10.4	N/A
<b>Allergic reactions</b>	10.4	1.8	5.8	0
<b>Fluid retention*</b>	14.9	0	4.0	0.4
<b>Edema*</b>	13.1	0	3.1	0.4
<b>Lethargy</b>	62.9	21.3	58.0	17.9
<b>Neurosensory</b>	38.0	7.7	24.6	3.1
<b>Neuromotor</b>	8.6	3.2	7.6	2.7
<b>Dizziness</b>	15.8	4.5	8.0	1.8
<b>Alopecia</b>	66.5	5.0	41.1	1.3
<b>Rash/itch</b>	11.8	0.9	8.5	0.0
<b>Nail changes</b>	8.1	0.0	0.0	0.0
<b>Skin desquamation</b>	1.8	0.0	0.4	0.0
<b>Nausea</b>	73.3	15.8	76.3	18.8
<b>Vomiting</b>	66.5	14.9	73.2	18.8
<b>Anorexia</b>	50.7	13.1	54.0	11.6
<b>Stomatitis</b>	59.3	20.8	61.2	27.2
<b>Diarrhea</b>	77.8	20.4	49.6	8.0
<b>Constipation</b>	25.3	1.8	33.9	3.1
<b>Esophagitis/dysphagia/ odynophagia</b>	16.3	1.8	13.8	4.9
<b>Gastrointestinal pain/cramping</b>	11.3	1.8	7.1	2.7
<b>Cardiac dysrhythmias</b>	4.5	2.3	2.2	0.9
<b>Myocardial ischemia</b>	0.9	0.0	2.7	2.2
<b>Tearing</b>	8.1	0	2.2	0.4
<b>Altered hearing</b>	6.3	0	12.5	1.8

1 Clinically important TEAEs were determined based upon frequency, severity, and clinical impact of  
2 the adverse reaction.

3 \*Related to treatment

4

- Head and Neck Cancer

*Combination therapy with TAXOTERE in head and neck cancer*

Table 12 summarizes the safety data obtained from patients that received induction chemotherapy with TAXOTERE 75 mg/m<sup>2</sup> 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 12 – 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 %	G3/4 %	Any %	G3/4 %	Any %	G3/4 %	Any %	G3/4 %
<b>Neutropenia</b>	93.1	76.3	86.7	52.8	94.8	83.5	84.2	56.0
<b>Anemia</b>	89.1	9.2	87.8	13.8	90.0	12.4	86.0	9.5
<b>Thrombocytopenia</b>	23.6	5.2	47.0	18.2	27.5	4.0	30.9	10.7
<b>Infection</b>	27.0	8.6	26.0	7.7	23.1	6.4	27.6	5.3
<b>Febrile neutropenia*</b>	5.2	N/A	2.2	N/A	12.1	N/A	6.6	N/A
<b>Neutropenic infection</b>	13.9	N/A	8.3	N/A	11.7	N/A	8.3	N/A
<b>Cancer pain</b>	20.7	4.6	16.0	3.3	17.1	8.8	20.2	11.1
<b>Lethargy</b>	40.8	3.4	38.1	3.3	61.4	4.8	55.6	10.3
<b>Fever in the absence of infection</b>	31.6	0.6	36.5	0	29.5	3.6	27.6	3.3
<b>Myalgia</b>	9.8	1.1	7.2	0	6.8	0.4	7.0	1.6
<b>Weight loss</b>	20.7	0.6	26.5	0.6	14.3	1.6	14.0	2.1
<b>Allergy</b>	6.3	0	2.8	0	2.0	0	0.4	0
<b>Fluid retention**</b>	20.1	0	14.4	0.6	13.1	1.2	7.0	1.6
<b>Edema only</b>	12.6	0	6.6	0	12.0	1.2	5.8	1.2
<b>Weight gain only</b>	5.7	0	6.1	0	0.4	0	0.8	0.4
<b>Dizziness</b>	2.3	0	5.0	0.6	15.9	4.0	15.2	1.6
<b>Neurosensory</b>	17.8	0.6	10.5	0.6	13.9	1.2	14.4	0.4
<b>Altered hearing</b>	5.7	0	9.9	2.8	12.7	1.2	18.5	2.5
<b>Neuromotor</b>	2.3	1.1	3.9	0.6	8.8	0.4	10.3	1.6
<b>Alopecia</b>	81.0	10.9	43.1	0	67.7	4.0	43.6	1.2
<b>Rash/itch</b>	11.5	0	6.1	0	19.9	0	16.0	0.8
<b>Dry skin</b>	5.7	0	1.7	0	4.8	0.4	3.3	0
<b>Desquamation</b>	4.0	0.6	5.5	0	2.4	0	4.5	0.4
<b>Nausea</b>	47.1	0.6	51.4	7.2	76.5	13.9	79.8	14.0
<b>Stomatitis</b>	42.5	4.0	47.0	11.0	65.7	21.1	67.5	27.2
<b>Vomiting</b>	26.4	0.6	38.7	5.0	56.2	8.4	62.6	10.3

	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 %	G3/4 %	Any %	G3/4 %	Any %	G3/4 %	Any %	G3/4 %
<b>Diarrhea</b>	32.8	2.9	23.8	4.4	47.8	7.2	40.3	3.3
<b>Constipation</b>	16.7	0.6	16.0	1.1	27.1	1.2	37.9	0.8
<b>Anorexia</b>	16.1	0.6	24.9	3.3	40.2	12.4	34.2	11.5
<b>Esophagitis/dysphagia/ Odynophagia</b>	12.6	1.1	18.2	2.8	25.1	12.7	26.3	9.5
<b>Taste, sense of smell altered</b>	10.3	0	5.0	0	20.3	0.4	16.9	0.8
<b>Gastrointestinal pain/cramping</b>	7.5	0.6	8.8	0.6	14.7	4.8	10.3	1.6
<b>Heartburn</b>	6.3	0	6.1	0	12.7	1.6	12.8	0.8
<b>Gastrointestinal bleeding</b>	4.0	1.7	0	0	5.2	0.4	2.1	0.4
<b>Cardiac dysrhythmia</b>	1.7	1.7	1.7	0.6	6.0	2.8	4.5	2.5
<b>Venous***</b>	3.4	2.3	5.5	1.7	3.6	2.4	4.9	3.7
<b>Ischemia myocardial</b>	1.7	1.7	0.6	0	1.6	1.2	1.2	1.2
<b>Tearing</b>	1.7	0	0.6	0	1.6	0	2.1	0
<b>Conjunctivitis</b>	1.1	0	1.1	0	1.2	0	0.4	0

1 Clinically important treatment emergent adverse reactions based upon frequency, severity, and clinical impact.

2 \*Febrile neutropenia: grade  $\geq 2$  fever concomitant with grade 4 neutropenia requiring i.v. antibiotics and/or  
3 hospitalization.

4 \*\*Related to treatment.

5 \*\*\* Includes superficial and deep vein thrombosis and pulmonary embolism

6  
7

## 8 **6.2 Post-marketing Experiences**

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

12

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

14

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

17

18 **Cutaneous:** very rare cases of cutaneous lupus erythematosus and rare cases of bullous eruptions  
19 such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. In some  
20 cases multiple factors may have contributed to the development of these effects. Severe hand and  
21 foot syndrome has been reported.

