CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-449 / S-039

Trade Name: Taxotere Injection Concentrate

Generic Name: docetaxel

Sponsor: Sanofi-Aventis

Approval Date: October 17, 2006

Indications: *For the use of TAXOTERE® (docetaxel) Injection Concentrate in combination with cisplatin and fluorouracil for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN).*

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-449/S-039

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 April 14, 2006, received April 17, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAXOTERE® (docetaxel) Injection Concentrate, 20 mg and 80 mg.

We acknowledge receipt of your submissions dated April 14; May 30; June 8, 15, 16, and 21; July 6, and 11; August 11; and September 13 (e-mail), 16 (e-mail), and 17 (e-mail), 2006.

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 inoperable 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) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert).

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-039."** Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submissions dated November 21, 1995, (Original NDA) and August 18, 2004 (S-029). These commitments are listed below.

COMMITMENT 5 (Original NDA):

Ongoing and future studies in patients with elevated bilirubin or patients with combined elevations of transaminase and alkaline phosphatase to define safe and effective doses in such patients. Such studies should include pharmacokinetic evaluation in addition to assessment of efficacy and safety.

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 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 H. Cross, Jr., Chief Project Management Staff, at (301) 796-0876.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

/s/

Robert Justice
10/17/2006 01:52:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449 / S-039

LABELING

PATIENT INFORMATION LEAFLET
Detach and give to Patient

Rev October 16, 2006

PATIENT INFORMATION LEAFLET

Questions and Answers About Taxotere® Injection Concentrate
(generic name = docetaxel)
(pronounced as TAX-O-TEER)

What is Taxotere?

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

What is the most important information about Taxotere?

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

How does Taxotere work?

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

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

How will I receive Taxotere?

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

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

What should be avoided while receiving Taxotere?

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

What are the possible side effects of Taxotere?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Rev. October 16, 2006

Every three-week injection of TAXOTERE for breast, non-small cell lung, 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

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:_____

Rev. October 16, 2006

℞ only

TAXOTERE®
(docetaxel)

Injection Concentrate

WARNING

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

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

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

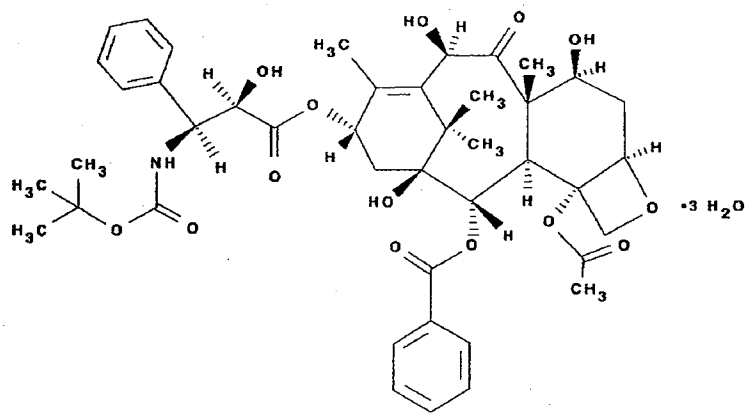
TAXOTERE therapy should not be given to patients with neutrophil counts of < 1500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving TAXOTERE.

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. Hypersensitivity reactions require immediate discontinuation of the TAXOTERE infusion and administration of appropriate therapy. TAXOTERE must not be given to patients who have a history of severe hypersensitivity reactions to TAXOTERE or to other drugs formulated with polysorbate 80 (see **WARNINGS**).

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

DESCRIPTION

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



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

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

CLINICAL PHARMACOLOGY

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

HUMAN PHARMACOKINETICS

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m^2 in phase I studies. The area under the curve (AUC) was dose proportional following doses of 70-115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with

half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due,. in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean values for total body clearance and steady state volume of distribution were 21 L/h/m^2 and 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of 10-90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

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

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

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

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

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

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

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

In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism can be inhibited by CYP3A4 inhibitors, such as ketoconazole,

erythromycin, troleandomycin, and nifedipine. Based on *in vitro* findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood concentrations. No clinical studies have been performed to evaluate this finding (see **PRECAUTIONS**).

CLINICAL STUDIES

Breast Cancer

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

Randomized Trials

In one randomized trial, patients with a history of prior treatment with an anthracycline-containing regimen were assigned to treatment with TAXOTERE (100 mg/m^2 every 3 weeks) or the combination of mitomycin (12 mg/m^2 every 6 weeks) and vinblastine (6 mg/m^2 every 3 weeks). 203 patients were randomized to TAXOTERE and 189 to the comparator arm. Most patients had received prior chemotherapy for metastatic disease; only 27 patients on the TAXOTERE arm and 33 patients on the comparator arm entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The following table summarizes the study results (See Table 1).

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

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

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

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

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

Efficacy Parameter	**Docetaxel (n=161)**	**Doxorubicin (n=165)**	**p-value**
Median Survival	14.7 months	14.3 months	
Risk Ratio*, Mortality (Docetaxel: Control)	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%	

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

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

Single Arm Studies

TAXOTERE at a dose of 100 mg/m^2 was studied in six single arm studies involving a total of 309 patients with metastatic breast cancer in whom previous chemotherapy had failed. Among these, 190 patients had anthracycline-resistant breast cancer, defined as progression during an anthracycline-containing chemotherapy regimen for metastatic disease, or relapse during an anthracycline-containing adjuvant regimen. In anthracycline-resistant patients, the overall

response rate was 37.9% (72/190; 95% C.I.: 31.0-44.8) and the complete response rate was 2.1%.

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

Adjuvant Treatment of Breast Cancer

A multicenter, open-label, randomized trial (TAX316) evaluated the efficacy and safety of TAXOTERE for the adjuvant treatment of patients with axillary-node-positive breast cancer and no evidence of distant metastatic disease. After stratification according to the number of positive lymph nodes (1-3, 4+), 1491 patients were randomized to receive either TAXOTERE 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC arm), or doxorubicin 50 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclosphosphamide 500 mg/m^2 (FAC arm). Both regimens were administered every 3 weeks for 6 cycles. TAXOTERE was administered as a 1-hour infusion; all other drugs were given as 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 TAX 316, 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 - TAX 316 Disease Free Survival K-M curve

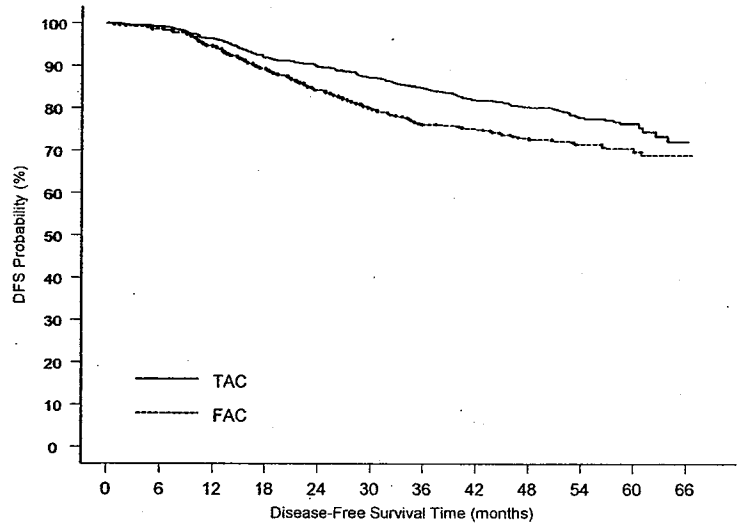
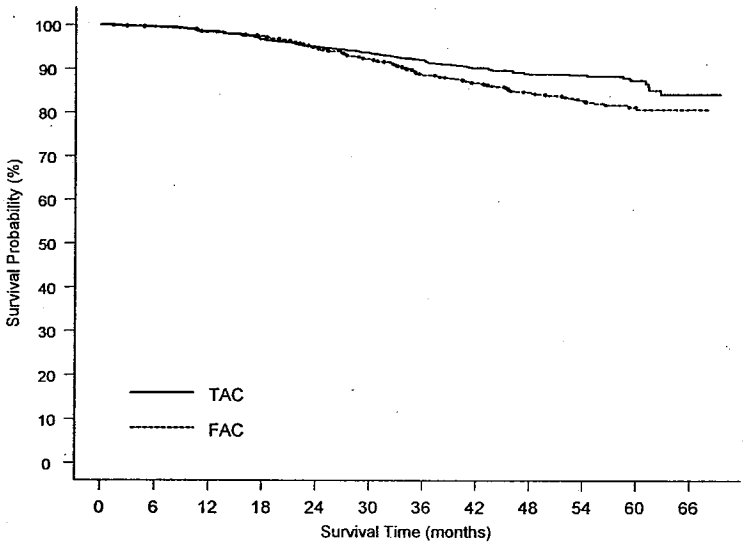


Figure 2 - TAX 316 Overall Survival K-M Curve



The following table describes the results of subgroup analyses for DFS and OS (See Table 3).

Table 3 - Subset Analyses-Adjuvant Breast Cancer Study

Patient subset	Number of patients	Disease Free Survival		Overall Survival	
		Hazard ratio*	95% CI	Hazard ratio*	95% CI
No. of positive nodes					
Overall	744	0.74	(0.60, 0.92)	0.69	(0.53, 0.90)
1-3	467	0.64	(0.47, 0.87)	0.45	(0.29, 0.70)
4+	277	0.84	(0.63, 1.12)	0.93	(0.66, 1.32)
Receptor status					
Positive	566	0.76	(0.59, 0.98)	0.69	(0.48, 0.99)
Negative	178	0.68	(0.48, 0.97)	0.66	(0.44, 0.98)

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

Non-Small Cell Lung Cancer (NSCLC)

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

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

Two randomized, controlled trials established that a TAXOTERE dose of 75 mg/m^2 was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy (see below). TAXOTERE at a dose of 100 mg/m^2, however, was associated with unacceptable hematologic toxicity, infections, and treatment-related mortality and this dose should not be used (see **BOXED WARNING, WARNINGS**, and **DOSAGE AND ADMINISTRATION** sections).

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

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

Table 4 - Efficacy of TAXOTERE in the Treatment of Non-Small Cell Lung Cancer Patients Previously Treated with a Platinum-Based Chemotherapy Regimen (Intent-to-Treat Analysis)

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

* p≤0.05; † uncorrected for multiple comparisons; †† a value less than 1.00 favors docetaxel.

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

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

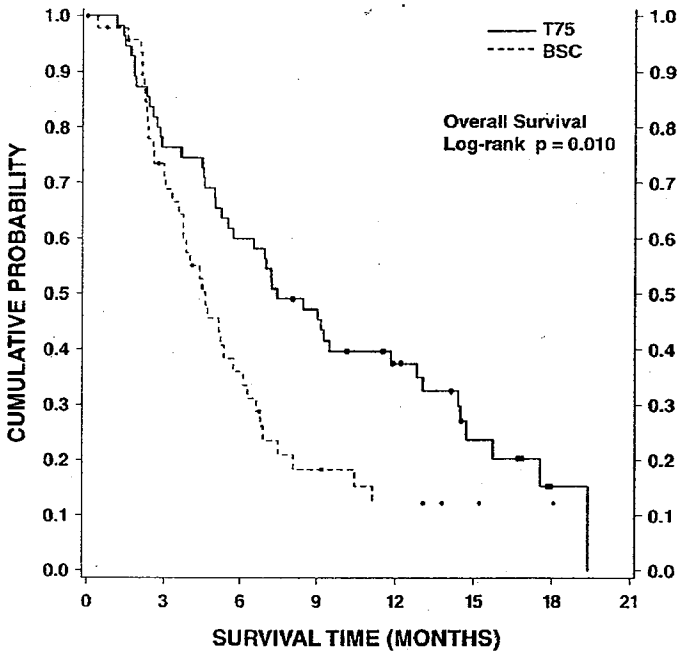
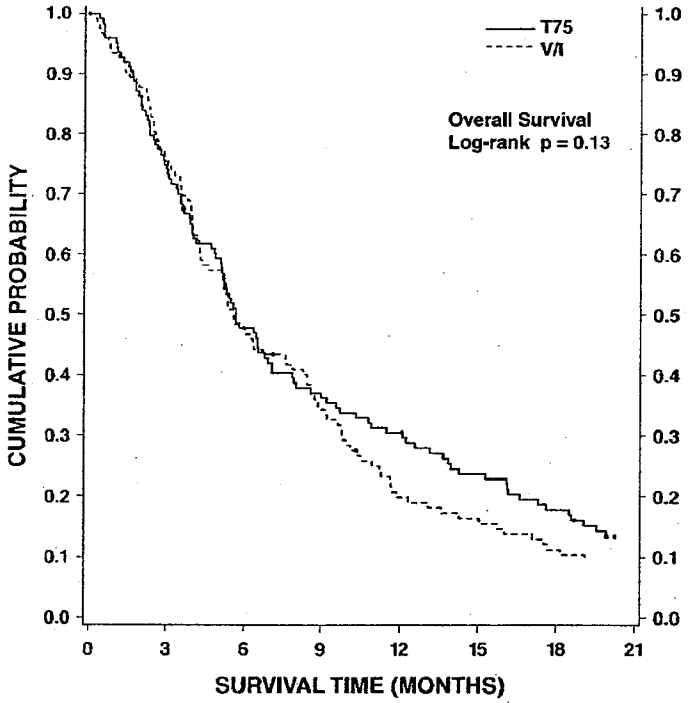


Figure 4 - TAX320 Survival K-M Curves - TAXOTERE 75 mg/m^2 vs. Vinorelbine or Ifosfamide Control



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

Combination Therapy with TAXOTERE for Chemotherapy-Naïve NSCLC

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

The primary efficacy endpoint was overall survival. Treatment with TAXOTERE+cisplatin did not result in a statistically significantly superior survival compared to vinorelbine+cisplatin (see table below). The 95% confidence interval of the hazard ratio (adjusted for interim analysis and multiple comparisons) shows that the addition of TAXOTERE to cisplatin results in an outcome ranging from a 6% inferior to a 26% superior survival compared to the addition of vinorelbine to cisplatin. The results of a further statistical analysis showed that at least (the lower bound of the 95% confidence interval) 62% of the known survival effect of vinorelbine when added to cisplatin (about a 2-month increase in median survival; Wozniak et al. JCO, 1998) was maintained. The efficacy data for the TAXOTERE+cisplatin arm and the comparator arm are summarized in Table 5.

