DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF DIRECTOR

ACTION REFERRAL

TO	DATE
Myers	2-11-08

DIRECTOR'S USE ONLY	ACTION REQUESTED
1. LOG NUMBER 000419	[ ] Prepare reply for the Director's signature DATE DUE _____
2. DATE SIGNED BY DIRECTOR _____ 	[ ] Prepare reply for appropriate signature DATE DUE _____ [ ] FOIA DATE DUE _____ [X] Necessary Action

APPROVALS (Only when prepared for director's signature)	APPROVE	* DISAPPROVE (Note reason for disapproval and return to preparer.)	COMMENT
1.			
2.			
3.			
4.			

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Log: Myers
N/A

NDA 20-449/S-045

Eric Phillips, M.S., Sc.D.
Associate Director, Oncology Products
Corporate Regulatory Affairs
Sanofi-aventis U.S. Inc.
300 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Dr. Phillips:

Please refer to your supplemental new drug application dated March 29, 2007, received March 29, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAXOTERE® (docetaxel) Injection Concentrate, 20 mg and 80mg.

We acknowledge receipt of your submissions dated May 11 and 22, June 29, July 27, August 17, September 14, 18, and 26 (electronic), 2007.

This supplemental new drug application provides for the use of TAXOTERE® (docetaxel) Injection Concentrate in combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

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

The final printed labeling (FPL) for this supplement S-045 must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Please note that your final printed labeling submitted December 19, 2006, for S-039 has been superseded but will be retained in the file.

Submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-449/S-045.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitment in your submission dated August 18, 2004 (S-029). This commitment is listed below.

COMMITMENT 1 (S-029):

To submit a complete report of the updated TAX 316 data to verify the efficacy based on 700 events of DFS and safety of Taxotere in the adjuvant treatment of women with operable node-positive breast cancer and to submit the final analysis of overall survival (expected to occur in the year 2010).

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."

Promotional materials should be submitted, in duplicate, directly to:

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

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

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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

If you have any questions, please call Frank Cross, Jr., Regulatory Project Manager, at (301) 796-0876.

Sincerely,

{See appended electronic signature page}

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

Enclosure

sanofi aventis

Because health matters

Re: TAXOTERE® (docetaxel) Injection Concentrate Receives Expanded FDA Approval for the Induction Treatment of Locally Advanced Head and Neck Cancer

Dear Healthcare Professional:

FDA granted an expanded indication on September 29, 2007, approving TAXOTERE® (docetaxel) injection concentrate in combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). The expanded indication in locally advanced SCCHN offers physicians and their patients an important new option for treating this often devastating disease.

The FDA based its decision on results from the TAX 324 study, a multicenter, randomized phase III clinical trial involving 501 patients with locally advanced squamous cell carcinoma of the head and neck. Patients treated with the TAXOTERE®-based induction regimen (TAXOTERE® + cisplatin + fluorouracil [TPF]) followed by concomitant chemoradiotherapy (carboplatin + radiation) experienced significantly longer median overall survival compared with patients who received a current standard treatment of cisplatin + fluorouracil (PF) followed by the same concomitant chemoradiation (70.6 months vs 30.1 months, HR=0.70 [95% CI: 0.54– 0.90; *P*=.0058]).[1]

About the TAX 324 Study

The treatment strategy for this trial consisted of sequential combined modality therapy with induction chemotherapy followed by chemoradiotherapy, then surgery to areas of initial bulk disease if appropriate. Treatment-naïve patients with stage III or IV disease primarily of the oropharynx, larynx, hypopharynx, and oral cavity with PS 0 or 1 were included in the study. The study contained technically unresectable patients, as well as patients who had resectable disease but with low curability, and those in whom organ preservation was desired. The median age of patients in the TPF arm 55 years (a range of 38 to 82 years), with almost 85% of the population being men. The median age in the PF arm was 56 years (range of 30 to 80 years) with 83% of male.

The primary study endpoint was overall survival (OS), which was significantly improved with TPF compared with PF, with a 30% reduction in the risk of death (70.6 months vs 30.1 months, *P*=.0058). Secondary endpoints included progression-free survival, time to progression, and site of treatment failure.[1,2]

Overall, the incidence of grade ¾ toxicity was 65% in the Taxotere arm (TPF) compared to 62% in the group receiving cisplatin and florouracil (PF). Patients treated with TPF had more febrile neutropenia (12% vs. 7%), neutropenic infection (12% vs. 8%), and grade ¾ neutropenia (84% vs. 56%), dizziness (4% vs. 2%), alopecia (4% vs.1%) and diarrhea (7% vs. 3%) than those in the PF group. Patients in the PF group had more grade ¾ thrombocytopenia (11% vs. 4%), stomatitis (27% vs. 21%), lethargy (10% vs. 5%) and vomiting (10% vs. 8%). The incidence of other grade ¾ events was similar between the two groups, such as nausea, anorexia and constipation.