22

23 **Gastrointestinal:** abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis,  
24 gastrointestinal hemorrhage, gastrointestinal perforation, ischemic colitis, colitis, intestinal

1 obstruction, ileus, neutropenic enterocolitis and dehydration as a consequence to gastrointestinal  
2 events have been reported.

3  
4 **Hematologic:** bleeding episodes. Disseminated intravascular coagulation (DIC), often in  
5 association with sepsis or multiorgan failure, has been reported. Very rare cases of acute  
6 myeloid leukemia and myelodysplastic syndrome have been reported in association with  
7 TAXOTERE when used in combination with other chemotherapy agents and/or radiotherapy.

8  
9 **Hypersensitivity:** rare cases of anaphylactic shock have been reported. Very rarely these cases  
10 resulted in a fatal outcome in patients who received premedication.

11  
12 **Hepatic:** rare cases of hepatitis, sometimes fatal primarily in patients with pre-existing liver  
13 disorders, have been reported.

14  
15 **Neurologic:** confusion, rare cases of seizures or transient loss of consciousness have been  
16 observed, sometimes appearing during the infusion of the drug.

17  
18 **Ophthalmologic:** conjunctivitis, lacrimation or lacrimation with or without conjunctivitis.  
19 Excessive tearing which may be attributable to lacrimal duct obstruction has been reported. Rare  
20 cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring  
21 during drug infusion and in association with hypersensitivity reactions have been reported.  
22 These were reversible upon discontinuation of the infusion.

23  
24 **Hearing:** rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported,  
25 including cases associated with other ototoxic drugs.

26  
27 **Respiratory:** dyspnea, acute pulmonary edema, acute respiratory distress syndrome, interstitial  
28 pneumonia. Pulmonary fibrosis has been rarely reported. Rare cases of radiation pneumonitis  
29 have been reported in patients receiving concomitant radiotherapy.

30  
31 **Renal:** renal insufficiency.

## 32 33 **7. DRUG INTERACTIONS**

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

## 40 41 **8. USE IN SPECIFIC POPULATIONS**

### 42 43 **8.1 Pregnancy**

44 Pregnancy Category D.

45 *[see Warnings and Precautions (5.7)]*

46



### 8.3 Nursing Mothers

It is not known whether TAXOTERE is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from TAXOTERE, 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 safety and effectiveness of docetaxel in pediatric patients have not been established.

### 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.

In a study conducted in chemotherapy-naïve patients with NSCLC (TAX326), 148 patients (36%) in the TAXOTERE+cisplatin group were 65 years of age or greater. There were 128 patients (32%) in the vinorelbine+cisplatin group 65 years of age or greater. In the TAXOTERE+cisplatin group, patients less than 65 years of age had a median survival of 10.3 months (95% CI: 9.1 months, 11.8 months) and patients 65 years or older had a median survival of 12.1 months (95% CI : 9.3 months, 14 months). In patients 65 years of age or greater treated with TAXOTERE+cisplatin, diarrhea (55%), peripheral edema (39%) and stomatitis (28%) were observed more frequently than in the vinorelbine+cisplatin group (diarrhea 24%, peripheral edema 20%, stomatitis 20%). Patients treated with TAXOTERE+cisplatin who were 65 years of age or greater were more likely to experience diarrhea (55%), infections (42%), peripheral edema (39%) and stomatitis (28%) compared to patients less than the age of 65 administered the same treatment (43%, 31%, 31% and 21%, respectively).

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

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 TEAEs occurred at rates  $\geq 10\%$  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.

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.

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

1 patients. The incidence of the following adverse reactions (all grades, regardless of  
2 relationship): lethargy, stomatitis, diarrhea, dizziness, edema, febrile neutropenia/neutropenic  
3 infection occurred at rates  $\geq 10\%$  higher in patients who were 65 years of age or older compared  
4 to younger patients. Elderly patients treated with TCF should be closely monitored.

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

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

### 13 **8.6 Hepatic Impairment**

14 Patients with bilirubin  $>ULN$  should generally not receive TAXOTERE. Also, patients with  
15 SGOT and/or SGPT  $>1.5 \times ULN$  concomitant with alkaline phosphatase  $>2.5 \times ULN$  should  
16 generally not receive TAXOTERE.  
17

## 18 **10. OVERDOSAGE**

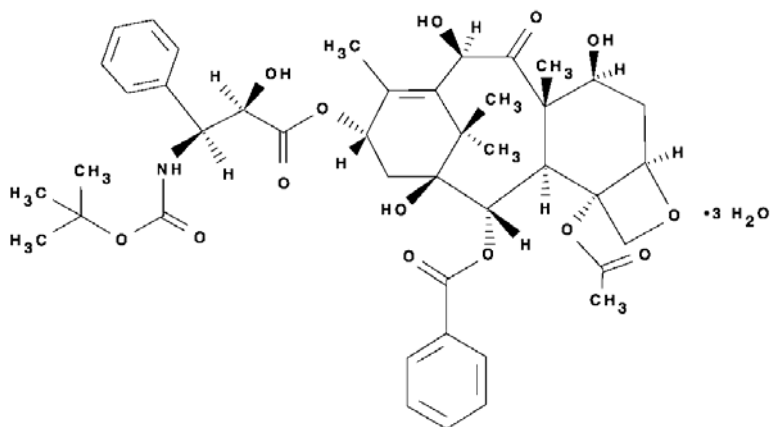
19 There is no known antidote for TAXOTERE overdose. In case of overdose, the patient  
20 should be kept in a specialized unit where vital functions can be closely monitored. Anticipated  
21 complications of overdose include: bone marrow suppression, peripheral neurotoxicity, and  
22 mucositis. Patients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

24 In two reports of overdose, one patient received  $150 \text{ mg/m}^2$  and the other received  $200 \text{ mg/m}^2$  as  
25 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous  
26 reactions, and mild paresthesia, and recovered without incident.

27 In mice, lethality was observed following single IV doses that were  $\geq 154 \text{ mg/kg}$  (about 4.5 times  
28 the recommended human dose on a  $\text{mg/m}^2$  basis); neurotoxicity associated with paralysis, non-  
29 extension of hind limbs, and myelin degeneration was observed in mice at  $48 \text{ mg/kg}$  (about  
30 1.5 times the recommended human dose on a  $\text{mg/m}^2$  basis). In male and female rats, lethality  
31 was observed at a dose of  $20 \text{ mg/kg}$  (comparable to the recommended human dose on a  $\text{mg/m}^2$   
32 basis) and was associated with abnormal mitosis and necrosis of multiple organs.  
33

## 34 **11. DESCRIPTION**

35 Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by  
36 semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew  
37 plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl  
38 ester, 13-ester with  $5\beta$ -20-epoxy-1,2 $\alpha$ ,4,7 $\beta$ ,10 $\beta$ ,13 $\alpha$ -hexahydroxytax-11-en-9-one 4-acetate  
39 2-benzoate, trihydrate. Docetaxel has the following structural formula:  
40



1  
2 Docetaxel is a white to almost-white powder with an empirical formula of  $C_{43}H_{53}NO_{14} \cdot 3H_2O$ ,  
3 and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.  
4 TAXOTERE (docetaxel) Injection Concentrate is a clear yellow to brownish-yellow viscous  
5 solution. TAXOTERE is sterile, non-pyrogenic, and is available in single-dose vials containing  
6 20 mg (0.5 mL) or 80 mg (2 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel  
7 (anhydrous) and 1040 mg polysorbate 80.