Table 5 - Survival Analysis of TAXOTERE in Combination Therapy for Chemotherapy-Naïve NSCLC

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

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

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

[c] Adjusted for interim analysis and multiple comparisons.

The second comparison in the 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 6).

Table 6 - 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)[a]	31.6% (26.5%, 36.8%)	24.4% (19.8%, 29.2%)	Not Significant
Median Time to Progression[b] (95% CI)[a]	21.4 weeks (19.3, 24.6)	22.1 weeks (18.1, 25.6)	Not Significant

[a]Adjusted for multiple comparisons.

[b]Kaplan-Meier estimates.

Prostate Cancer

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

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

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

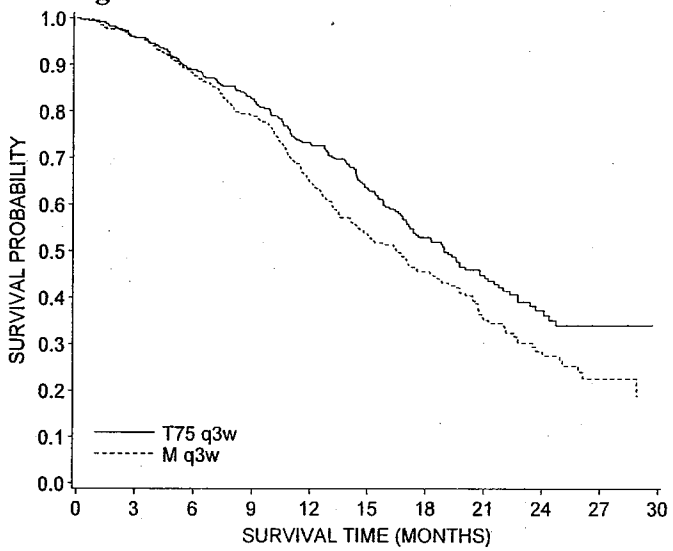
In the TAXOTERE every three week arm, a statistically significant overall survival advantage was demonstrated compared to mitoxantrone. In the TAXOTERE weekly arm, no overall survival advantage was demonstrated compared to the mitoxantrone control arm. Efficacy results for the TAXOTERE every 3 week arm versus the control arm are summarized in Table 7 and Figure 5.

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

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

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

Figure 5 - TAX327 Survival K-M Curves



Gastric Adenocarcinoma

A multicenter, open-label, randomized trial was conducted to evaluate the safety and efficacy of TAXOTERE for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for advanced disease. A total of 445 patients with KPS>70 were treated with either TAXOTERE (T) (75 mg/m^2 on day 1) in combination with cisplatin (C) (75 mg/m^2 on day 1) and fluorouracil (F) (750 mg/m^2 per day for 5 days) or cisplatin (100 mg/m^2 on day 1) and fluorouracil (1000 mg/m^2 per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The demographic characteristics were balanced between the two treatment arms. The median age was 55 years, 71% were male, 71% were Caucasian, 24% were 65 years of age or older, 19% had a prior curative surgery and 12% had palliative surgery. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint and was defined as time from randomization to disease progression or death from any cause within 12 weeks of the last evaluable tumor assessment or within 12 weeks of the first infusion of study drugs for patients with no evaluable tumor assessment after randomization. The hazard ratio (HR) for TTP was 1.47 (CF/TCF, 95% CI: 1.19-1.83) with a significantly longer TTP (p=0.0004) in the TCF arm. Approximately 75% of patients had died at the time of this analysis. Overall survival was significantly longer (p=0.0201) in the TCF arm with a HR of 1.29 (95% CI: 1.04-1.61). Efficacy results are summarized in Table 8 and Figures 6 and 7.

Table 8 - Efficacy of TAXOTERE in the treatment of patients with gastric adenocarcinoma

Endpoint	TCF n=221	CF n=224
Median TTP (months)	5.6	3.7
(95%CI)	(4.86-5.91)	(3.45-4.47)
Hazard ratio†	1.47	
(95%CI)	(1.19-1.83)	
*p-value	0.0004	
Median survival (months)	9.2	8.6
(95%CI)	(8.38-10.58)	(7.16-9.46)
Hazard ratio†	1.29	
(95%CI)	(1.04-1.61)	
*p-value	0.0201	
Overall Response Rate (CR+PR) (%)	36.7	25.4
p-value	0.0106	

*Unstratified logrank test

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

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

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

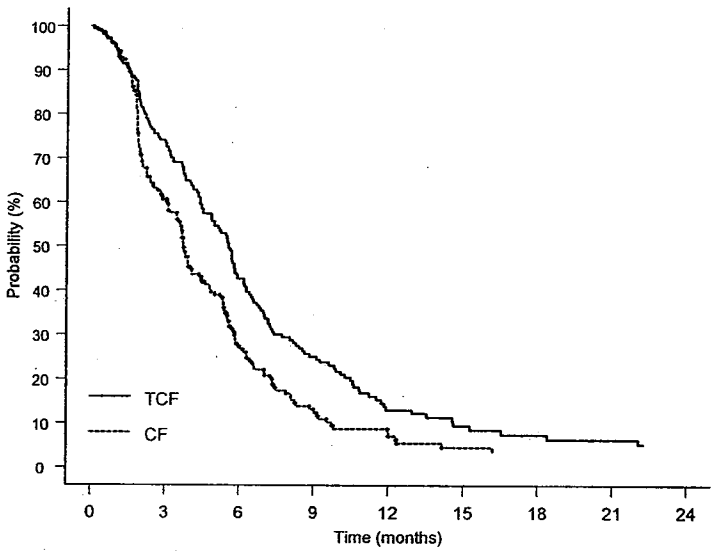
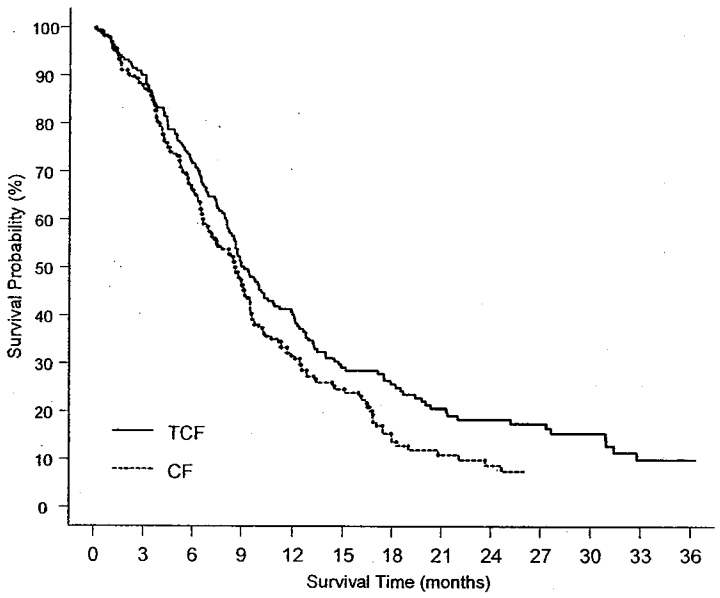


Figure 7 - Gastric Cancer Study (TAX325) Survival K-M Curve



Head and Neck Cancer

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

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

Table 9 - Efficacy of TAXOTERE in the induction treatment of patients with inoperable locally advanced SCCHN (Intent-to-Treat Analysis)

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

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

* Stratified log-rank test based on primary tumor site

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

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

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

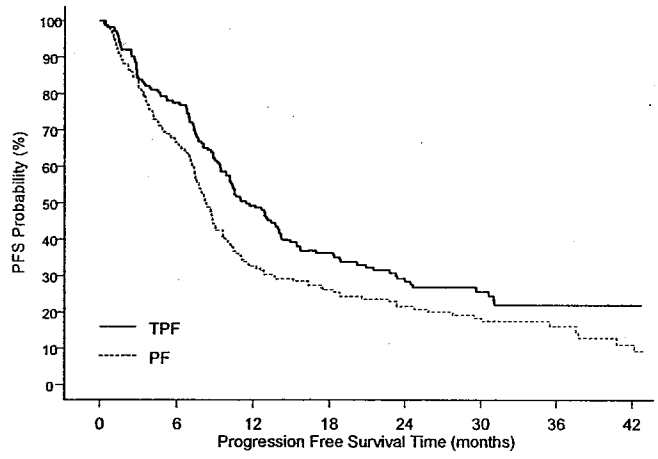
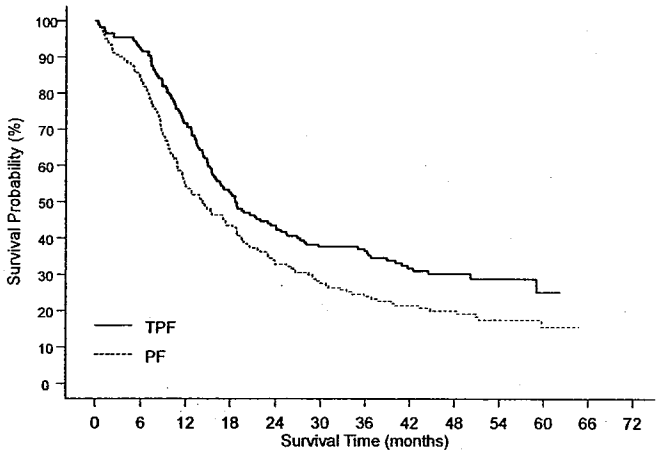


Figure 9 - TAX323 Overall Survival K-M Curve



INDICATIONS AND USAGE

Breast Cancer

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

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

Non-Small Cell Lung Cancer

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

TAXOTERE in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

Prostate Cancer

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

Gastric Adenocarcinoma

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

Head and Neck Cancer

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

CONTRAINDICATIONS

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

TAXOTERE should not be used in patients with neutrophil counts of <1500 cells/mm^3.

WARNINGS

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

Toxic Deaths

Breast Cancer

TAXOTERE administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function (SGOT and/or SGPT > 1.5 times ULN together with AP > 2.5 times ULN). Among patients dosed at 60 mg/m^2, mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Non-Small Cell Lung Cancer

TAXOTERE administered at a dose of 100 mg/m^2 in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at

the 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had a PS of 2 at study entry (see **BOXED WARNING, CLINICAL STUDIES**, and **DOSAGE AND ADMINISTRATION** sections).

Premedication Regimen

All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg per day (*e.g.*, 8 mg BID) for 3 days starting 1 day prior to TAXOTERE to reduce the severity of fluid retention and hypersensitivity reactions (see **DOSAGE AND ADMINISTRATION** section). This regimen was evaluated in 92 patients with metastatic breast cancer previously treated with chemotherapy given TAXOTERE at a dose of 100 mg/m^2 every 3 weeks.

The pretreatment regimen for hormone-refractory metastatic prostate cancer is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the TAXOTERE infusion (see **DOSAGE AND ADMINISTRATION** section).

Hypersensitivity Reactions

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

Hematologic Effects

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

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related and are described in **CLINICAL STUDIES**.

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

In gastric cancer patients treated with TAXOTERE in combination with cisplatin and fluorouracil (TCF), febrile neutropenia and/or neutropenic infection occurred in 12% of patients receiving G-CSF compared to 28% who did not. Patients receiving TCF should be closely monitored during the first and subsequent cycles for febrile neutropenia and neutropenic infection. (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION/Dosage Adjustments** sections).

Hepatic Impairment

(see **BOXED WARNING**).

Fluid Retention

(see **BOXED WARNING**).

Acute Myeloid Leukemia

Treatment-related acute myeloid leukemia (AML) has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. In the adjuvant

breast cancer trial (TAX316, see CLINICAL STUDIES) AML occurred in 3 of 744 patients who received TAXOTERE, doxorubicin and cyclophosphamide and in 1 of 736 patients who received fluorouracil, doxorubicin and cyclophosphamide (see ADVERSE REACTIONS).

Pregnancy

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

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

PRECAUTIONS

General

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

Hematologic Effects

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

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

Hypersensitivity Reactions

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

Cutaneous

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

Fluid Retention

Severe fluid retention has been reported following TAXOTERE therapy (see **BOXED WARNING** and **WARNINGS: Premedication Regimen**). Patients should be premedicated with oral corticosteroids prior to each TAXOTERE administration to reduce the incidence and severity of fluid retention (see **DOSAGE AND ADMINISTRATION** section). Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

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

Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/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).

Neurologic

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

Asthenia

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

Information for Patients

For additional information, see the accompanying Patient Information Leaflet.

Drug Interactions

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

Carcinogenicity, Mutagenicity, Impairment of Fertility

No studies have been conducted to assess the carcinogenic potential of TAXOTERE. TAXOTERE has been shown to be clastogenic in the *in vitro* chromosome aberration test in CHO-K_1 cells and in the *in vivo* micronucleus test in the mouse, but it did not induce

mutagenicity in the Ames test or the CHO/HGPRT gene mutation assays. TAXOTERE produced no impairment of fertility in rats when administered in multiple IV doses of up to 0.3 mg/kg (about 1/50 the recommended human dose on a mg/m^2 basis), but decreased testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at IV doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/3 and 1/15 the recommended human dose on a mg/m^2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

Pregnancy

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

Nursing Mothers

It is not known whether TAXOTERE is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from TAXOTERE, mothers should discontinue nursing prior to taking the drug.

Pediatric Use

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

Geriatric Use

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 events was higher in the elderly patients compared to younger patients. The incidence of the following adverse events (all grades): lethargy, stomatitis, diarrhea, dizziness, edema, febrile neutropenia/neutropenic infection occurred at rates ≥ 10% higher in patients who were 65 years of age or older compared to younger patients. Elderly patients treated with TCF should be closely monitored.