The results of the TAX 324 study were initially presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2006 and recently published in the *New England Journal of Medicine*.

US.DOC.07.11.029

sanofi-aventis U.S., 55 Corporate Drive, P.O. Box 5925, Bridgewater, NJ 08807-5925
Tel: (908) 981-5000 - www.sanofi-aventis.us

About Head and Neck Cancer
Head and neck cancer accounts for about 3% to 5% of all cancers in the United States. It is estimated that 45,660 people (33,140 men and 12,520 women) will develop head and neck cancer; and an estimated 11,210 deaths (8,080 men and 3,130 women) will occur in 2007.[3]

Please see important safety information and enclosed full prescribing information, including boxed **WARNING.**

TAXOTERE® is indicated:

- For the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy
- In combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable, node-positive breast cancer
- As a single agent for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of prior platinum-based chemotherapy
- In combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic NSCLC who have not previously received chemotherapy for this condition
- In combination with prednisone for the treatment of patients with androgen-independent (hormone-refractory) metastatic prostate cancer
- In combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease
- In combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck

For the convenience of payers, attached you will find a list of all ICD-9 codes for this expanded indication.

For more information about TAXOTERE'S FDA approved indications or the TAX 324 study, please call sanofi-aventis Medical Information Services at 1-800-633-1610.

Sincerely,

Nassir Habboubi, MD
Vice President, US Medical Affairs Oncology
sanofi-aventis

Enclosures

- TAXOTERE® (docetaxel) Injection Concentrate Prescribing Information, sanofi-aventis
- ICD-9 Diagnosis Codes for TAXOTERE®
- FDA approval letter

Please see important safety information and enclosed full prescribing information, including boxed **WARNING.**

References: 1. TAXOTERE® Prescribing Information. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2007. **2.** Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer.*New Engl J Med.* 2007:357(17);1705-1715. **3.** American Cancer Society: Facts and Figures

Fair Balance for Taxotere® - All Indications

IMPORTANT SAFETY INFORMATION

WARNING

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

- The incidence of treatment-related mortality associated with Taxotere® therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive Taxotere® as a single agent at a dose of 100 mg/m^2 (see **WARNINGS** section of the prescribing information)

- Taxotere® should generally not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with serum glutamic-oxaloacetic transaminase (SGOT) and/or serum glutamic-pyruvic transaminase (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^3

  — In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood-cell counts should be performed on all patients receiving Taxotere®

- 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

  — Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions

- 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

  — All patients should be premedicated with oral corticosteroids such as dexamethasone (see **DOSAGE AND ADMINISTRATION** section of the prescribing information)

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

Additional Warnings

- Treatment-related acute myeloid leukemia (AML) or myelodysplasia has occurred in patients given anthracyclines and/or cyclophosphamide, including use with Taxotere® in **adjuvant therapy** of breast cancer

- Taxotere® can cause fetal harm when administered to pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Taxotere®

Precautions

- Localized erythema of the extremities with edema followed by desquamation has been observed

  — In case of severe skin toxicity, an adjustment in dosage is recommended (see **DOSAGE AND ADMINISTRATION** section of the prescribing information)

- Severe neurosensory symptoms (paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of **metastatic breast cancer** patients, and resulted in treatment discontinuation in 6.1%

  — When these symptoms occur, dosage must be adjusted; if symptoms persist, treatment should be discontinued (see **DOSAGE AND ADMINISTRATION** section of the prescribing information)

- Severe asthenia was reported in 14.9% (144/965) of **metastatic breast cancer** patients, but 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

- In patients treated with TCF for gastric cancer, the incidence of serious adverse events was higher in patients ≥65 years than in younger patients. Adverse events (all grades) occurring at rates ≥10% higher in elderly patients included lethargy, stomatitis, diarrhea, dizziness, edema, and febrile neutropenia/neutropenic infection.

Please see important safety information and full prescribing information, including boxed **WARNING**.