8 TAXOTERE Injection Concentrate requires dilution prior to use. A sterile, non-pyrogenic,  
9 single-dose diluent is supplied for that purpose. The diluent for TAXOTERE contains 13%  
10 ethanol in water for injection, and is supplied in vials.

## 11 12. CLINICAL PHARMACOLOGY

### 12 12.1 Mechanism of Action

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

### 22 23 12.3 Human Pharmacokinetics

24 The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of  
25 20-115  $mg/m^2$  in phase I studies. The area under the curve (AUC) was dose proportional  
26 following doses of 70-115  $mg/m^2$  with infusion times of 1 to 2 hours. Docetaxel's  
27 pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with  
28 half-lives for the  $\alpha$ ,  $\beta$ , and  $\gamma$  phases of 4 min, 36 min, and 11.1 hr, respectively. The initial rapid  
29 decline represents distribution to the peripheral compartments and the late (terminal) phase is  
30 due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean  
31 values for total body clearance and steady state volume of distribution were 21  $L/h/m^2$  and  
32 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of  
33 10-90  $mg/m^2$  was similar to that of European/American populations dosed at 100  $mg/m^2$ ,  
34 suggesting no significant difference in the elimination of docetaxel in the two populations.

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

7 A population pharmacokinetic analysis was carried out after TAXOTERE treatment of  
8 535 patients dosed at 100 mg/m<sup>2</sup>. Pharmacokinetic parameters estimated by this analysis were  
9 very close to those estimated from phase I studies. The pharmacokinetics of docetaxel were not  
10 influenced by age or gender and docetaxel total body clearance was not modified by pretreatment  
11 with dexamethasone. In patients with clinical chemistry data suggestive of mild to moderate liver  
12 function impairment (SGOT and/or SGPT >1.5 times the upper limit of normal [ULN]  
13 concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an  
14 average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average,  
15 however, includes a substantial range and there is, at present, no measurement that would allow  
16 recommendation for dose adjustment in such patients. Patients with combined abnormalities of  
17 transaminase and alkaline phosphatase should, in general, not be treated with TAXOTERE.

18 Clearance of docetaxel in combination therapy with cisplatin was similar to that previously  
19 observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in  
20 combination therapy with docetaxel was similar to that observed with cisplatin alone.

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

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

26 A study was conducted in 30 patients with advanced breast cancer to determine the potential for  
27 drug-drug-interactions between docetaxel (75 mg/m<sup>2</sup>), doxorubicin (50 mg/m<sup>2</sup>), and  
28 cyclophosphamide (500 mg/m<sup>2</sup>) when administered in combination. The coadministration of  
29 docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the  
30 three drugs were given in combination compared to coadministration of doxorubicin and  
31 cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on  
32 docetaxel plasma clearance when the three drugs were given in combination compared to  
33 historical data for docetaxel monotherapy.

34 *In vitro* studies showed that docetaxel is about 94% protein bound, mainly to  $\alpha_1$ -acid  
35 glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma  
36 proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding  
37 of docetaxel.

38 *In vitro* drug interaction studies revealed that docetaxel is metabolized by the CYP3A4  
39 isoenzyme, and its metabolism can be inhibited by CYP3A4 inhibitors, such as ketoconazole,  
40 erythromycin, troleandomycin, and nifedipine. Based on *in vitro* findings, it is likely that  
41 CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood  
42 concentrations. No clinical studies have been performed to evaluate this finding [*see Drug*  
43 *Interactions (7)*].

44

1 **13. NONCLINICAL TOXICOLOGY**

2  
3 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

4 Long-term animal studies have not been performed to evaluate the carcinogenic potential of  
5 docetaxel.

6  
7 Docetaxel has been shown to be clastogenic in the *in vitro* chromosome aberration test in CHO-  
8 K<sub>1</sub> cells and in the *in vivo* micronucleus test in mice administered doses of 0.39 to 1.56 mg/kg  
9 (about 1/60<sup>th</sup> to 1/15<sup>th</sup> the recommended human dose on a mg/m<sup>2</sup> basis). Docetaxel did not  
10 induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assays. Docetaxel  
11 produced no impairment of fertility in rats when administered in multiple IV doses of up to 0.3  
12 mg/kg (about 1/50<sup>th</sup> the recommended human dose on a mg/m<sup>2</sup> basis), but decreased testicular  
13 weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once  
14 every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was  
15 observed at IV doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/3<sup>rd</sup> and 1/15<sup>th</sup> the  
16 recommended human dose on a mg/m<sup>2</sup> basis, respectively). An increased frequency of dosing in  
17 rats produced similar effects at lower dose levels.

18  
19 **14. CLINICAL STUDIES**

20  
21 **14.1 Breast Cancer**

22 The efficacy and safety of TAXOTERE have been evaluated in locally advanced or metastatic  
23 breast cancer after failure of previous chemotherapy (alkylating agent-containing regimens or  
24 anthracycline-containing regimens).

25  
26 • **Randomized Trials**

27 In one randomized trial, patients with a history of prior treatment with an anthracycline-  
28 containing regimen were assigned to treatment with TAXOTERE (100 mg/m<sup>2</sup> every 3 weeks) or  
29 the combination of mitomycin (12 mg/m<sup>2</sup> every 6 weeks) and vinblastine (6 mg/m<sup>2</sup> every  
30 3 weeks). 203 patients were randomized to TAXOTERE and 189 to the comparator arm. Most  
31 patients had received prior chemotherapy for metastatic disease; only 27 patients on the  
32 TAXOTERE arm and 33 patients on the comparator arm entered the study following relapse  
33 after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The  
34 primary endpoint was time to progression. The following table summarizes the study results (See  
35 Table 13).