Of the 174 patients who received the induction treatment with TAXOTERE in combination with cisplatin and fluorouracil for SCCHN (TAX323), 18 (10%) patients were 65 years of age or older.

The clinical study of TAXOTERE in combination with cisplatin and fluorouracil in patients with SCCHN (TAX323) did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience with this treatment regimen has not identified differences in responses between elderly and younger patients.

ADVERSE REACTIONS

Adverse reactions are described for TAXOTERE according to indication:
-in the treatment of breast cancer, at the maximum dose of 100 mg/m^2
-in the treatment of advanced breast cancer at doses of 60, 75, and 100 mg/m^2
-in the adjuvant therapy of breast cancer at a dose of 75 mg/m^2, in combination with doxorubicin and cyclophosphamide
-in the treatment of advanced non-small cell lung cancer after prior platinum-based chemotherapy, at a dose of 75 mg/m^2
-in the treatment of non-small cell lung cancer in patients who have not previously received chemotherapy for this condition, at a dose of 75 mg/m^2, in combination with cisplatin
-in the treatment of androgen independent (hormone refractory) metastatic prostate cancer, at a dose of 75 mg/m^2 every three weeks in combination with prednisone
-in the treatment of advanced gastric adenocarcinoma in patients who have not received prior chemotherapy for advanced disease, at a dose of 75 mg/m^2 in combination with cisplatin and fluorouracil
-in the induction treatment of SCCHN, at a dose of 75 mg/m^2 every three weeks in combination with cisplatin and fluorouracil.

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 10).

Table 10 - Summary of Adverse Events in Patients Receiving TAXOTERE at 100 mg/m^2

Adverse Event	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
Hematologic			
Neutropenia			
<2000 cells/mm^3	95.5	96.4	98.5
<500 cells/mm^3	75.4	87.5	85.9
Leukopenia			
<4000 cells/mm^3	95.6	98.3	98.6
<1000 cells/mm^3	31.6	46.6	43.7
Thrombocytopenia			
<100,000 cells/mm^3	8.0	24.6	9.2
Anemia			
<11 g/dL	90.4	91.8	93.6
<8 g/dL	8.8	31.1	7.7
Febrile Neutropenia***	11.0	26.2	12.3
Septic Death	1.6	4.9	1.4
Non-Septic Death	0.6	6.6	0.6
Infections			
Any	21.6	32.8	22.2
Severe	6.1	16.4	6.4
Fever in Absence of Infection			
Any	31.2	41.0	35.1
Severe	2.1	8.2	2.2
Hypersensitivity Reactions			
Regardless of Premedication			
Any	21.0	19.7	17.6
Severe	4.2	9.8	2.6
With 3-day Premedication	n=92	n=3	n=92
Any	15.2	33.3	15.2
Severe	2.2	0	2.2
Fluid Retention			
Regardless of Premedication			
Any	47.0	39.3	59.7

Adverse Event	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
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**).

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** sections. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after discontinuing the infusion and appropriate therapy.

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

Cutaneous

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

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

Neurologic: (see **PRECAUTIONS**).

Gastrointestinal

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

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

Cardiovascular

Hypotension occurred in 2.8% of patients with solid tumors; 1.2% required treatment. Clinically meaningful events such as heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension occurred rarely. 8.1% (7/86) of metastatic breast cancer patients receiving TAXOTERE 100 mg/m^2 in a randomized trial and who had serial left

ventricular ejection fractions assessed developed deterioration of LVEF by ≥ 10% associated with a drop below the institutional lower limit of normal.

Infusion Site Reactions

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

Hepatic

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

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

Hematologic and other toxicity is increased at higher doses and in patients with elevated baseline liver function tests (LFTs). In the following tables, adverse drug reactions are compared for three populations: 730 patients with normal LFTs given TAXOTERE at 100 mg/m^2 in the randomized and single arm studies of metastatic breast cancer after failure of previous chemotherapy; 18 patients in these studies who had abnormal baseline LFTs (defined as 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^2 who had normal LFTs (see Tables 11 and 12).

Table 11 - Hematologic Adverse Events in Breast Cancer Patients Previously Treated with Chemotherapy Treated at TAXOTERE 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

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

*Normal Baseline LFTs: Transaminases ≤ 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^2, ANC grade 4 and fever > 38°C with IV antibiotics and/or hospitalization; for 60 mg/m^2, ANC grade 3/4 and fever > 38.1°C

Table 12 - Non-Hematologic Adverse Events in Breast Cancer Patients Previously Treated with Chemotherapy Treated at TAXOTERE 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

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

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

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

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

NA = not available

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

Combination Therapy with TAXOTERE in the Adjuvant Treatment of Breast Cancer

The following table presents treatment emergent adverse events (TEAEs) observed in 744 patients, who were treated with TAXOTERE 75 mg/m^2 every 3 weeks in combination with doxorubicin and cyclophosphamide (see Table13).

Table 13 - Clinically Important Treatment Emergent Adverse Events Regardless of Causal Relationship in Patients Receiving TAXOTERE in Combination with Doxorubicin and Cyclophosphamide (TAX 316).

	TAXOTERE 75 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (TAC) n=744 %		Fluorouracil 500 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (FAC) n=736 %	
Adverse Event	**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
Neuro-cortical	5.1	0.5	6.4	0.7
Neuropathy motor	3.8	0.1	2.2	0.0
Neuro-cerebellar	2.4	0.1	2.0	0.0
Syncope	1.6	0.5	1.2	0.3
Alopecia	97.8	N/A	97.1	N/A
Skin toxicity	26.5	0.8	17.7	0.4
Nail disorders	18.5	0.4	14.4	0.1
Nausea	80.5	5.1	88.0	9.5
Stomatitis	69.4	7.1	52.9	2.0
Vomiting	44.5	4.3	59.2	7.3
Diarrhea	35.2	3.8	27.9	1.8
Constipation	33.9	1.1	31.8	1.4
Taste perversion	27.8	0.7	15.1	0.0
Anorexia	21.6	2.2	17.7	1.2
Abdominal Pain	10.9	0.7	5.3	0.0
Amenorrhea	61.7	N/A	52.4	N/A
Cough	13.7	0.0	9.8	0.1
Cardiac dysrhythmias	7.9	0.3	6.0	0.3

	TAXOTERE 75 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (TAC) n=744 %		Fluorouracil 500 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (FAC) n=736 %	
Vasodilatation	27.0	1.1	21.2	0.5
Hypotension	2.6	0.0	1.1	0.1
Phlebitis	1.2	0.0	0.8	0.0
Asthenia	80.8	11.2	71.2	5.6
Myalgia	26.7	0.8	9.9	0.0
Arthralgia	19.4	0.5	9.0	0.3
Lacrimation disorder	11.3	0.1	7.1	0.0
Conjunctivitis	5.1	0.3	6.9	0.1

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

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

Fever and Infection

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

Gastrointestinal events

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

Cardiovascular events

More cardiovascular events were reported in the TAC arm vs. the FAC arm; dysrhythmias, all grades (7.9% vs. 6.0%), hypotension, all grades (2.6% vs. 1.1%) and CHF (1.6% vs. 0.5%). One patient in each arm died due to heart failure.

Acute Myeloid Leukemia

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

0.1% for FAC-treated patients. This risk of AML is comparable to the risk observed for other anthracyclines/cyclophosphamide containing adjuvant breast chemotherapy regimens.

Monotherapy with TAXOTERE for Unresectable, Locally Advanced or Metastatic NSCLC Previously Treated with Platinum-Based Chemotherapy

TAXOTERE 75 mg/m^2: Treatment emergent adverse drug reactions are shown in Table 14. Included in this table are safety data for a total of 176 patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who were treated in two randomized, controlled trials. These reactions were described using NCI Common Toxicity Criteria regardless of relationship to study treatment, except for the hematologic toxicities or otherwise noted.

Table 14 - Treatment Emergent Adverse Events Regardless of Relationship to Treatment in Patients Receiving TAXOTERE as Monotherapy for Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy*

Adverse Event	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Neutropenia			
Any	84.1	14.3	83.2
Grade ¾	65.3	12.2	57.1
Leukopenia			
Any	83.5	6.1	89.1
Grade ¾	49.4	0	42.9
Thrombocytopenia			
Any	8.0	0	7.6
Grade ¾	2.8	0	1.7
Anemia			
Any	91.0	55.1	90.8
Grade ¾	9.1	12.2	14.3
Febrile Neutropenia**	6.3	NA†	0.8
Infection			
Any	33.5	28.6	30.3
Grade ¾	10.2	6.1	9.2
Treatment Related Mortality	2.8	NA†	3.4
Hypersensitivity Reactions			
Any	5.7	0	0.8
Grade ¾	2.8	0	0
Fluid Retention			

Adverse Event	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Any	33.5	ND††	22.7
Severe	2.8		3.4
Neurosensory			
Any	23.3	14.3	28.6
Grade ¾	1.7	6.1	5.0
Neuromotor			
Any	15.9	8.2	10.1
Grade ¾	4.5	6.1	3.4
Skin			
Any	19.9	6.1	16.8
Grade ¾	0.6	2.0	0.8
Gastrointestinal			
Nausea			
Any	33.5	30.6	31.1
Grade 3/4	5.1	4.1	7.6
Vomiting			
Any	21.6	26.5	21.8
Grade 3/4	2.8	2.0	5.9
Diarrhea			
Any	22.7	6.1	11.8
Grade 3/4	2.8	0	4.2
Alopecia	56.3	34.7	49.6
Asthenia			
Any	52.8	57.1	53.8
Severe***	18.2	38.8	22.7
Stomatitis			
Any	26.1	6.1	7.6
Grade 3/4	1.7	0	0.8
Pulmonary			
Any	40.9	49.0	45.4
Grade 3/4	21.0	28.6	18.5
Nail Disorder			
Any	11.4	0	1.7
Severe***	1.1	0	0
Myalgia			
Any	6.3	0	2.5

Adverse Event	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Severe***	0	0	0
Arthralgia			
Any	3.4	2.0	1.7
Severe***	0	0	0.8
Taste Perversion			
Any	5.7	0	0
Severe***	0.6	0	0

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

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

***COSTART term and grading system

†Not Applicable; †† Not Done

Combination Therapy with TAXOTERE in Chemotherapy-Naïve Advanced Unresectable or Metastatic NSCLC

Table 15 presents safety data from two arms of an open label, randomized controlled trial (TAX326) that enrolled patients with unresectable stage IIIB or IV non-small cell lung cancer and no history of prior chemotherapy. Adverse reactions were described using the NCI Common Toxicity Criteria except where otherwise noted.

Table 15 - Adverse Events Regardless of Relationship to Treatment in Chemotherapy-Naïve Advanced Non-Small Cell Lung Cancer Patients Receiving TAXOTERE in Combination with Cisplatin

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

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

* Replaces NCI term "Allergy"
** COSTART term and grading system

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

Combination Therapy with TAXOTERE in Patients with Prostate Cancer

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

Table 16 - Clinically Important Treatment Emergent Adverse Events (Regardless of Relationship) in Patients with Prostate Cancer who Received TAXOTERE in Combination with Prednisone (TAX 327)

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

Tearing	9.9	0.6	1.5	0.0
Arthralgia	8.1	0.6	5.1	1.2

*Related to treatment

Combination therapy with TAXOTERE in gastric adenocarcinoma

Data in the following table are based on the experience of 221 patients with advanced gastric adenocarcinoma and no history of prior chemotherapy for advanced disease, who were treated with TAXOTERE 75 mg/m^2 in combination with cisplatin and fluorouracil (see Table 17).

Table 17- Clinically Important Treatment Emergent Adverse Events Regardless of Relationship to Treatment in the Gastric Cancer Study

	TAXOTERE 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=221		**Cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 n=224**	
Adverse Event	**Any %**	**G3/4 %**	**Any %**	**G3/4 %**
Anemia	96.8	18.2	93.3	25.6
Neutropenia	95.5	82.3	83.3	56.8
Fever in the absence of infection	35.7	1.8	22.8	1.3
Thrombocytopenia	25.5	7.7	39.0	13.5
Infection	29.4	16.3	22.8	10.3
Febrile neutropenia	16.4	N/A	4.5	N/A
Neutropenic infection	15.9	N/A	10.4	N/A
Allergic reactions	10.4	1.8	5.8	0
Fluid retention*	14.9	0	4.0	0.4
Edema*	13.1	0	3.1	0.4
Lethargy	62.9	21.3	58.0	17.9
Neurosensory	38.0	7.7	24.6	3.1
Neuromotor	8.6	3.2	7.6	2.7
Dizziness	15.8	4.5	8.0	1.8
Alopecia	66.5	5.0	41.1	1.3
Rash/itch	11.8	0.9	8.5	0.0
Nail changes	8.1	0.0	0.0	0.0
Skin desquamation	1.8	0.0	0.4	0.0
Nausea	73.3	15.8	76.3	18.8
Vomiting	66.5	14.9	73.2	18.8
Anorexia	50.7	13.1	54.0	11.6
Stomatitis	59.3	20.8	61.2	27.2

	TAXOTERE 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=221		Cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 n=224	
Adverse Event	**Any %**	**G3/4 %**	**Any %**	**G3/4 %**
Diarrhea	77.8	20.4	49.6	8.0
Constipation	25.3	1.8	33.9	3.1
Esophagitis/dysphagia/ odynophagia	16.3	1.8	13.8	4.9
Gastrointestinal pain/cramping	11.3	1.8	7.1	2.7
Cardiac dysrhythmias	4.5	2.3	2.2	0.9
Myocardial ischemia	0.9	0.0	2.7	2.2
Tearing	8.1	0	2.2	0.4
Altered hearing	6.3	0	12.5	1.8

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

Combination Therapy with TAXOTERE in Head and Neck Cancer

The following table summarizes the safety data obtained in 174 patients with locally advanced inoperable SCCHN, who were treated with TAXOTERE 75 mg/m^2 in combination with cisplatin and fluorouracil (Table 18).