Diagnosis Codes for TAXOTERE®—Head & Neck Cancer

140.0 - Malignant neoplasm of upper lip, vermilion border
140.1 - Malignant neoplasm of lower lip, vermilion border
140.3 - Malignant neoplasm of upper lip, inner aspect
140.4 - Malignant neoplasm of lower lip, inner aspect
140.5 - Malignant neoplasm of lip, inner aspect, unspecified as to upper or lower
140.6 - Malignant neoplasm of commissure of lip
140.8 - Malignant neoplasm of other sites of lip
140.9 - Malignant neoplasm of lip, vermilion border, unspecified as to upper or lower
141.0 - Malignant neoplasm of base of tongue
141.1 - Malignant neoplasm of dorsal surface of tongue
141.2 - Malignant neoplasm of tip and lateral border of tongue
141.3 - Malignant neoplasm of ventral surface of tongue
141.4 - Malignant neoplasm of anterior two-thirds of tongue, part unspecified
141.5 - Malignant neoplasm of junctional zone of tongue
141.6 - Malignant neoplasm of lingual tonsil
141.8 - Malignant neoplasm of other sites of tongue
141.9 - Malignant neoplasm of tongue, unspecified site
142.0 - Malignant neoplasm of parotid gland
142.1 - Malignant neoplasm of submandibular gland
142.2 - Malignant neoplasm of sublingual gland
142.8 - Malignant neoplasm of other major salivary glands
142.9 - Malignant neoplasm of salivary gland, unspecified
143.0 - Malignant neoplasm of upper gum
143.1 - Malignant neoplasm of lower gum
143.8 - Malignant neoplasm of other sites of gum
143.9 - Malignant neoplasm of gum, unspecified site
144.0 - Malignant neoplasm of anterior portion of floor of mouth
144.1 - Malignant neoplasm of lateral portion of floor of mouth
144.8 - Malignant neoplasm of other sites of floor of mouth
144.9 - Malignant neoplasm of floor of mouth, part unspecified
145.0 - Malignant neoplasm of cheek mucosa
145.1 - Malignant neoplasm of vestibule of mouth
145.2 - Malignant neoplasm of hard palate
145.3 - Malignant neoplasm of soft palate
145.4 - Malignant neoplasm of uvula
145.5 - Malignant neoplasm of palate, unspecified
145.6 - Malignant neoplasm of retromolar area
145.8 - Malignant neoplasm of other specified parts of mouth
145.9 - Malignant neoplasm of mouth, unspecified site

Please see important safety information and enclosed full prescribing information, including boxed **WARNING.**

Diagnosis Codes for TAXOTERE®—Head & Neck Cancer
(continued)

146.0 - Malignant neoplasm of tonsil
146.1 - Malignant neoplasm of tonsillar fossa
146.2 - Malignant neoplasm of tonsillar pillars (anterior) (posterior)
146.3 - Malignant neoplasm of vallecula
146.4 - Malignant neoplasm of anterior aspect of epiglottis
146.5 - Malignant neoplasm of junctional region of oropharynx
146.6 - Malignant neoplasm of lateral wall of oropharynx
146.7 - Malignant neoplasm of posterior wall of oropharynx
146.8 - Malignant neoplasm of other specified sites of oropharynx
146.9 - Malignant neoplasm of oropharynx, unspecified site
147.0 - Malignant neoplasm of superior wall of nasopharynx
147.1 - Malignant neoplasm of posterior wall of nasopharynx
147.2 - Malignant neoplasm of lateral wall of nasopharynx
147.3 - Malignant neoplasm of anterior wall of nasopharynx
147.8 - Malignant neoplasm of other specified sites of nasopharynx
147.9 - Malignant neoplasm of nasopharynx, unspecified
148.0 - Malignant neoplasm of postcricoid region of hypopharynx
148.1 - Malignant neoplasm of pyriform sinus
148.2 - Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect
148.3 - Malignant neoplasm of posterior hypopharyngeal wall
148.8 - Malignant neoplasm of other specified sites of hypopharynx
148.9 - Malignant neoplasm of hypopharynx, unspecified site
149.0 - Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx, pharynx unspecified
149.1 - Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx, Waldeyer's ring
149.8 - Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx, sites within the lip and oral cavity, other
149.9 - Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx, ill-defined
160.0 - Malignant neoplasm of nasal cavities
160.1 - Malignant neoplasm of auditory tube, middle ear, and mastoid air cells
160.2 - Malignant neoplasm of maxillary sinus
160.3 - Malignant neoplasm of ethmoidal sinus
160.4 - Malignant neoplasm of frontal sinus
160.5 - Malignant neoplasm of sphenoidal sinus
160.8 - Malignant neoplasm of other sites of nasal cavities, middle ear, and accessory sinuses, other
160.9 - Malignant neoplasm of site of nasal cavities, middle ear, and accessory sinus, unspecified

Diagnosis Codes for TAXOTERE®—Head & Neck Cancer
(continued)