1 **Table 13 - Efficacy of TAXOTERE in the Treatment of Breast Cancer Patients Previously**  
 2 **Treated with an Anthracycline-Containing Regimen (Intent-to-Treat Analysis)**

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

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

4  
 5 In a second randomized trial, patients previously treated with an alkylating-containing regimen  
 6 were assigned to treatment with TAXOTERE (100 mg/m<sup>2</sup>) or doxorubicin (75 mg/m<sup>2</sup>) every  
 7 3 weeks. 161 patients were randomized to TAXOTERE and 165 patients to doxorubicin.  
 8 Approximately one-half of patients had received prior chemotherapy for metastatic disease, and  
 9 one-half entered the study following relapse after adjuvant therapy. Three-quarters of patients  
 10 had measurable, visceral metastases. The primary endpoint was time to progression. The study  
 11 results are summarized below (See Table 14).  
 12

1 **Table 14 - Efficacy of TAXOTERE in the Treatment of Breast Cancer Patients Previously**  
 2 **Treated with an Alkylating-Containing Regimen (Intent-to-Treat Analysis)**

<b>Efficacy Parameter</b>	<b>Docetaxel (n=161)</b>	<b>Doxorubicin (n=165)</b>	<b>p-value</b>
Median Survival	14.7 months	14.3 months	
Risk Ratio*, Mortality (Docetaxel: Control)	0.89		p=0.39 Log Rank
95% CI (Risk Ratio)	0.68-1.16		
Median Time to Progression	6.5 months	5.3 months	
Risk Ratio*, Progression (Docetaxel: Control)	0.93		p=0.45 Log Rank
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%	

3 \*For the risk ratio, a value less than 1.00 favors docetaxel.  
 4

5 In another multicenter open-label, randomized trial (TAX313), in the treatment of patients with  
 6 advanced breast cancer who progressed or relapsed after one prior chemotherapy regimen,  
 7 527 patients were randomized to receive TAXOTERE monotherapy 60 mg/m<sup>2</sup> (n=151),  
 8 75 mg/m<sup>2</sup> (n=188) or 100 mg/m<sup>2</sup> (n=188). In this trial, 94% of patients had metastatic disease  
 9 and 79% had received prior anthracycline therapy. Response rate was the primary endpoint.  
 10 Response rates increased with TAXOTERE dose: 19.9% for the 60 mg/m<sup>2</sup> group compared to  
 11 22.3% for the 75 mg/m<sup>2</sup> and 29.8% for the 100 mg/m<sup>2</sup> group; pair-wise comparison between the  
 12 60 mg/m<sup>2</sup> and 100 mg/m<sup>2</sup> groups was statistically significant (p=0.037).  
 13

14 • **Single Arm Studies**

15 TAXOTERE at a dose of 100 mg/m<sup>2</sup> was studied in six single arm studies involving a total of  
 16 309 patients with metastatic breast cancer in whom previous chemotherapy had failed. Among  
 17 these, 190 patients had anthracycline-resistant breast cancer, defined as progression during an  
 18 anthracycline-containing chemotherapy regimen for metastatic disease, or relapse during an  
 19 anthracycline-containing adjuvant regimen. In anthracycline-resistant patients, the overall  
 20 response rate was 37.9% (72/190; 95% C.I.: 31.0-44.8) and the complete response rate was  
 21 2.1%.

22 TAXOTERE was also studied in three single arm Japanese studies at a dose of 60 mg/m<sup>2</sup>, in  
 23 174 patients who had received prior chemotherapy for locally advanced or metastatic breast  
 24 cancer. Among 26 patients whose best response to an anthracycline had been progression, the  
 25 response rate was 34.6% (95% C.I.: 17.2-55.7), similar to the response rate in single arm studies  
 26 of 100 mg/m<sup>2</sup>.  
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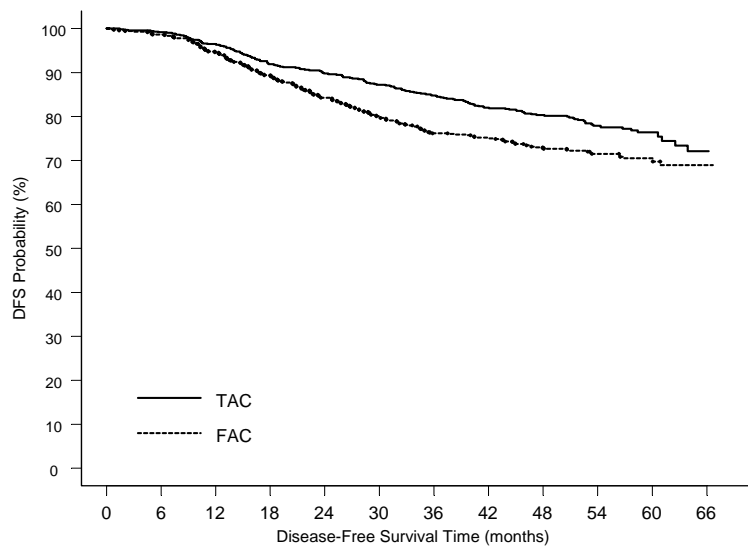
## 14.2 Adjuvant Treatment of Breast Cancer

A multicenter, open-label, randomized trial (TAX316) evaluated the efficacy and safety of TAXOTERE for the adjuvant treatment of patients with axillary-node-positive breast cancer and no evidence of distant metastatic disease. After stratification according to the number of positive lymph nodes (1-3, 4+), 1491 patients were randomized to receive either TAXOTERE 75 mg/m<sup>2</sup> administered 1-hour after doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> (TAC arm), or doxorubicin 50 mg/m<sup>2</sup> followed by fluorouracil 500 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> (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 IV 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**

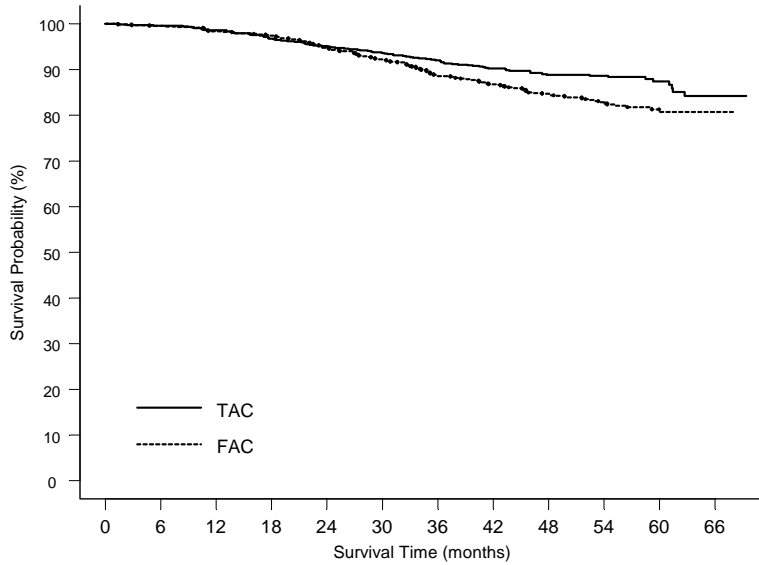


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**Figure 2 - TAX316 Overall Survival K-M Curve**



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The following table describes the results of subgroup analyses for DFS and OS (See Table 15).

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**Table 15 - Subset Analyses-Adjuvant Breast Cancer Study**

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Patient subset	Number of patients	Disease Free Survival		Overall Survival	
		Hazard ratio*	95% CI	Hazard ratio*	95% CI
<b>No. of positive nodes</b>					
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)
<b>Receptor status</b>					
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)

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

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**14.3 Non-Small Cell Lung Cancer (NSCLC)**

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

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

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Two randomized, controlled trials established that a TAXOTERE dose of 75 mg/m<sup>2</sup> was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy (see below). TAXOTERE at a dose of 100 mg/m<sup>2</sup>, however, was associated with unacceptable hematologic toxicity, infections, and treatment-related mortality and this dose

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1 should not be used [see **Boxed Warning, Warnings and Precautions (5.4), Dosage Adjustment**  
 2 **During Treatment (2.7)**].