Table 18 – Clinically Important Treatment Emergent Adverse Events (Regardless of Relationship) in Patients with SCCHN Receiving TAXOTERE in Combination with Cisplatin and fluorouracil (TAX 323).

	TAXOTERE 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=174		Cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 n=181	
Adverse Event	**Any %**	**G3/4 %**	**Any %**	**G3/4 %**
Neutropenia	93.1	76.3	86.7	52.8
Anemia	89.1	9.2	87.8	13.8
Thrombocytopenia	23.6	5.2	47.0	18.2
Infection	27.0	8.6	26.0	7.7
Fever in the absence of infection	31.6	0.6	36.5	0
Febrile neutropenia*	5.2	N/A	2.2	N/A
Neutropenic infection	13.9	N/A	8.3	N/A
Allergy	6.3	0	2.8	0
Fluid retention	20.1	0	14.4	0.6
Edema only	12.6	0	6.6	0
Weight gain only	5.7	0	6.1	0
Lethargy	40.8	3.4	38.1	3.3
Neurosensory	17.8	0.6	10.5	0.6
Dizziness	2.3	0	5.0	0.6
Alopecia	81.0	10.9	43.1	0
Rash/itch	11.5	0	6.1	0
Dry skin	5.7	0	1.7	0
Desquamation	4.0	0.6	5.5	0
Nausea	47.1	0.6	51.4	7.2
Stomatitis	42.5	4.0	47.0	11.0
Diarrhea	32.8	2.9	23.8	4.4
Vomiting	26.4	0.6	38.7	5.0
Anorexia	16.1	0.6	24.9	3.3
Constipation	16.7	0.6	16.0	1.1
Esophagitis/dysphagia/ Odynophagia	12.6	1.1	18.2	2.8
Gastrointestinal pain/cramping	7.5	0.6	8.8	0.6
Heartburn	6.3	0	6.1	0
Gastrointestinal bleeding	4.0	1.7	0	0
Taste, sense of smell altered	10.3	0	5.0	0
Cardiac dysrhythmia	1.7	1.7	1.7	0.6
Ischemia myocardial	1.7	1.7	0.6	0
Venous	3.4	2.3	5.5	1.7

	TAXOTERE 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=174		Cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 n=181	
Adverse Event	**Any %**	**G3/4 %**	**Any %**	**G3/4 %**
Myalgia	9.8	1.1	7.2	0
Cancer pain	20.7	4.6	16.0	3.3
Tearing	1.7	0	0.6	0
Conjunctivitis	1.1	0	1.1	0
Altered hearing	5.7	0	9.9	2.8
Weight loss	20.7	6.6	26.5	0.6

*Febrile neutropenia: grade ≥2 fever concomitant with grade 4 neutropenia requiring i.v. antibiotics and/or hospitalization.

Post-marketing Experiences

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

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

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

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

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

Hematologic: bleeding episodes

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

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

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

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

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

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

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

Breast Cancer

The recommended dose of TAXOTERE is 60-100 mg/m^2 administered intravenously over 1 hour every 3 weeks.

In the adjuvant treatment of operable node-positive breast cancer, the recommended TAXOTERE dose is 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities (see also **Dosage Adjustments**).

Non-Small Cell Lung Cancer

For treatment after failure of prior platinum-based chemotherapy, TAXOTERE was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials (see **BOXED WARNING, WARNINGS** and **CLINICAL STUDIES** sections).

For chemotherapy-naïve patients, TAXOTERE was evaluated in combination with cisplatin. The recommended dose of TAXOTERE is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks.

Prostate cancer

For hormone-refractory metastatic prostate cancer, the recommended dose of TAXOTERE is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5 mg orally twice daily is administered continuously.

Gastric adenocarcinoma

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

Head and Neck Cancer

For the induction treatment of locally advanced inoperable SCCHN, the recommended dose of TAXOTERE is 75 mg/m^2 as a 1 hour intravenous infusion followed by cisplatin 75 mg/m^2 intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy. Patients must receive premedication with antiemetics and appropriate hydration (prior to and after cisplatin administration). All patients on the Taxotere-containing arm of the TAX 323 study received prophylactic antibiotics.

For cisplatin and fluorouracil dose modifications, see manufacturer's prescribing information.

Premedication Regimen

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

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

Dosage Adjustments During Treatment

Breast Cancer

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

Combination Therapy with TAXOTERE in the Adjuvant Treatment of Breast Cancer

TAXOTERE in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is ≥ 1,500 cells/mm^3. Patients who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their TAXOTERE dose reduced to 60 mg/m^2. Patients who

experience Grade 3 or 4 stomatitis should have their TAXOTERE dose decreased to 60 mg/m². Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during TAXOTERE therapy should have their dosage of TAXOTERE reduced from 75 to 60 mg/m². If the patient continues to experience these reactions at 60 mg/m², treatment should be discontinued.

Non-Small Cell Lung Cancer

Monotherapy with TAXOTERE for NSCLC Treatment After Failure of Prior Platinum-Based Chemotherapy

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

Combination Therapy with TAXOTERE for Chemotherapy-Naïve NSCLC

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

Combination Therapy with TAXOTERE for Hormone-Refractory Metastatic Prostate Cancer

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

TAXOTERE in combination with cisplatin and fluorouracil in Gastric Cancer or Head and Neck Cancer.

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

Recommended dose modifications for toxicities in patients treated with TAXOTERE in combination with cisplatin and fluorouracil are shown in Table 19.

Table 19 - Recommended Dose Modifications for Toxicities in Patients Treated with TAXOTERE in Combination with Cisplatin and Fluorouracil

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

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

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

Cisplatin dose modifications and delays
Peripheral neuropathy: A neurological examination should be performed before entry into the study, and then at least every 2 cycles and at the end of treatment. In the case of neurological signs or symptoms, more frequent examinations should be performed and the following dose modifications can be made according to NCIC-CTC grade:
• Grade 2: Reduce cisplatin dose by 20%.
• Grade 3: Discontinue treatment.
Ototoxicity: In the case of grade 3 toxicity, discontinue treatment.
Nephrotoxicity: In the event of a rise in serum creatinine ≥ grade 2 (> 1.5 x normal value) despite adequate rehydration, CrCl should be determined before each subsequent cycle and the following dose reductions should be considered (see Table 20):

Table 20 – Dose Reductions for Evaluation of Creatinine Clearance

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

CrCl = Creatinine clearance

Fluorouracil dose modifications and treatment delays

For diarrhea and stomatitis/mucositis, see Table 19.

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

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

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

Special Populations

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

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

Elderly: See **Precautions, 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.

PREPARATION AND ADMINISTRATION

Administration Precautions

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

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

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

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

The table below provides the fill range of the diluent, the approximate extractable volume of diluent when the entire contents of the diluent vial are withdrawn, and the concentration of the initial diluted solution for TAXOTERE 20 mg and TAXOTERE 80 mg (see Table 21).

Table 21 – 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

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 10mg docetaxel/mL will result.**

3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.

4. The initial diluted TAXOTERE solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

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

B. Final Dilution for Infusion

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

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

2. Thoroughly mix the infusion by manual rotation.

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

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

Stability

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

HOW SUPPLIED

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

TAXOTERE 80 mg/2 ML (NDC 0075-8001-80)

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

TAXOTERE 20 mg/0.5 ML (NDC 0075-8001-20)

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

Storage

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

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

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

Rev. October 16, 2006

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449 / S-039

SUMMARY REVIEW

Division Director Summary Review of an Efficacy Supplement

NDA: 20-449/S-039
Drug: Taxotere® (docetaxel) Injection Concentrate
Applicant: sanofi-aventis
Date: October 13, 2006

This efficacy supplement seeks approval of Taxotere for the following indication: "TAXOTERE in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN)." The study design and results are summarized in the following excerpts from the agreed upon labeling.

> The safety and efficacy of TAXOTERE in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a multicenter, open-label, randomized trial (TAX323). In this study, 358 patients with inoperable locally advanced SCCHN, and WHO performance status 0 or 1, received either TAXOTERE 75 mg/m^2 followed by cisplatin 75 mg/m^2 on Day 1, followed by fluorouracil 750 mg/m^2 per day as a continuous infusion on Days 1-5 (TPF) or cisplatin 100 mg/m^2 on Day 1, followed by fluorouracil 1000 mg/m^2/day as a continuous infusion on Days 1-5 (PF). These regimens were administered every three weeks for 4 cycles. At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines. Locoregional therapy with radiation was delivered either with a conventional fraction (1.8 Gy-2.0 Gy) once a day, 5 days per week for a total dose of 66 to 70 Gy); accelerated/hyperfractionated regimens of radiation therapy (twice a day, with a minimum interfraction interval of 6 hours, 5 days per week, for a total dose of 70 to 74 Gy for accelerated or hyperfractionated regimens, respectively. Surgical resection was allowed following chemotherapy, before or after radiotherapy.
>
> The primary endpoint in this study, progression-free survival (PFS), was significantly longer in the TPF arm compared to the PF arm, p=0.0077 (median PFS: 11.4 vs. 8.3 months respectively) with an overall median follow up time of 33.7 months. Median overall survival with a median follow-up of 51.2 months was also significantly longer in favor of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.2 months respectively). Efficacy results are presented in Table 9 and Figures 8 and 9.

Table 9 - Efficacy of TAXOTERE in the induction treatment of patients with inoperable locally advanced SCCHN (Intent-to-Treat Analysis)

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

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

* Stratified log-rank test based on primary tumor site

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

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

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

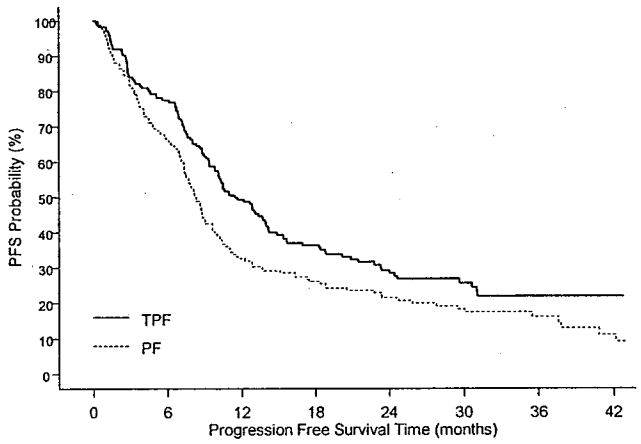


Figure 9 - TAX323 Overall Survival K-M Curve

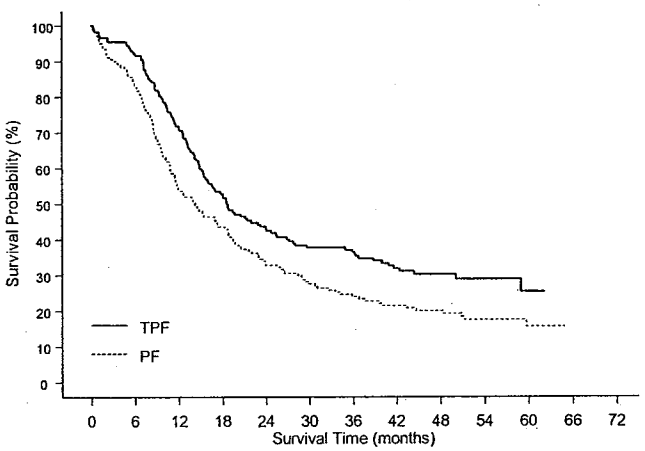


Table 18 lists the clinically important treatment emergent adverse events (regardless of relationship) in the TAX323 study.

Table 18 – Clinically Important Treatment Emergent Adverse Events (Regardless of Relationship) in Patients with SCCHN Receiving TAXOTERE in Combination with Cisplatin and fluorouracil (TAX 323).

	TAXOTERE 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=174		Cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 n=181	
Adverse Event	**Any %**	**G3/4 %**	**Any %**	**G3/4 %**
Neutropenia	93.1	76.3	86.7	52.8
Anemia	89.1	9.2	87.8	13.8
Thrombocytopenia	23.6	5.2	47.0	18.2
Infection	27.0	8.6	26.0	7.7
Fever in the absence of infection	31.6	0.6	36.5	0
Febrile neutropenia*	5.2	N/A	2.2	N/A
Neutropenic infection	13.9	N/A	8.3	N/A
Allergy	6.3	0	2.8	0
Fluid retention	20.1	0	14.4	0.6
Edema only	12.6	0	6.6	0
Weight gain only	5.7	0	6.1	0
Lethargy	40.8	3.4	38.1	3.3
Neurosensory	17.8	0.6	10.5	0.6
Dizziness	2.3	0	5.0	0.6
Alopecia	81.0	10.9	43.1	0
Rash/itch	11.5	0	6.1	0
Dry skin	5.7	0	1.7	0
Desquamation	4.0	0.6	5.5	0
Nausea	47.1	0.6	51.4	7.2
Stomatitis	42.5	4.0	47.0	11.0
Diarrhea	32.8	2.9	23.8	4.4
Vomiting	26.4	0.6	38.7	5.0
Anorexia	16.1	0.6	24.9	3.3
Constipation	16.7	0.6	16.0	1.1
Esophagitis/dysphagia/ Odynophagia	12.6	1.1	18.2	2.8
Gastrointestinal pain/cramping	7.5	0.6	8.8	0.6
Heartburn	6.3	0	6.1	0
Gastrointestinal bleeding	4.0	1.7	0	0
Taste, sense of smell altered	10.3	0	5.0	0
Cardiac dysrhythmia	1.7	1.7	1.7	0.6
Ischemia myocardial	1.7	1.7	0.6	0

	TAXOTERE 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=174		Cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 n=181	
Adverse Event	**Any %**	**G3/4 %**	**Any %**	**G3/4 %**
Venous	3.4	2.3	5.5	1.7
Myalgia	9.8	1.1	7.2	0
Cancer pain	20.7	4.6	16.0	3.3
Tearing	1.7	0	0.6	0
Conjunctivitis	1.1	0	1.1	0
Altered hearing	5.7	0	9.9	2.8
Weight loss	20.7	6.6	26.5	0.6

*Febrile neutropenia: grade ≥2 fever concomitant with grade 4 neutropenia requiring i.v. antibiotics and/or hospitalization.