161.0 - Malignant neoplasm of larynx, glottis
161.1 - Malignant neoplasm of larynx, supraglottis
161.2 - Malignant neoplasm of larynx, subglottis
161.3 - Malignant neoplasm of larynx, laryngeal cartilages
161.8 - Malignant neoplasm of larynx, other specified sites of larynx
161.9 - Malignant neoplasm of larynx, unspecified
170.0 - Malignant neoplasm of bone and articular cartilage, bones of skull and face, except mandible
170.1 - Malignant neoplasm of bone and articular cartilage, mandible
171.0 - Malignant neoplasm of connective and other soft tissue of head, face, and neck
172. 0 - Malignant melanoma of skin, lip
172. 1 - Malignant melanoma of skin, eyelid including canthus
172. 2 - Malignant melanoma of skin, ear and external auditory canal
172. 3 - Malignant melanoma of skin, other and unspecified parts of the face
172. 4 - Malignant melanoma of skin, scalp and neck
173.0 - Other malignant neoplasm of skin, skin of lip
173.2 - Other malignant neoplasm of skin, skin of ear and external auditory canal
173.3 - Other malignant neoplasm of skin, skin of other and unspecified parts of face
173.4 - Other malignant neoplasm of skin, scalp and skin of neck
195.0 - Malignant neoplasm of head, face, and neck
196.0 - Secondary and unspecified malignant neoplasm of lymph nodes of head, face, and neck
198.89 - Secondary malignant neoplasm of other specified sites

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

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

5.11 Neurologic

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

5.12 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^2: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received TAXOTERE administered at 100 mg/m^2 as a 1- hour infusion every 3 weeks: 2045 patients with various tumor types and normal baseline liver function tests; the subset of 965 patients with locally advanced or metastatic breast cancer, both previously treated and untreated with chemotherapy, who had normal baseline liver function tests; and an additional 61 patients with various tumor types who had abnormal liver function tests at baseline. These reactions were described using COSTART terms and were considered possibly or probably related to TAXOTERE. At least 95% of these patients did not receive hematopoietic support. The safety profile is generally similar in patients receiving TAXOTERE for the treatment of breast cancer and in patients with other tumor types (See Table 4).

Table 4 - Summary of Adverse Reactions in Patients Receiving TAXOTERE at 100 mg/m^2

Adverse Reaction	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
Hematologic			
Neutropenia			
<2000 cells/mm^3	95.5	96.4	98.5
<500 cells/mm^3	75.4	87.5	85.9
Leukopenia			
<4000 cells/mm^3	95.6	98.3	98.6
<1000 cells/mm^3	31.6	46.6	43.7
Thrombocytopenia			
<100,000 cells/mm^3	8.0	24.6	9.2
Anemia			
<11 g/dL	90.4	91.8	93.6
<8 g/dL	8.8	31.1	7.7
Febrile Neutropenia***	11.0	26.2	12.3
Septic Death	1.6	4.9	1.4
Non-Septic Death	0.6	6.6	0.6
Infections			
Any	21.6	32.8	22.2
Severe	6.1	16.4	6.4
Fever in Absence of Infection			
Any	31.2	41.0	35.1
Severe	2.1	8.2	2.2
Hypersensitivity Reactions			
Regardless of Premedication			
Any	21.0	19.7	17.6
Severe	4.2	9.8	2.6
With 3-day Premedication	n=92	n=3	n=92
Any	15.2	33.3	15.2
Severe	2.2	0	2.2
Fluid Retention			
Regardless of Premedication			
Any	47.0	39.3	59.7
Severe	6.9	8.2	8.9
With 3-day Premedication	n=92	n=3	n=92
Any	64.1	66.7	64.1
Severe	6.5	33.3	6.5
Neurosensory			
Any	49.3	34.4	58.3
Severe	4.3	0	5.5
Cutaneous			
Any	47.6	54.1	47.0
Severe	4.8	9.8	5.2
Nail Changes			
Any	30.6	23.0	40.5
Severe	2.5	4.9	3.7
Gastrointestinal			
Nausea	38.8	37.7	42.1
Vomiting	22.3	23.0	23.4
Diarrhea	38.7	32.8	42.6
Severe	4.7	4.9	5.5
Stomatitis			
Any	41.7	49.2	51.7
Severe	5.5	13.0	7.4
Alopecia	75.8	62.3	74.2
Asthenia			
Any	61.8	52.5	66.3
Severe	12.8	24.6	14.9
Myalgia			
Any	18.9	16.4	21.1
Severe	1.5	1.6	1.8
Arthralgia	9.2	6.6	8.2
Infusion Site Reactions	4.4	3.3	4.0

*Normal Baseline LFTs: Transaminases ≤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

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

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

Reversible marrow suppression was the major dose-limiting toxicity of TAXOTERE. The median time to nadir was 7 days, while the median duration of severe neutropenia (<500 cells/mm^3) was 7 days. Among 2045 patients with solid tumors and normal baseline LFTs, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles. Febrile neutropenia (<500 cells/mm^3 with fever >38°C with IV antibiotics and/or hospitalization) occurred in 11% of patients with solid tumors, in 12.3% of patients with metastatic breast cancer, and in 9.8% of 92 breast cancer patients premedicated with 3-day corticosteroids.

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

Thrombocytopenia (<100,000 cells/mm^3) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity Reactions

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

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

Cutaneous

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

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

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

Gastrointestinal

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