3 One trial (TAX317), randomized patients with locally advanced or metastatic non-small cell lung  
 4 cancer, a history of prior platinum-based chemotherapy, no history of taxane exposure, and an  
 5 ECOG performance status  $\leq 2$  to TAXOTERE or best supportive care. The primary endpoint of  
 6 the study was survival. Patients were initially randomized to TAXOTERE 100 mg/m<sup>2</sup> or best  
 7 supportive care, but early toxic deaths at this dose led to a dose reduction to TAXOTERE  
 8 75 mg/m<sup>2</sup>. A total of 104 patients were randomized in this amended study to either  
 9 TAXOTERE 75 mg/m<sup>2</sup> or best supportive care.

10 In a second randomized trial (TAX320), 373 patients with locally advanced or metastatic non-  
 11 small cell lung cancer, a history of prior platinum-based chemotherapy, and an ECOG  
 12 performance status  $\leq 2$  were randomized to TAXOTERE 75 mg/m<sup>2</sup>, TAXOTERE 100 mg/m<sup>2</sup> and  
 13 a treatment in which the investigator chose either vinorelbine 30 mg/m<sup>2</sup> days 1, 8, and  
 14 15 repeated every 3 weeks or ifosfamide 2 g/m<sup>2</sup> days 1-3 repeated every 3 weeks. Forty percent  
 15 of the patients in this study had a history of prior paclitaxel exposure. The primary endpoint was  
 16 survival in both trials. The efficacy data for the TAXOTERE 75 mg/m<sup>2</sup> arm and the comparator  
 17 arms are summarized in Table 16 and Figures 3 and 4 showing the survival curves for the two  
 18 studies.

19  
 20 **Table 16 - Efficacy of TAXOTERE in the Treatment of Non-Small Cell Lung Cancer**  
 21 **Patients Previously Treated with a Platinum-Based Chemotherapy Regimen**  
 22 **(Intent-to-Treat Analysis)**

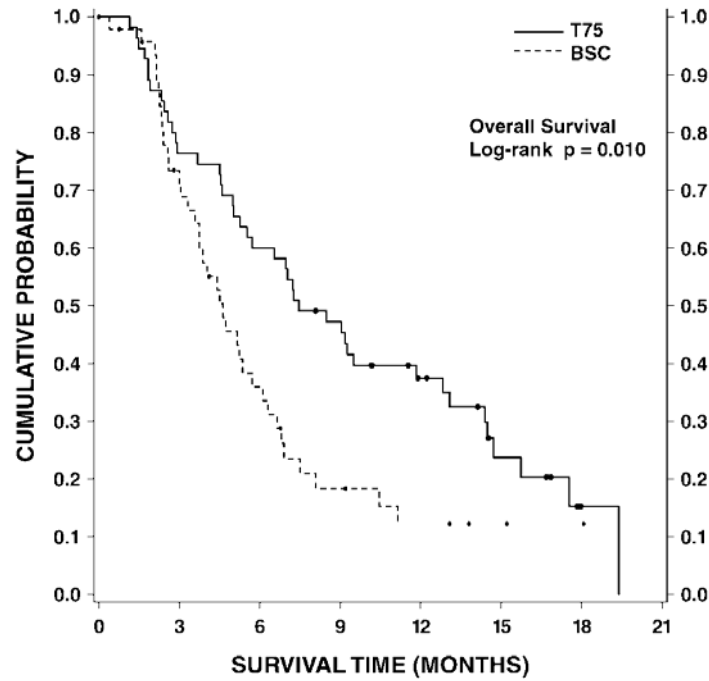
	TAX317		TAX320	
	Docetaxel 75 mg/m <sup>2</sup> n=55	Best Supportive Care/75 n=49	Docetaxel 75 mg/m <sup>2</sup> n=125	Control (V/I) n=123
Overall Survival Log-rank Test	p=0.01		p=0.13	
Risk Ratio <sup>††</sup> , Mortality (Docetaxel: Control) 95% CI (Risk Ratio)	0.56 (0.35, 0.88)		0.82 (0.63, 1.06)	
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%* <sup>†</sup> (24, 50)	12% (2, 23)	30%* <sup>†</sup> (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)

23 \* p $\leq$ 0.05; <sup>†</sup> uncorrected for multiple comparisons; <sup>††</sup> a value less than 1.00 favors docetaxel.

1 Only one of the two trials (TAX317) showed a clear effect on survival, the primary endpoint;  
2 that trial also showed an increased rate of survival to one year. In the second study (TAX320) the  
3 rate of survival at one year favored TAXOTERE 75 mg/m<sup>2</sup>.

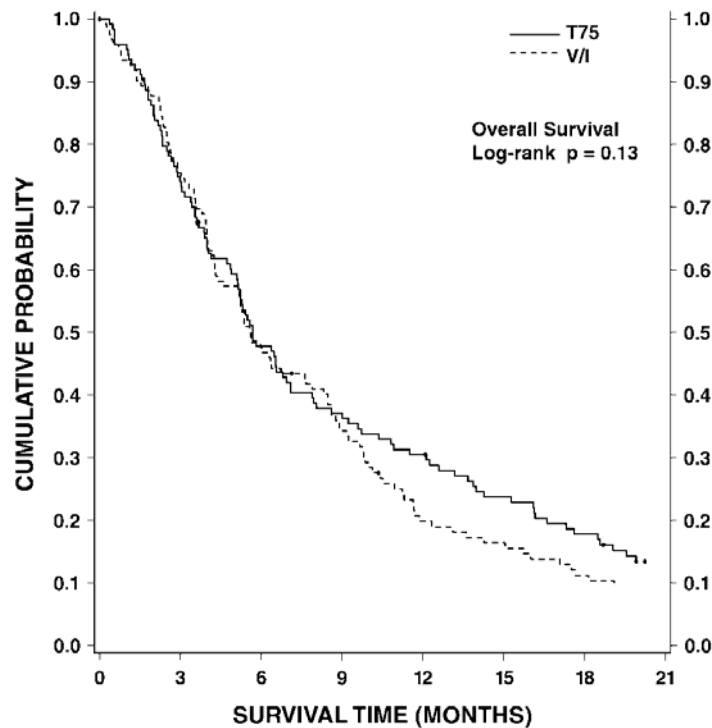
4

5 **Figure 3 - TAX317 Survival K-M Curves - TAXOTERE 75 mg/m<sup>2</sup> vs. Best Supportive**  
6 **Care**



7

1 **Figure 4 - TAX320 Survival K-M Curves - TAXOTERE 75 mg/m<sup>2</sup> vs. Vinorelbine or**  
 2 **Ifosfamide Control**



3  
 4 Patients treated with TAXOTERE at a dose of 75 mg/m<sup>2</sup> experienced no deterioration in  
 5 performance status and body weight relative to the comparator arms used in these trials.