The most frequent adverse events on the TPF arm were neutropenia (93%), anemia (89%), alopecia (81%), stomatitis/esophagitis (55%), and nausea (47%). Grade 3 or 4 adverse events with a greater than 5% frequency in patients on the TPF arm were neutropenia (76%), alopecia (11%), infection (9%), weight loss (7%), stomatitis/esophagitis (5%) and thrombocytopenia (5%). Approximately 5% of the TPF arm patients had febrile neutropenia and 14% had neutropenic infection. Compared to patients receiving PF, patients receiving TPF had more alopecia, neutropenia, diarrhea, neurosensory abnormality, neutropenic infection, fluid retention, and altered taste or sense of smell.

Clinical Review

The Clinical Review by Qin Ryan, M.D., Ph.D. was completed on October 6, 2006. Dr. Ryan's recommendation on regulatory action is quoted below.

> We recommend the approval of Taxotere in combination with cisplatin and fluorouracil for the following indication:
>
> "TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck."
>
> This recommendation is based on the review of the results of the sNDA, discussion within the divisions based on the improvement in Time to Tumor Progression supported by an improvement in overall survival and an acceptable toxicity profile.

Dr. Ryan had no recommendations for postmarketing actions, risk management activity, or phase 4 commitments.

Medical Team Leader Memo

The Medical Team Leader Memo by Amna Ibrahim, M.D. was completed on October 6, 2006. Dr. Ibrahim recommended that "This Taxotere supplemental NDA should be approved based on the improvement in Progression-free Survival and Overall Survival for the following indication:

TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck"

Clinical Inspection Summary

The Clinical Inspection Summary by Lauren Iacono-Connors, Ph.D. is dated July 17, 2006. A single study site that enrolled approximately 10% of the total study population was inspected. The overall assessment of findings and general recommendations are provided below.

> The study data collected by Eva Remenar appear reliable. The FDA investigator, Mr. Patrick Stone reported in preliminary communications to DSI that he audited 15 of 38 randomized subjects' records under the responsible care of Eva Remenar in the execution of study TAX323. Each of 15 subject's records, source documents, CRFs and sponsor-submitted data listings, were reconciled. Adverse events were recorded and reported in accordance with the protocol. No notable objectionable observations were made. An FDA Form 483 was not issued.
>
> Observations noted above are based on the preliminary communications provided the field investigator Mr. Patrick Stone. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

Statistical Review and Evaluation

The Statistical Review and Evaluation by Kun He was completed on September 15, 2006. The conclusions and recommendations are quoted below.

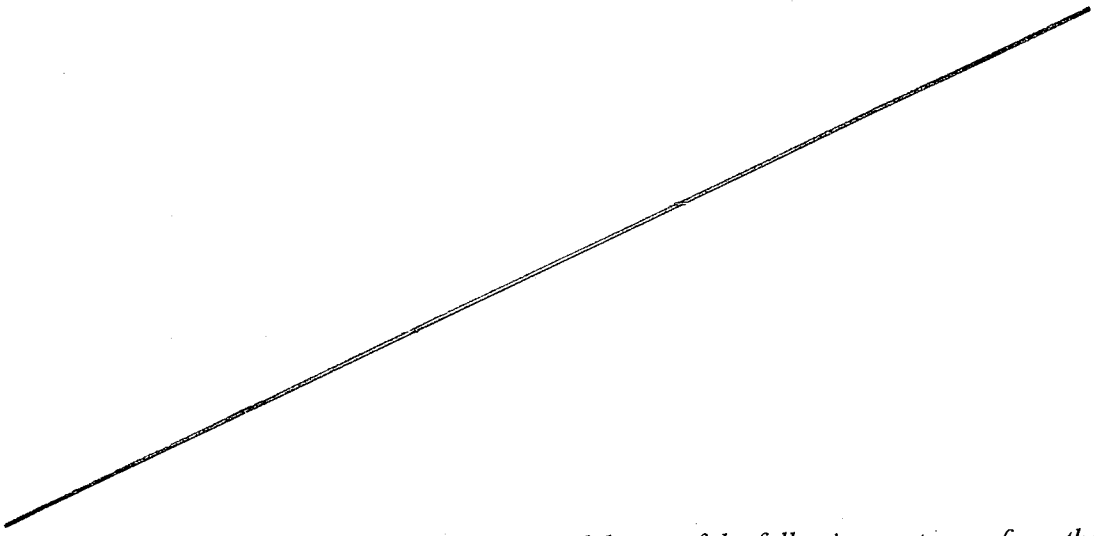
> The applicant is seeking an approval for Taxotere in combination with cisplatin and 5-fluorouracil for the induction treatment of patients with locally advanced inoperable squamous cell carcinoma of head and neck (SCCHN).
>
> The data and analyses from the current submission demonstrated that patients with locally advanced inoperable squamous cell carcinoma of head and neck in the Taxotere plus cisplatin and 5-FU (TPF) group had a larger median progression-free survival time (11.4 months, 95% CI: 10.1-14.0) than in the

cisplatin and 5-FU (PF) group (8.3 months, 95% CI: 7.4-9.1). The difference was approximately 3.1 months, had a nominal p-value .0077 based on a stratified log-rank test with the primary tumor site as stratification factor, and had a 29% progression risk reduction (HR 0.71, 95% CI: 0.56-0.91).

The updated overall survival data and analyses also demonstrated that patients in the Taxotere plus cisplatin and 5-FU (TPF) group had a larger median overall survival time (18.6 months, 95% CI: 15.7-24.0) than in the cisplatin and 5-FU (PF) group (14.2 months, 95% CI: 11.5-18.7). The difference was approximately 4.4 months, had a p-value .0055 based on a stratified log-rank test with the primary tumor site as stratification factor, and had a 29% progression risk reduction (HR 0.71, 95% CI: 0.56-0.90).

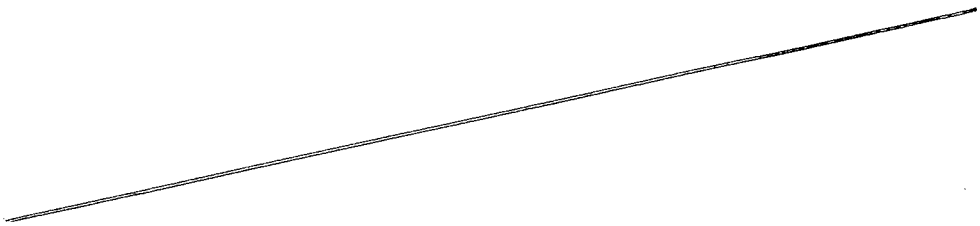
Study Endpoint Review

The Study Endpoint Review by Melissa Furness was completed on September 26, 2006 and had the following comments regarding the proposed package insert.



b(4)

2. Consequently, we recommend the deletion of the following sentences from the firm's April 14, 2006 proposed package insert:



b(4)

Chemistry Review

The Chemistry Review by Liang Zhou, Ph.D. was completed on October 10, 2006. The reviewer found the justification to support categorical exclusion from the environmental assessment requirements to be acceptable.

Conclusion

I concur with the reviewers' recommendations for approval of this efficacy supplement. The improvements in progression-free and overall survival resulting from the addition of docetaxel to cisplatin and fluorouracil as induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck were both clinically and statistically significant. Although patients receiving TPF had more alopecia, neutropenia, diarrhea, neurosensory abnormalities, neutropenic infections, fluid retention, and altered taste or sense of smell, these toxicities are outweighed by the demonstrated clinical benefit.

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

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

/s/

Robert Justice
10/13/2006 06:52:30 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449 / S-039

MEDICAL REVIEW(S)

Amendment to NDA Review
120 day safety up date and Post Marketing Risk Management

Application Type	NDA Supplement
Submission Number	20449
Submission Code	S39
Letter Date	April 14, 2006
Stamp Date	April 16, 2006
PDUFA Goal Date	October 17, 2006
Reviewer Name	Qin Ryan, MD, PhD
Original Review Completion Date	October 5, 2006
Amendment Date	October 14, 2006
Established Name	Docetaxel
Trade Name	Taxotere
Therapeutic Class	Antineoplastic
Applicant	Sanofi Aventis
Priority Designation	P
Formulation	IV
Dosing Regimen	75 mg/m2 in TPF combination
Indication	Squamous cell carcinoma of the head and neck."
Intended Population	Patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

1. **The safety update:**

The 120-day safety update for TAX 323, the pivotal randomized trial supporting the efficacy and safety of sNDA 20-449/S-039, did not include any new safety information, as all of the patients were off-study as of the cut-off dates used for compiling the TAX 323 CSR.

Both literature searches and ongoing postmarketing surveillance confirm the safety profile of Taxotere used in combination with cisplatin and 5-FU for the treatment of patients with advanced SCCHN presented in the TAX 323 CSR.

2. Post marketing risk management

As indicated in the original review, no new toxicity of Taxotere was identified in the study TAX323. Therefore, no new post marketing risk management is proposed for this new indication.

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

/s/

Qin Ryan
10/16/2006 08:37:42 AM
MEDICAL OFFICER

Amna Ibrahim
10/16/2006 08:46:49 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA Supplement
Submission Number	20449
Submission Code	S39
Letter Date	April 14, 2006
Stamp Date	April 16, 2006
PDUFA Goal Date	October 17, 2006
Reviewer Name	Qin Ryan, MD, PhD
Review Completion Date	October 5, 2006
Established Name	Docetaxel
Trade Name	Taxotere
Therapeutic Class	Antineoplastic
Applicant	Sanofi Aventis
Priority Designation	P
Formulation	IV
Dosing Regimen	75 mg/m2 in TPF combination
Indication	Squamous cell carcinoma of the head and neck."
Intended Population	Patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

Clinical Review
Qin Ryan MD, PhD
NDA 20449 S39
Taxotere (Docetaxel)

Table of Contents

FIGURES

TABLES

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

We recommend the approval of Taxotere in combination with cisplatin and fluorouracil for the following indication:

"TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck."

This recommendation is based on the review of the results of the sNDA, discussion within the divisions based on the improvement in Time to Tumor Progression supported by an improvement in overall survival and an acceptable toxicity profile.

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The safety and efficacy of Taxotere in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) were evaluated in a multicenter, open-label, two-arm randomized trial. In this study, 358 patients with previously untreated inoperable locally advanced SCCHN, and WHO performance status 0 or 1, received either Taxotere 75 mg/m^2 followed by cisplatin 75 mg/m^2 on Day 1, followed by fluorouracil 750 mg/m^2 per day as a

continuous infusion on Days 1-5 (TPF) or cisplatin 100 mg/m^2 on Day 1, followed by fluorouracil 1000 mg/m^2/day as a continuous infusion on Days 1-5 (PF).

Table 1: Treatment regimens use in study TAX 323

TPF	Docetaxel (T): 75 mg/m^2 IV administered first as a 1-hour infusion, day 1 every 3 weeks. Cisplatin (C): 75 mg/m^2, I.V. as a 3 to 4-hour infusion, day 1 every 3 weeks. 5-FU (F): 750 mg/m^2 CIV, day 1-5 every 3 weeks after the end of CDDP administration
PF	Cisplatin (C): 100 mg/m^2, day 1 as a 3 to 4-hour infusion every 3 weeks 5-FU (F): 1000 mg/m^2 CIV, day 1-5 every 3 weeks

Three hundred and fifty five patients were treated (TPF = 174, PF = 181). These regimens were administered every three weeks for 4 cycles. With a minimal interval of 4 weeks and a maximal interval of 7 weeks after chemotherapy, patients whose disease did not progress received radiotherapy. Locoregional therapy with radiation was delivered either with a conventional fraction, or an accelerated/hyperfractionated regimen of radiation therapy. Surgical resection was allowed following chemotherapy, before or after radiotherapy.

1.3.2 Efficacy

The primary endpoint in this study, progression-free survival (PFS, defined as time from randomization to disease progression or death from any cause, whichever occurred first), was significantly longer in the TPF arm compared to the PF arm, [hazard ratio 0.71 (0.56, 0.91)], p=0.0077 (median PFS: 11.4 vs. 8.3 months respectively) with an overall median follow up time of 33.7 months. Median overall survival with a median follow up of 51.2 months was also significantly longer in favor of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.2 months respectively) with hazard ratio of 0.71 (0.56, 0.90), Efficacy results are presented in the table below:

Table 2: Efficacy of Taxotere in the induction treatment of patients with inoperable locally advanced SCCHN (ITT)

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

TPF = Taxotere + Cisplatin + 5-FU, PF = Cisplatin + 5-FU, PFS = progression free survival, OS = overall survival.

A Hazard ratio of less than 1 favors TAXOTERE+Cisplatin+5-FU

* Stratified log-rank test based on primary tumor site

1.3.3 Safety

The safety data was obtained in 174 patients with locally advanced inoperable squamous cell carcninoma of the head and neck (SCCHN), who were treated with TAXOTERE 75 mg/m^2 in combination with cisplatin and 5-fluorouracil compared with 181 patients received cisplatin and fluorouracil.

The most frequent adverse events on the TPF arm were neutropenia (93%), anemia (89%), alopecia (81%), stomatitis/esophagitis (55%), and nausea (47%). Grade 3 or 4 adverse events with a greater than 5% frequency in patients on the TPF arm were neutropenia (76%), alopecia (11%), infection (9%), weight loss (7%), stomatitis/esophagitis (5%) and thrombocytopenia (5%). Approximately 5% of the TPF arm patients had febrile neutropenia and 14% had neutropenic infection. Compared to patients receiving PF, patients receiving TPF had more alopecia, neutropenia, diarrhea, neurosensory abnormality, neutropenic infection, fluid retention, and altered taste or sense of smell.

1.3.4 Dosing Regimen and Administration

For squamous cell carcinoma of the head and neck, the recommended dose of Taxotere is 75 mg/m^2 administered as a 1-hour intravenous infusion, followed by cisplatin 75 mg/m^2, as a 1 —— hour intravenous infusion (——on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as a ——— intravenous continuous infusion for 5 days. Treatment is repeated every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy. Patients must receive premedication with antiemetics and appropriate hydration (prior to and after cisplatin administration). b(4)

1.3.5 Special Populations

No special population analysis conducted for the following reasons:
1. There were only about 10% each of female and elderly (age > 65) participate TAX 323 study.
2. No ethnic recorded for the subjects who participated study TAX 323.

1.3.6 Significant Findings from Other Review Disciplines

The CMC, animal pharmacology and toxicology, or pharmacokinetic analysis and drug and drug interaction of Taxotere were review in the previous NDAs. No new data were submitted or reviewed this time.

2 Introduction and Background

2.1 Product Information

Established Name: docetaxel
Proprietary Name: Taxotere

Applicant: Sanofi Aventis Pharmaceuticals
Route 202-206
PO Box 6800
Bridgewater, NJ 08807-2800

Drug Class: Antineoplastic

Proposed Indication:

TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

Proposed Dosage and Administration
The dosing regimen as proposed by the applicant in the label is as follows:

For the neoadjuvant treatment of locally advanced inoperable squamous cell carcinoma of the head neck (SCCHN), the recommended dose of TAXOTERE is 75 mg/m^2 as a 1 hour infusion followed by cisplatin 75 mg/m^2 over 1 hour, on day one, followed by 5-fluorouracil as a continuous infusion at 750 mg/m^2 per day for five days, as shown below.

Table 3: Proposed chemotherapy regimen

Agent	Dose	Administration
Taxotere	75 mg/m^2	IV, 1 hour on day 1
cisplatin	75 mg/m^2	IV, 1 hour on day 1 following Taxotere
5-FU	750 mg/m^2/day	CIV following Cisplatin on day 1 through 5.

This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy. Patients must receive premedication with antiemetics and appropriate hydration (prior to and after cisplatin administration). [redacted] b(4)
[redacted]. For cisplatin and 5-fluorouracil dose modifications, see manufacturer's prescribing information.

2.2 Currently Available Treatment for Indications

Neoadjuvant chemotherapy with 5-FU and Cisplatin followed by local radiotherapy with the option of surgery for locally advanced, inoperable head and neck squamous cell carcinoma.

2.3 Availability of Proposed Active Ingredient in the United States

Taxotere is presently marketed in US for 6 indications and regimens which are listed in the table below:

Table 4: Taxotere current indications and usages

Year of approval	Taxotere Indications	Taxotere Dose and Schedule
1996, 1999	locally advanced or metastatic breast cancer after failure of prior chemotherapy	60-100 mg/m^2 administered intravenously over 1 hour every 3 weeks
2004	in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer	75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities
1999	locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy	75 mg/m^2 administered intravenously over 1 hour every 3 weeks
2002	in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition	75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks
2004	in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer	75 mg/m^2 every 3 weeks as a 1 hour infusion. Prednisone 5 mg orally twice daily is administered continuously
2006	in combination with cisplatin and 5-FU indicated for the treatment of patients with advanced gastric adenocarcinoma, including gestroesophageal junction, who have not received chemotherapy for advanced gastric cancer	75 mg/m2 as a 1 hour infusion, followed by cisplatin 75 mg/m2, as a 1 to 3 hour infusion (both on day 1 only), followed by 5-fluorouracil 750 mg/m2 per day given as a 24-hour continuous infusion for 5 days, repeat every 3 weeks.

2.4 Important Issues With Pharmacologically Related Products

The dose limiting toxicity of Taxotere was myelosupression, fluid retention and fatigue.

2.5 Presubmission Regulatory Activity

No special protocol assessment or EOP2 meeting conducted regarding study TAX 323.

1-25-2006, pre-NDA meeting FDA and applicant met to discuss design and results of study TAX 322, 323 and 324, for sNDA. The finding of TAX 323 was positive whereas TAX 322, with a different study design and patient population, was negative. The TAX 324 (enrollment and randomization between May 21, 1999 and December 3, 2003) has the best study design of the 3, but the cut off date for overall survival analysis was December 3, 2005. It was agreed that the pivotal study TAX 323 will be submitted to support efficacy claim and a survival up date (6 month after the cut off date) will be submitted during the NDA review. Due to the apparent imbalances of surgery and radiation between TAX 323 arms, FDA requested a summary of survival analysis of TAX 324 to confirm the TAX 323 result and strengthen this sNDA.

2.6 Other Relevant Background Information

5/14/96 Approved for use in patients with locally advanced or metastatic breast cancer who have progressed or relapsed during anthracycline-based therapy (original NDA 20449).

b(4)

12/23/99 Approved for use in locally advanced or metastatic breast cancer after failure of prior chemotherapy (S-005).

12/23/99 Approved for use in locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy (S-011).

02/01/02 Approved in combination with cisplatin for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition (S-018).

5/19/04 Approved for use of Taxotere q3 weeks in combination with prednisone in the treatment of metastatic hormone-refractory prostate cancer (S-028).

8/18/04 Approved for use of Taxotere in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer (S29).

3/24/2006 Approved for use of Taxotere in combination with cisplatin and 5-FU for advanced or metastatic gastric carcinoma.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This sNDA application is based on 3 comparative study of TPF combination in chemotherapy naïve advanced gastric cancer patients, TAX 323, TAX 324 (summary only), and TAX 322 (summary requested by FDA), with support of two TPF combination Phase 1-II studies (TAX 017 and TAX 708). The TAX 323 study is most relevant to the proposed indication.

4.2 Tables of Clinical Studies

Table 5: Clinical Studies Included in sNDA 20491 SE 35

Study	Title	Subjects (n)
TAX 323	A randomized phase III multicenter trial of neoadjuvant docetaxel (Taxotere) plus cisplatin plus 5-fluorouracil (5-FU) versus neoadjuvant cisplatin plus 5-fluorouracil in patients with locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN)	358
TAX 017	Docetaxel in combination with cisplatin and 5-fluorouracil in patients with advanced, previously untreated squamous cell carcinoma of the head and neck : phase I-II study	43
TAX 708	A phase I/II pilot study of neoadjuvant chemotherapy with docetaxel in combination with cisplatin and 5-fluorouracil (5-FU) in locally advanced squamous cell carcinoma of the head and neck (SCCHN)	48
TAX 324*	A Randomized Phase III Multicenter Trial of Neoadjuvant Docetaxel (Taxotere®) Plus Cisplatin and 5-Fluorouracil (TPF) Versus Neoadjuvant Cisplatin Plus 5 Fluorouracil Followed by Concomitant Chemoradiotherapy to Improve the Overall Survival and Progression Free Survival in Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck	538
TAX 322*	A randomized phase II-III multicenter trial of docetaxel (taxotere.) plus cisplatin and docetaxel plus 5-fluorouracil (5-FU) versus cisplatin plus 5-fluorouracil to improve time to progression and overall survival in the first line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck	102/236 evaluable for phase 3 study

* A preliminary summary of efficacy and safety TAX 324 was submitted with this sNDAas per FDA request. The randomized study TAX 322, which was not included in this NDA, was also completed and did not demonstrate efficacy. The reviewer requested a summary of this study.

Reviewer Note: TAX 323 provided major efficacy and safety evidence. The safety is supported by TAX 017 and 708. The study report of the pharmacokinetic interaction study TAX 1001, A pharmacokinetic interaction study of 75 mg/m^2 of docetaxel (RP56976, Taxotere) plus cisplatin (75 mg/m^2) and 5- FU (750 mg/m^2/day for 5 days) in the treatment of patients with recurrent or metastatic solid tumors, is available in Section 5.3.3.4 of the previous dossier submitted for the indication for the treatment of advanced gastric adenocarcinoma.

4.3 Review Strategy

This NDA clinical review is primarily based on the efficacy and safety data of TAX 323, which are most relevant to the proposed indication. The electronic submission, with the CSRs, and other relevant portions of TAX 323 were reviewed and analyzed. The study summary of TAX 324 and TAX 322 were also reviewed. The key review materials and activities are outlined as blow:
the electronic submission of the sNDA;
relevant published literature;
relevant submissions in response to medical officer's questions;
sponsor presentation slides to FDA on Nov. 2nd, 2005;
major efficacy and safety analyses reproduced or audited using the SAS datasets using raw data;
other non-clinical review;
Discussion's with consultants.

An ODAC consultant, Dr. , was consulted to discuss efficacy and safety results. A SEALD consult was requested to assist in evaluation the Quality of Life data.

4.4 Data Quality and Integrity

A number of methods were utilized in order to evaluate the quality and integrity of the data from study TAX 323 as outlined below:

Clinical inspections: The clinical inspection was focused on the trial TAX 323 since it provided the most crucial efficacy data for this NDA application. The Division of Scientific Investigations (DSI), Clinical Practice Branch I, conducted clinical inspection of one site of study TAX 323 in the Hungary. A number of factors were considered for site selection, including accrual numbers and data documentation. Conflicts of interest of investigator would be considering factor if there was any claim. However, there was no claim of conflicts of interest for study TAX 323. The response rate was not the primary endpoint in this study and therefore, the site selection was primarily based on the accrual numbers. Only one site with highest enrollment was selected for inspection, site of principle investigator, Dr. Eva Emenar (Orszagos onkologigai Intezet, H-1122 Budapast, Rath Gyorgy u. 7/9). The inspectors of DSI found that Trial conduction in accordance with accepted ethical standards and no major deficiency were noted.

The medical and statistical reviewers have conducted independent efficacy and safety analyses based on the primary data submitted in SAS transport format and the JMP counterpart. Any discrepancies between the reviewers' results and those of the sponsor are disclosed in relevant sections of this joint medical/statistical review.

Case report forms in electronic format were reviewed in selected patients. The CRF were randomly sampled at one per each country initially. Problem oriented samplings on specific files were used along the review process. There were about 30 CRFs reviewed in various details.

4.5 Compliance with Good Clinical Practices

According to the applicant, "Clinical trials adhered to the International Conference on Harmonization guidelines for Good Clinical Practice. Subjects and volunteers were accorded all rights granted by the Declaration of Helsinki. All protocols received approval by the appropriate governing investigational review board, ethics committee, or similar authority. Standard research methodology was utilized for the conduct and performance of each clinical trial under consideration." No major violations were found by DSI during their audit.

4.6 Financial Disclosures

Certification of financial disclosure was provided by Sanofi Aventis. There were total of 188 investigators participated TAX 325/325a trial and 164 of them claimed no financial interest in the study. Twenty -four of them (12.8%) failed to disclose their financial interest due relocation during the early stage of the study and lost contact. However, these investigator did not have impact on the results of this study, since no patient enrolled by them.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the neoadjuvant treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

6.1.1 Methods

As described in section 4.1 and 4.3, the efficacy review is primarily based on the TAX 323 data.

6.1.2 General Discussion of Endpoints

The primary endpoint of TAX 323 is Progression Free Survival (PFS) with the study powered for overall survival. The PFS is measured from the date of randomization until the date of progression or the date of death of any reason, which ever occur first. The survival is measured from the date of randomization up to the date of death of any reason.

For newly diagnosed local regional advanced HNSCC patients, neoadjuvant chemotherapy in conjunction to definitive radiotherapy and/or surgery, the local recurrence and distant metastasis is the major concern. The PFS measurement in combination with overall survival should be able to adequately reflect the treatment effectiveness in this particular disease setting. Therefore, this design is adequate to assess clinical benefit for proposed indication. However, the apparent

imbalance of surgical and radiation treatment between the two arms may introduce bias to the PFS and survival outcome.

The disease progression and response is determined by WHO criteria. The disease progression is defined as follows:

25% increase in the size of at least 1 bidimensionally or unidementional measurable lesion (in comparison with the measurements at its nadir) or appearance of a new lesion.
The occurrence of pleural effusion or ascites was also considered as PD if this was substantiated by positive cytology.
Pathological fracture or collapse of bone was not necessarily evidence of disease progression.

6.1.3 Study Design

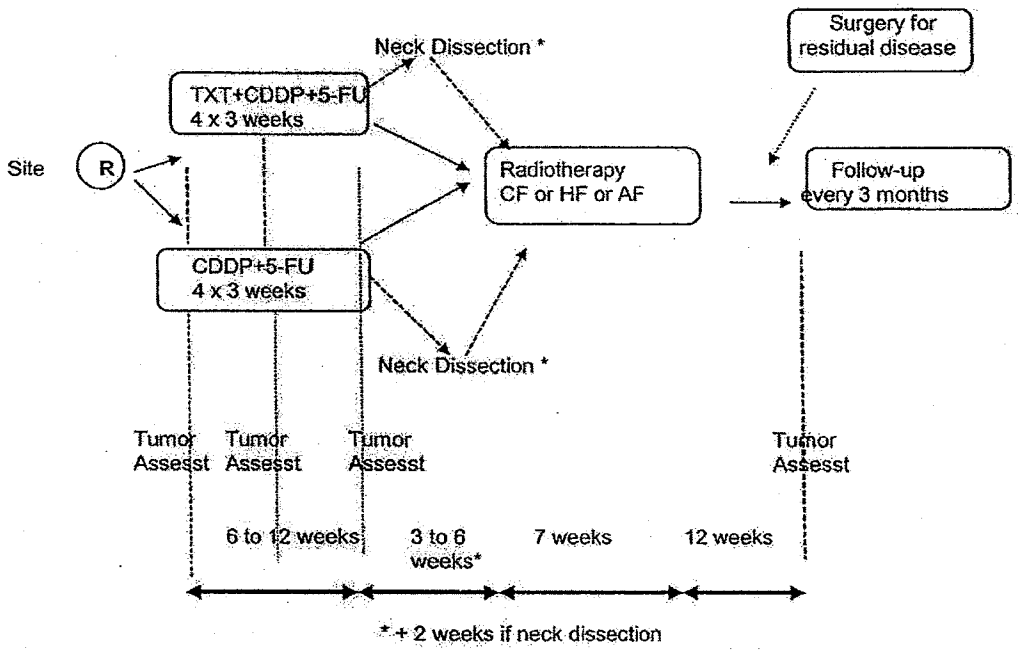
Study TAX 323 is a multicenter, non blinded, randomized phase Ill study comparing two combination chemotherapy regimens as neoadjuvant treatment before radiotherapy for locally advanced inoperable SCCHN. Patients will be randomized to receive either the test triple therapy (TPF: Taxotere 75 mg/m^2 + cisplatin 75 mg/m^2 + 5-fluorouracil 750 mg/m^2/day CIV for five days) or the control treatment (PF: cisplatin 100 mg/m^2 + 5-fluorouracil 1000 mg/m^2/day CIV for five days), followed by radiotherapy in both groups. Random assignment of patients in the 2 arms will be carried out centrally using the minimization technique.