6  
 7 • **Combination Therapy with TAXOTERE for Chemotherapy-Naïve NSCLC**

8 In a randomized controlled trial (TAX326), 1218 patients with unresectable stage IIIB or  
 9 IV NSCLC and no prior chemotherapy were randomized to receive one of three treatments:  
 10 TAXOTERE 75 mg/m<sup>2</sup> as a 1 hour infusion immediately followed by cisplatin 75 mg/m<sup>2</sup> over  
 11 30-60 minutes every 3 weeks; vinorelbine 25 mg/m<sup>2</sup> administered over 6-10 minutes on days 1,  
 12 8, 15, 22 followed by cisplatin 100 mg/m<sup>2</sup> administered on day 1 of cycles repeated every  
 13 4 weeks; or a combination of TAXOTERE and carboplatin.

14 The primary efficacy endpoint was overall survival. Treatment with TAXOTERE+cisplatin did  
 15 not result in a statistically significantly superior survival compared to vinorelbine+cisplatin (see  
 16 table below). The 95% confidence interval of the hazard ratio (adjusted for interim analysis and  
 17 multiple comparisons) shows that the addition of TAXOTERE to cisplatin results in an outcome  
 18 ranging from a 6% inferior to a 26% superior survival compared to the addition of vinorelbine to  
 19 cisplatin. The results of a further statistical analysis showed that at least (the lower bound of the  
 20 95% confidence interval) 62% of the known survival effect of vinorelbine when added to  
 21 cisplatin (about a 2-month increase in median survival; Wozniak et al. JCO, 1998) was  
 22 maintained. The efficacy data for the TAXOTERE+cisplatin arm and the comparator arm are  
 23 summarized in Table 17.

**Table 17 - Survival Analysis of TAXOTERE in Combination Therapy for Chemotherapy-Naïve NSCLC**

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

<sup>a</sup> From the superiority test (stratified log rank) comparing TAXOTERE+cisplatin to vinorelbine+cisplatin

<sup>b</sup> Hazard ratio of TAXOTERE+cisplatin vs. vinorelbine+cisplatin. A hazard ratio of less than 1 indicates that TAXOTERE+cisplatin is associated with a longer survival.

<sup>c</sup> Adjusted for interim analysis and multiple comparisons.

The second comparison in the 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 18).

**Table 18 - Response and TTP Analysis of TAXOTERE in Combination Therapy for Chemotherapy-Naïve NSCLC**

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

<sup>a</sup> Adjusted for multiple comparisons.

<sup>b</sup> Kaplan-Meier estimates.

#### 14.4 Prostate Cancer

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

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

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

1 In the TAXOTERE every three week arm, a statistically significant overall survival advantage  
 2 was demonstrated compared to mitoxantrone. In the TAXOTERE weekly arm, no overall  
 3 survival advantage was demonstrated compared to the mitoxantrone control arm. Efficacy results  
 4 for the TAXOTERE every 3 week arm versus the control arm are summarized in Table 19 and  
 5 Figure 5.

6

7 **Table 19 - Efficacy of TAXOTERE in the Treatment of Patients with Androgen**  
 8 **Independent (Hormone Refractory) Metastatic Prostate Cancer (Intent-to-Treat Analysis)**

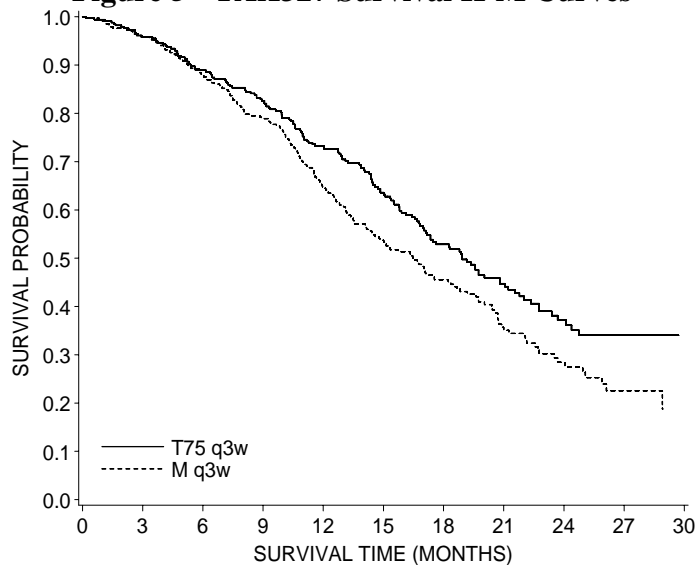
	<b>TAXOTERE every 3 weeks</b>	<b>Mitoxantrone every 3 weeks</b>
Number of patients	335	337
Median survival (months)	18.9	16.5
95% CI	(17.0-21.2)	(14.4-18.6)
Hazard ratio	0.761	--
95% CI	(0.619-0.936)	--
p-value*	0.0094	--

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

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**Figure 5 - TAX327 Survival K-M Curves**



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14 **14.5 Gastric Adenocarcinoma**

15 A multicenter, open-label, randomized trial was conducted to evaluate the safety and efficacy of  
 16 TAXOTERE for the treatment of patients with advanced gastric adenocarcinoma, including  
 17 adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for  
 18 advanced disease. A total of 445 patients with KPS >70 were treated with either TAXOTERE  
 19 (T) (75 mg/m<sup>2</sup> on day 1) in combination with cisplatin (C) (75 mg/m<sup>2</sup> on day 1) and fluorouracil  
 20 (F) (750 mg/m<sup>2</sup> per day for 5 days) or cisplatin (100 mg/m<sup>2</sup> on day 1) and fluorouracil  
 21 (1000 mg/m<sup>2</sup> per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm  
 22 and 4 weeks for the CF arm. The demographic characteristics were balanced between the two  
 23 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 20 and Figures 6 and 7.

**Table 20 - Efficacy of TAXOTERE in the treatment of patients with gastric adenocarcinoma**

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

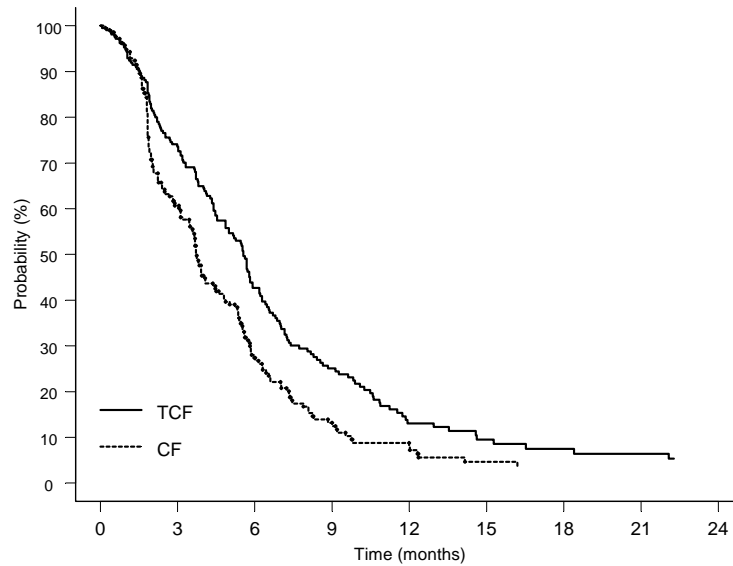
\*Unstratified log-rank test

<sup>†</sup>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.