Major eligibility criteria were (1) Histologically or cytologically proven squamous cell carcinoma of the head and neck presenting with locally advanced disease at diagnosis. Primary tumor sites of the nasopharynx, the nasal and paranasal cavities were excluded., (2) measurable disease, (3) No previous chemotherapy or radiotherapy, (4) Age between 18 and 70 years, (5) WHO performance status 0 or 1, (6) Excluding pregnant, lactating women or of childbearing potential unless adequate contraception, and (7) adequate renal, hepatic and bone marrow function.

Patients were stratified at inclusion by the following categories:
primary tumor site (oral cavity versus oropharynx versus hypopharynx versus larynx)
institution

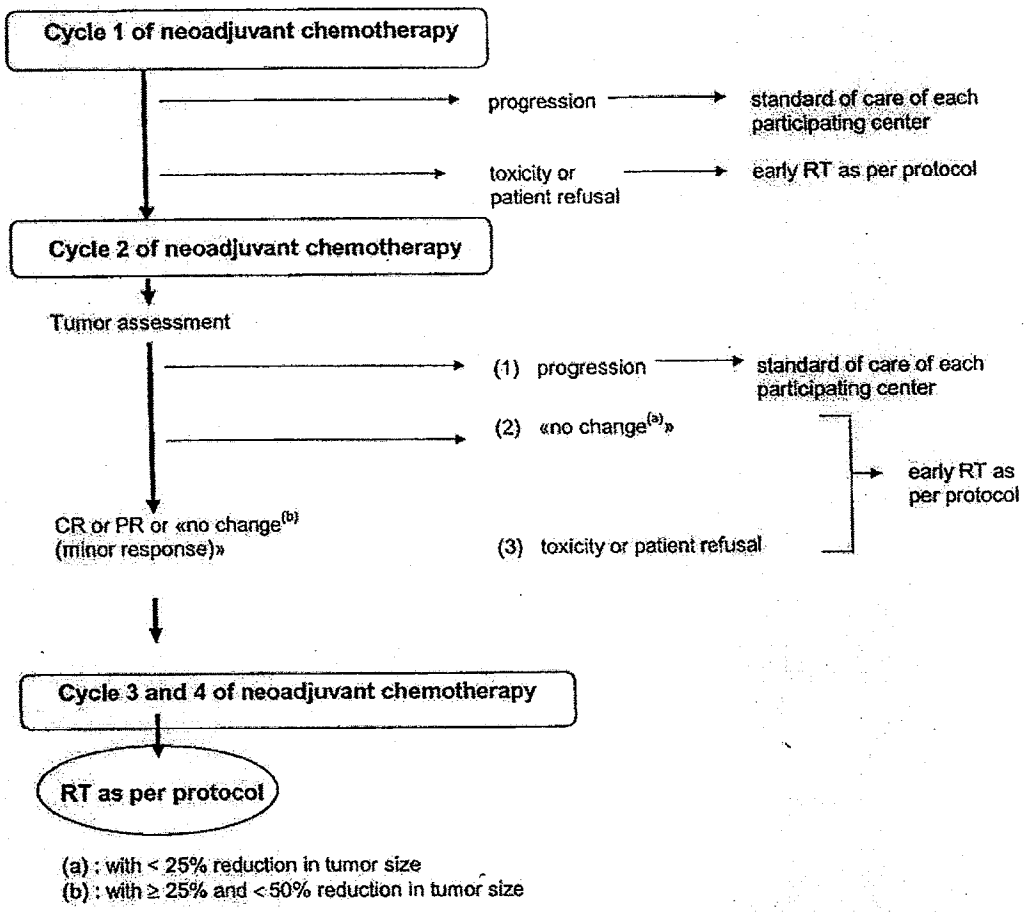
The trial is described in the figure below:

Figure 1: Study design



Reviewer Note: Therefore, the chemoradiation is the standard treatment for HNSCC patients in US, since the chemoradiation with cisplatin is superior than radiation in CR rate and survival.

Figure 2: Tumor Assessment Guided Treatment Decision During Neoadjuvant Chemotherapy



Reviewer note: The US standard primary therapy for locally advanced, inoperable HNSCC patients is chemoradiotherapy with or without preceding neoadjuvant chemotherapy. However, the study 323 used radiotherapy alone after neoadjuvant chemotherapy, which is considered suboptimal the targeted patient population. In addition, two optional windows for surgical removal of residual disease introduced more variables into the study. With all above concerns, the reviewer has requested brief reports of study TAX 324 and 322 as supporting information to this NDA. Based on the sponsor provided information, the study TAX 324 appears to have a better design in the similar patient population. Study TAX 324 has been submitted for information purpose only and not been submitted as a major study with data for the NDA. The FDA is not able to verify TAX 324 efficacy results. The study TAX 323 was done in a different patient population.

6.1.4 Efficacy Findings

In study TAX 323, a total of 358 patients were randomized between 14 April 1999 and 15 March 2002. One hundred and seventy-four (174) patients were treated with TPF, and 181 patients were treated with PF. The demographic characteristics of two treatment groups at baseline are shown as below.

Table 6: Patient demographics at baseline

	Randomization group		
	TPF (N=177)	PF (N=181)	All (N=358)
Sex			
Male	159 (89.8%)	162 (89.5%)	321 (89.7%)
Female	18 (10.2%)	19 (10.5%)	37 (10.3%)
Age (Years)			
Median	53	52	53
Minimum	30	30	30
Maximum	69	70	70
Age (Years)			
< 35	2 (1.1%)	4 (2.2%)	6 (1.7%)
[35-50[	53 (29.9%)	59 (32.6%)	112 (31.3%)
[50-65[	104 (58.8%)	100 (55.2%)	204 (57.0%)
[65-75[	18 (10.2%)	18 (9.9%)	36 (10.1%)
Height (cm)			
Median	170	170	170
Minimum	149	147	147
Maximum	194	192	194
Weight at Cycle 1 (kg)			
Median	64.30	65.00	65.00
Minimum	43.00	34.00	34.00
Maximum	108.00	101.00	108.00
PS WHO			
0	90 (50.8%)	91 (50.3%)	181 (50.6%)
1	86 (48.6%)	90 (49.7%)	176 (49.2%)
2	1 (0.6%)	0 (0.0%)	1 (0.3%)

TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; PS = performance status; WHO = World Health Organization Note: [x-y[refers to a range including x and excluding y
Data source: TAX323 study report.

Reviewer: The distribution of demographics appears to be balanced between the two arms. There were only about 10% each of female and elderly (age > 65). The primary disease and tumor characteristics also appear to be balanced between the two arms (Table 47and Table 48).

No information is available regarding race subgroup, since race data was not recorded for TAX 323.

The cut-off date of 21 September 2003 was used in all efficacy analyses included in the clinical study report (dated 09 February 2006).

6.1.4.1 TAX 323 Progression Free Survival (PFS)

As per study TAX 323 design, study patients received one or more treatments after randomization as summarized below.

Table 7: All randomized patients and treatment received (ITT)

Number of patients (%)	Randomized population in the treatment received		
	TPF (N=174)	PF (N=181)	All (N=358)
Received chemotherapy	174 (100.0%)	181 (100.0%)	355 (99.2%)
Received radiotherapy	130 (74.7%)	124 (68.5%)	254 (70.9%)
Received surgery	45 (25.9)	27 (14.9%)	72 (20.4%)

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Data source: TAX study report 323

The cut off date, September 21, 2003, corresponds of the 260th event was reported to the EORTC data center. At this cut off date, as summarized below, 273 events (PD or death) has been observed in 358 subjects (76.3%), with 10% more events observed in PF arm than that of TPF. Progression of disease accounted for the majority of events (218 of 273 events). The lost to follow-up was 2.5% (TPF and PF). Because the higher rate of PFS events on PF arm, there were 6% and 10% less patients received per protocol radiotherapy and surgery on PF arm, respectively.

Table 8: TAX 323 Patient Disposition at Progression-Free Survival Analysis Cut off Date (ITT)

	RANDOMIZATION GROUP		
	TPF (N=177)	PF (N=181)	ALL (N=358)
Number of patients with			
event	126 (71.2%)	147 (81.2%)	273 (76.3%)
censored data	51 (28.8%)	34 (18.8%)	85 (23.7%)
Event reasons (PFS)			
Progression	101 (57.1%)	117 (64.6%)	218 (60.9%)
Death	25 (14.1%)	30 (16.6%)	55 (15.4%)
Censoring reasons (PFS)			
Lost to follow-up	5 (2.8%)	4 (2.2%)	9 (2.5%)
No event at cutoff date	46 (26.0%)	30 (16.6%)	76 (21.2%)

ITT= intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; PFS = progression-free survival
Data source: TAX 323 study report

Reviewer Note: At the time of final PFS analysis, the PFS events rates were 71% for TPF arm and 81% for PF arm. The disease progression rate for TPF arm was 7.3% lower than that of PF arm, whereas the death rate for TPF arm was 2% lower. The statistical reviewer confirmed sponsor's PFS analysis. With the concern of open label design of study TAX 323, the medical reviewer examined data sets and sampled 10% CRFs, and find that tumor staging and event determination were satisfactory.

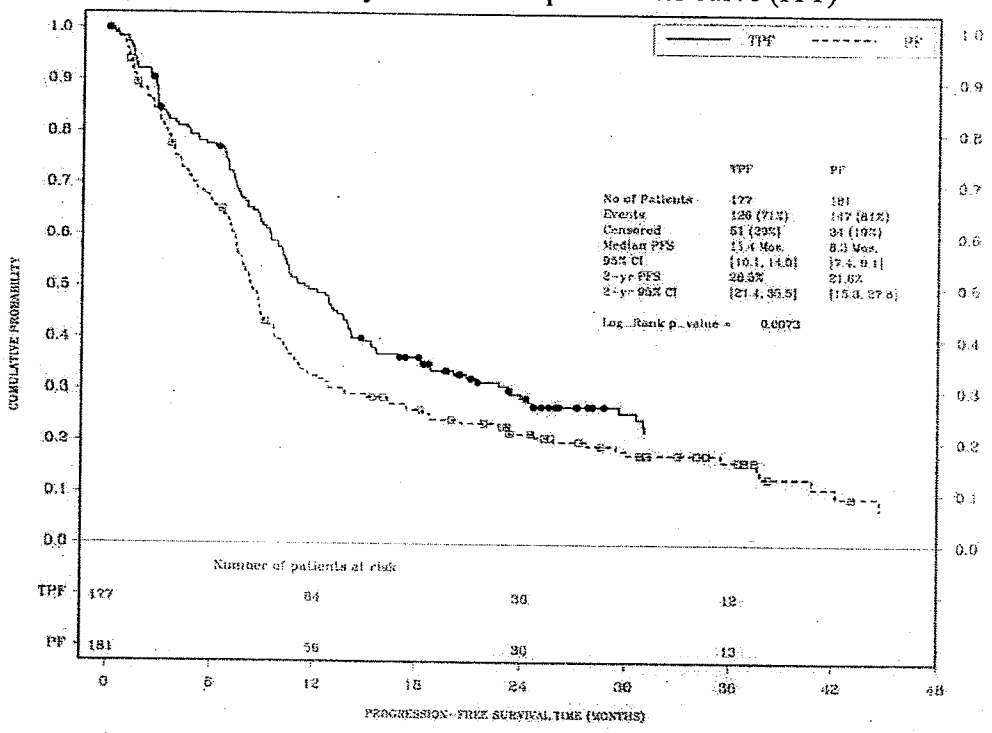
Applicant's summary statistics and Kaplan-Meier plot are shown below:

Table 9: TAX 323 final analysis: PFS (ITT)

	Randomization group	
	TPF (N=177)	PF (N=181)
Median PFS (months) [95% CI]	11.4 [10.1 - 14.0]	8.3 [7.4 - 9.1]
Kaplan-Meier estimates for PFS		
1-year estimate [95% CI]	49.3% [41.8 - 56.8]	32.6% [25.7 - 39.6]
2-year estimate [95% CI]	28.5% [21.4 - 35.5]	21.6% [15.3 - 27.8]
3-year estimate [95% CI]	22.0% [14.8 - 29.1]	16.2% [10.1 - 22.2]
Hazard ratio: TPF/PF [95% CI]	0.72 [0.57 - 0.92]	
Log-Rank p value	0.0073	

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; PFS = progression-free survival; CI = confidence interval
Data source: TAX 323 study report

Figure 3: TAX 323 final analuysis: PFS – Kaplan-Meier curve (ITT)



ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Event = progression of disease, relapse or death.
Data source: TAX 323 study report.

Reviewer note: As log-rank test indicated, the median PFS of TPF arm is 3.1 month longer than PF arm with statistical significance (p = 0.0073). The PFS data is mature at the cut off day with no further up date required. The FDA statistical reviewer's log-rank analysis on TAX 323 PFS results were same as that of the sponsor.