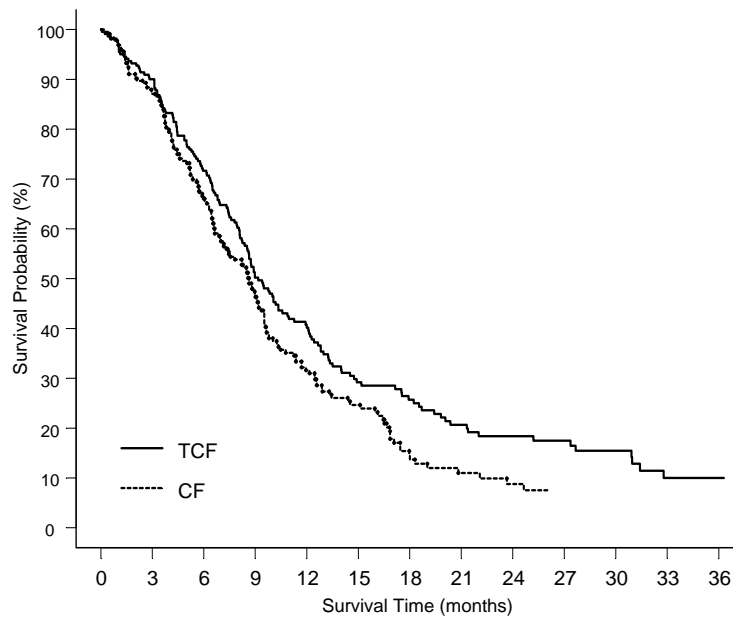
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**Figure 6 - Gastric Cancer Study (TAX325) Time to Progression K-M Curve**



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



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## 14.6 Head and Neck Cancer

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- 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



1 SCCHN, and WHO performance status 0 or 1, were randomized to one of two treatment arms.  
2 Patients on the TAXOTERE arm received TAXOTERE (T) 75 mg/m<sup>2</sup> followed by cisplatin (P)  
3 75 mg/m<sup>2</sup> on Day 1, followed by fluorouracil (F) 750 mg/m<sup>2</sup> per day as a continuous infusion on  
4 Days 1-5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did  
5 not progress received radiotherapy (RT) according to institutional guidelines (TPF/RT). Patients  
6 on the comparator arm received cisplatin (P) 100 mg/m<sup>2</sup> on Day 1, followed by fluorouracil (F)  
7 1000 mg/m<sup>2</sup>/day as a continuous infusion on Days 1-5. The cycles were repeated every three  
8 weeks for 4 cycles. Patients whose disease did not progress received RT according to  
9 institutional guidelines (PF/RT). At the end of chemotherapy, with a minimal interval of  
10 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received  
11 radiotherapy (RT) according to institutional guidelines. Locoregional therapy with radiation was  
12 delivered either with a conventional fraction regimen (1.8 Gy-2.0 Gy once a day, 5 days per  
13 week for a total dose of 66 to 70 Gy) or with an accelerated/hyperfractionated regimen (twice a  
14 day, with a minimum interfraction interval of 6 hours, 5 days per week, for a total dose of 70 to  
15 74 Gy, respectively). Surgical resection was allowed following chemotherapy, before or after  
16 radiotherapy.

17  
18 The primary endpoint in this study, progression-free survival (PFS), was significantly longer in  
19 the TPF arm compared to the PF arm, p=0.0077 (median PFS: 11.4 vs. 8.3 months respectively)  
20 with an overall median follow up time of 33.7 months. Median overall survival with a median  
21 follow-up of 51.2 months was also significantly longer in favor of the TPF arm compared to the  
22 PF arm (median OS: 18.6 vs. 14.2 months respectively). Efficacy results are presented in  
23 Table 21 and Figures 8 and 9.

24

**Table 21 - 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	

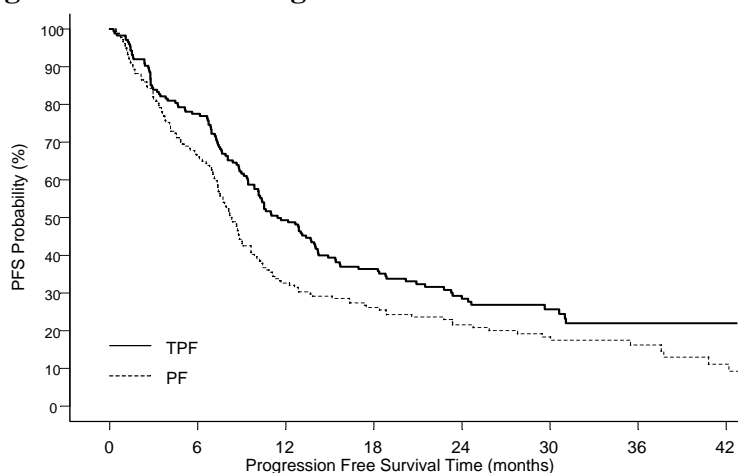
A Hazard ratio of less than 1 favors TAXOTERE+Cisplatin+Fluorouracil

\* Stratified log-rank test based on primary tumor site

\*\* Stratified log-rank test, not adjusted for multiple comparisons

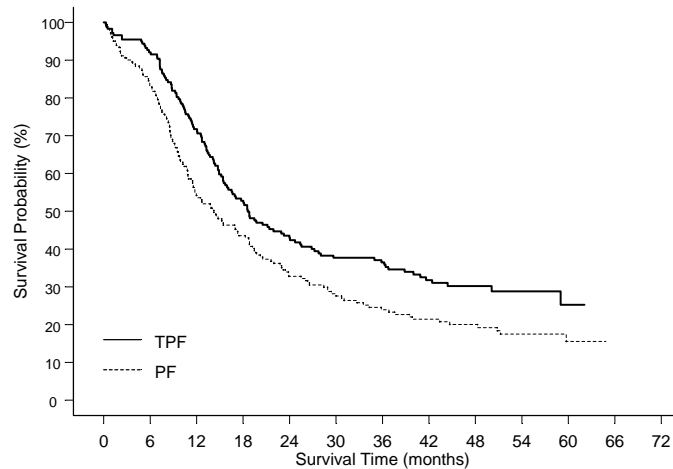
\*\*\* Chi square test, not adjusted for multiple comparisons

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



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**Figure 9 - TAX323 Overall Survival K-M Curve**



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- Induction chemotherapy followed by chemoradiotherapy (TAX324)

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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/m<sup>2</sup> by IV infusion on day 1 followed by cisplatin (P) 100 mg/m<sup>2</sup> administered as a 30-minute to three-hour IV infusion, followed by the continuous IV infusion of fluorouracil (F) 1000 mg/m<sup>2</sup>/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/m<sup>2</sup> as a 30-minute to three-hour IV infusion on day 1 followed by the continuous IV infusion of fluorouracil (F) 1000 mg/m<sup>2</sup>/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 IV infusion for a maximum of 7 doses. Radiation was delivered with megavoltage equipment using once daily fractionation (2 Gy per day, 5 days per week for 7 weeks for a total dose of 70-72 Gy). Surgery on the primary site of disease and/or neck could be considered at anytime following completion of CRT.

The primary efficacy endpoint, overall survival (OS), was significantly longer (log-rank test, p=0.0058) with the TAXOTERE-containing regimen compared to PF [median OS: 70.6 versus 30.1 months respectively, hazard ratio (HR)=0.70, 95% confidence interval (CI)= 0.54 – 0.90]. Overall survival results are presented in Table 22 and Figure 10.

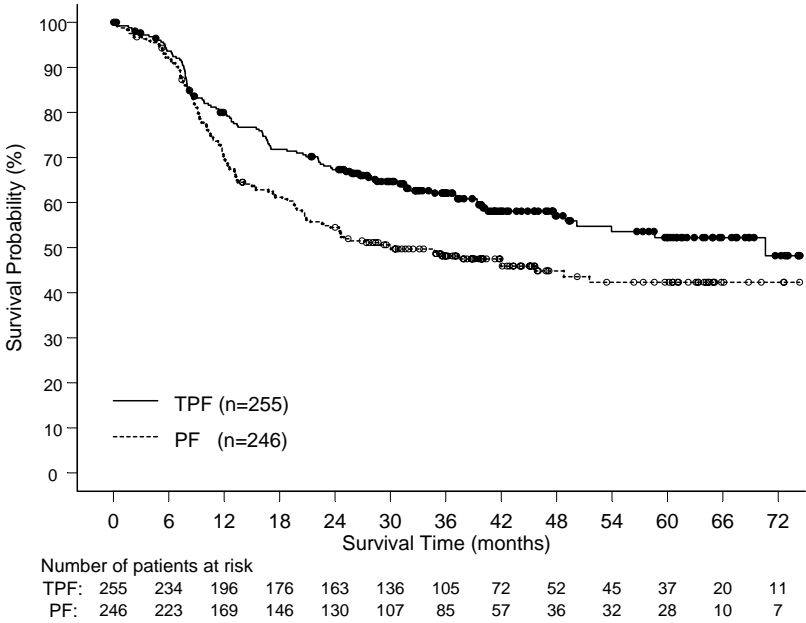
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**Table 22 - Efficacy of TAXOTERE in the induction treatment of patients with locally advanced SCCHN (Intent-to-Treat Analysis)**

<b>ENDPOINT</b>	<b>TAXOTERE+ Cisplatin+ Fluorouracil n=255</b>	<b>Cisplatin+ Fluorouracil n=246</b>
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	

4 A Hazard ratio of less than 1 favors TAXOTERE+cisplatin+fluorouracil  
5 \* un-adjusted log-rank test  
6 NE - not estimable  
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**Figure 10 - TAX324 Overall Survival K-M Curve**



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1 **15. REFERENCES**  
2

- 3 1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous  
4 drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public  
5 Health Service, Centers for Disease Control and Prevention, National Institute for  
6 Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.  
7  
8 2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational  
9 Exposure to Hazardous Drugs. OSHA, 1999.  
10 [http://www.osha.gov/dts/osta/otm/otm\\_vi/otm\\_vi\\_2.html](http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html)  
11  
12 3. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling  
13 Hazardous Drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193  
14  
15 4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy  
16 guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing  
17 Society.  
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20 **16. HOW SUPPLIED/STORAGE AND HANDLING**  
21

22 **16.1 How Supplied**

23 TAXOTERE Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free,  
24 non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, Diluent (13%  
25 ethanol in water for injection) vial. The following strengths are available:  
26

27 TAXOTERE 80 mg/2 mL (NDC 0075-8001-80)

28 TAXOTERE (docetaxel) Injection Concentrate 80 mg/2 mL: 80 mg docetaxel in 2 mL  
29 polysorbate 80 and Diluent for TAXOTERE 80 mg (13% (w/w) ethanol in water for injection).  
30 Both items are in a blister pack in one carton.  
31

32 TAXOTERE 20 mg/0.5 mL (NDC 0075-8001-20)

33 TAXOTERE (docetaxel) Injection Concentrate 20 mg/0.5 mL: 20 mg docetaxel in 0.5 mL  
34 polysorbate 80 and Diluent for TAXOTERE 20 mg (13% (w/w) ethanol in water for injection).  
35 Both items are in a blister pack in one carton.  
36

37 **16.2 Storage**

38 Store between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright  
39 light. Freezing does not adversely affect the product.  
40

41 **16.3 Handling and Disposal**

42 Procedures for proper handling and disposal of anticancer drugs should be considered. Several  
43 guidelines on this subject have been published<sup>1-4</sup>.  
44

1 **17. PATIENT COUNSELING INFORMATION**

2  
3 **Patient Information Leaflet**

4 **Questions and Answers About Taxotere® Injection Concentrate**

5 (generic name = docetaxel)

6 (pronounced as TAX-O-TEER)

7  
8 ***What is Taxotere?***

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

15  
16 ***What is the most important information about Taxotere?***

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

31  
32 ***How does Taxotere work?***

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

35 Here's how Taxotere works: Every cell in your body contains a supporting structure (like a  
36 skeleton). Damage to this "skeleton" can stop cell growth or reproduction. Taxotere makes the  
37 "skeleton" in some cancer cells very stiff, so that the cells can no longer grow.

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1  
2 ***How will I receive Taxotere?***

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

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

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12  
13 ***What should be avoided while receiving Taxotere?***

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

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17  
18 ***What are the possible side effects of Taxotere?***

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

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

27 **Low Red Blood Cell Count** – Taxotere can cause a drop in the number of red blood cells.  
28 These cells carry oxygen to different parts of the body. Your doctor will routinely check your  
29 red blood cell count and tell you if it is too low.

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

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

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

42 **Gastrointestinal** – Diarrhea has been associated with TAXOTERE use and can be severe in  
43 some patients. Constipation can also occur. Nausea and/or vomiting are common in patients  
44 receiving TAXOTERE. Severe inflammation of the bowel can also occur in some patients and  
45 may be life threatening.

1 **Hepatic** – Elevations in liver enzymes can occur.

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

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

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

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

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

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

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

26 **Eye Changes** – Excessive tearing, which can be related to conjunctivitis or blockage of the tear  
27 ducts, may occur.

28  
29 If you are interested in learning more about this drug, ask your doctor for a copy of the package  
30 insert.

31 

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32



1

**Every three-week injection of TAXOTERE for breast, non-small cell lung and stomach, and head and neck cancers**

**Take dexamethasone tablets, 8 mg twice daily.**

*Dexamethasone dosing:*

**Day 1** Date: \_\_\_\_\_ Time: \_\_\_\_\_ AM \_\_\_\_\_ PM

**Day 2** Date: \_\_\_\_\_ Time: \_\_\_\_\_ AM \_\_\_\_\_ PM  
**(Taxotere Treatment Day)**

**Day 3** Date: \_\_\_\_\_ Time: \_\_\_\_\_ AM \_\_\_\_\_ PM

2

**Every three-week injection of TAXOTERE for prostate cancer**

**Take dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before TAXOTERE infusion.**

*Dexamethasone dosing:*

Date: \_\_\_\_\_ Time: \_\_\_\_\_

Date: \_\_\_\_\_ Time: \_\_\_\_\_

**(Taxotere Treatment Day)**

Time: \_\_\_\_\_

3

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