The potential effects of baseline prognostic factors on PFS are analyzed by the applicant using the Cox model:

Table 10: Cox proportional hazards model – TAX 323 progression-free survival (ITT)

	Adjusted treatment effect on prospectively selected covariates			
			95% CI	
Covariate	P value	Hazard ratio	Lower	Upper
Randomization group: TPF / PF	0.0042	0.70	0.55	0.89
WHO performance score: PS null/ PS ≥ 1	0.0322	0.77	0.61	0.98
N stage: N2-3/N0-N1-NX	0.0360	1.34	1.02	1.77
Hypopharynx primary: yes/no [a]	0.0616	1.01	0.60	1.72
Oropharynx primary: yes/no [a]		0.77	0.46	1.29
Oral cavity primary: yes/no [a]		1.17	0.67	2.06
T stage: T4/T2-T3-T1	0.7495	1.05	0.78	1.41

ITT = intent-to-treat; CI = confidence interval; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; WHO = World Health Organization; PS = performance status
a The reference for each primary site variable is the larynx primary site. Then, these variables were evaluated with a single test.
Data source: TAX 323 study report.

Reviewer note: Similar to the existing data, the following covariates were statistically significant, confirming their prognostic value: WHO PS (P = 0.0322) and N stage (P = 0.0360). The primary site covariate was borderline (0.0616). All this factors were balanced between the two arms. These have been verified by the FDA statistical and medical reviewer.

More subsequent anti-cancer therapies were given post study for the TPF arm patients who did not received radiotherapy per protocol (29.5%, n=44) than that of the PF arm (12.3%, n=57). Table below has summarized all subsequent anticancer therapy after study treatment including chemotherapy, radiotherapy and surgery. The reviewer has verified the result by using sponsor provided data sets.

Table 11: Tax 323 further anti-cancer therapy during follow-up

	Treatment received			
	With radiotherapy as per protocol		Without radiotherapy as per protocol	
Further anticancer therapy	TPF (N=130)	PF (N=124)	TPF (N=44)	PF (N=57)
Number of patients with no further therapy	99 (76.2%)	86 (69.4%)	13 (29.5%)	26 (45.6%)
Number of patients with at least 1 further therapy	31 (23.8%)	38 (30.6%)	31 (70.5%)	31 (54.4%)
Chemotherapy	25 (19.2%)	29 (23.4%)	13 (29.5%)	7 (12.3%)
Radiotherapy	8 (6.2%)	6 (4.8%)	27 (61.4%)	30 (52.6%)
Surgery	17 (13.1%)	12 (9.7%)	11 (25.0%)	6 (10.5%)
Missing			1 (2.3%)	

TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Note: A patient may have several type of further therapy
Data source: TAX 323 study report

Reviewer note: With the questions of whether the imbalance in number of patients received per protocol surgery between the two arms is truly due to PF arm had more PFS events, and whether subsequent treatments and the type of the subsequent treatment would influence DFS and survival, the applicant conducted sensitivity analyses as shown below.

Table 12: TAX 323 sensitivity analyses of PFS with censoring specific factors (ITT, TPF/PF)

Censored Factor	HR	p-value
Non-tumor related death	0.71	0.0083
Surgery	0.76	0.0294
Further therapies	0.71	0.0048
Death 30 days due to toxicity	0.74	0.0168

Reviewer: However, the sponsor did not provide justification for the apparent imbalance of RT (74.7% for TPF and 68.5% for PF). The sensitivity analysis of PFS regarding radiotherapy was not performed because the large percentage patients who received radiotherapy would have to be censored and the number of events for the analysis would be too small. FDA statistical and medical reviewers investigated potential imbalance of radiation therapy between the two arms. The frequency and timing of PFS events in patients received or not received per protocol radiotherapy are tabulated as below.

Table 13: The frequency and timing of PFS events in patients with or without per protocol radiotherapy (ITT)

PSF events frequency and timing				TPF (N=177)	PF (N=181)
Radiotherapy	Total			130 (73.4%)	124 (68.5%)
	Event			83 (63.8%)	92 (74.2%)
	Censored			47 (36.2%)	32 (25.8%)
No Radiotherapy	Total			47 (26.6%)	57 (31.5%)
	Event	Total		43 (91.5%)	55 (96.5%)
		< 3.4 Months		33 (70.2%)	38 (66.7%)
		≥ 3.4 Months		14 (29.8%)	19 (33.3%)
			Event	13 (92.9%)	19 (100%)
			Censored	1 (7.1%)	0 (0%)
	Censored			4 (8.5%)	2 (3.5%)

Reviewer: According to the protocol, the radiotherapy starting time is 3 months. Actually, the median time from the chemotherapy starting date to radiotherapy starting date were 3.47 and 3.43 months for TPF and PF, respectively. Using 3.4 months as a cut-off time, patients whose PFS times are less than 3.4 months shouldn't receive per protocol radiotherapy, due to an event of disease progression or death. Patients whose PFS are greater than 3.4 months and did not receive per protocol radiotherapy, were 14/177 (7.9%) in TPF arm and 19/181 (10.5%) in PF arm. Only 2.6% more patients whose PFS > 3.4 months on PF arm did not received radiotherapy. Therefore, the reason that 5% less patients on PF arm received per protocol radiotherapy is mainly due to disease progression during chemotherapy (<3.4 months).

The PFS subgroup analyses by gender and age was conducted by FDA statistician (below):

Table 14: PFS analyses by subgroup (ITT)

Subgroup	Characteristics	Number (%) Months [95% CI]	TPF (N=177)	PF (N=181)
Gender	Male	Event Median	115/159 (72.3%) 11.0 [9.4 – 14.0]	131/162 (80.9%) 8.2 [7.4 – 9.0]
	Female	Event Median	11/18 (61.1%) 13.7 [10.4 -]	16/19 (75%) 10.2 [6.6 – 22.8]
Age	< 65	Event Median	112/159 (70.4%) 11.7 [9.9 – 14.0]	132/163 (81.0%) 8.6 [7.5 – 9.9]
	≥ 65	Event Median	14/18 (77.7%) 10.6 [7.2 – 14.9]	15/18 (83.3%) 7.1 [3.7 – 9.0]

Reviewer: In consistent with the primary PFS analysis, lower percentage of events and longer median PFS is observed in all subgroups for TPF arm.

6.1.4.2 Overall Survival (OS)

6.1.4.2.1 TAX 323 Overall Survival Analysis (at PFS cut off date)

At the study TAX 323 cut off date, 237 of 358 (66.2%) patients had died. Median follow-up time was 33.7 months, ranging from 13 months to 53 months. The number of events and censored data are summarized in table below, including reasons for censoring.

Table 15: TAX 323 event and censoring for overall survival (ITT)

	RANDOMIZATION GROUP		
	TPF (N=177)	PF (N=181)	ALL (N=358)
Number of patients with			
event	108 (61.0%)	129 (71.3%)	237 (66.2%)
censored data	69 (39.0%)	52 (28.7%)	121 (33.8%)
Censoring reasons (Survival)			
Lost to follow-up [a]	6 (3.4%)	8 (4.4%)	14 (3.9%)
No event at cutoff date	63 (35.6%)	44 (24.3%)	107 (29.9%)

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU Patient 00047 (randomized in TPF group) died from progressive disease but date of death is ———, by convention the date is set to ———
a Includes one patient (PF) not declared as lost to follow-up, for whom date of last contact was before cutoff date.
Data source: TAX 323 study report.

b(6)

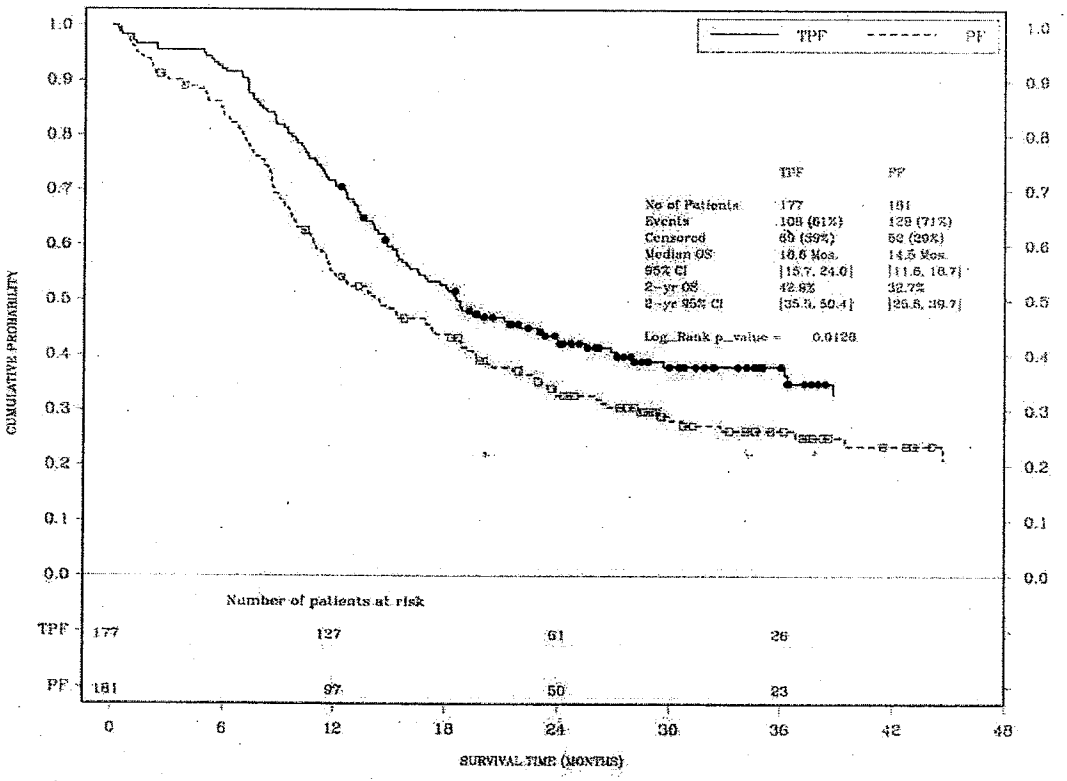
The overall survival analysis of TAX 323 is summarized as below.

Table 16: TAX 323 Overall Survival Analysis (ITT)

	Randomization group	
	TPF (N=177)	PF (N=181)
Median overall survival (months) [95% CI]	18.6 [15.7 - 24.0]	14.5 [11.6 - 18.7]
Kaplan-Meier estimates for overall survival		
1-year estimate [95% CI]	71.8% [65.1 - 78.4]	54.7% [47.4 - 62.0]
2-year estimate [95% CI]	42.9% [35.5 - 50.4]	32.7% [25.6 - 39.7]
3-year estimate [95% CI]	37.9% [30.3 - 45.5]	26.3% [19.4 - 33.3]
Hazard ratio: TPF/PF [95% CI]	0.72 [0.56 - 0.93]	
Log-Rank p value	0.0128	

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; CI = confidence interval
Data source: TAX 323 study report.

Figure 4: TAX 323Overall Survival – Kaplan-Meier Curve (ITT)



ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU Event = death
Data source: TAX 323 study report.

Reviewer: For TAX 323, the median survival of TPF was 4.1 month longer than that of PF with HR of 0.72 and statistically significant log rank test (p = 0.0128). The estimated 2-year and 3-year survival rates were also better for TPF arm. The medical and statistical reviewers

confirmed this result and point out that the upper limit of 95% CI for hazard ration (derived from 0.935) should be 0.94, in stead of 0.93 as in the TAX 323 study report.

Tax 323 Multivariable OS Analysis

Table 17: TAX 323OS Multivariable Analysis on Prognostic Factors Using Cox Proportional Hazards Models (ITT)

	Adjusted Treatment Effect on Prospectively Selected Covariates			
			95% CI	
Covariates	p-value	Hazard Ratio	Lower	Upper
WHO performance score: PS null/ PS >=1	0.0005	0.64	0.49	0.82
Randomization group: TPF / PF	0.0118	0.72	0.56	0.93
N stage: N2-3/N0-N1-NX	0.0500	1.36	1.00	1.84
Oral cavity primary: yes/no *	0.0711	1.79	0.99	3.25
Hypopharynx primary: yes/no *	.	1.44	0.82	2.55
Oropharynx primary: yes/no *	.	1.17	0.68	2.04

Reviewer: In study TAX 323, although both were balanced between the two arms, PS and N stage are statistically significant prognostic factors that influence OS.

Sensitivity OS Analysis of TAX 323

Table 18: TAX 323 Sensitivity Analyses of OS with Censoring Specific Factors (ITT, TPF/PF)

Censored Factor	HR	p-value
Non-tumor related death	0.71	0.0083
Surgery before PD	0.79	0.0809
All Surgeries (before and after PD)	0.70	0.0129
Death 30 days due to toxicity	0.75	0.0304

Reviewer: With Surgery before PD censored, the TPF does not have statistically significant OS advantage. Whereas when all surgery censored, the TPF does have significant OS advantage. The toxic death within 30 days or non tumor related death did not affect TPF OS advantage. The medical and statistical reviewers verified these results. Please note that the multiple sensitivity analyses are considered as exploratory only, since they were not adjusted for statistical significance.

Please note that above OS analysis is based on the PFS cut off date (260 PFS events and 253 deaths), and about 66% OS event were observed. To further confirm this result, an up date of OS analysis was submitted by the applicant for review, as shown below.

6.1.4.2.2 TAX 323 Overall Survival Update

The present report is an updated analysis of OS, extending the follow-up period by 18 additional months. The cut-off date is 21 March 2005 corresponds to an overall follow-up of 51.2 months

by the Kaplan-Meier method. A summary of events at this cut off date is presented as below. The proportion of patients lost to follow-up was similar in the 2 treatment groups (4.7% overall).

Table 19: Event Summary of Study TAX 323 at Cut Off Date 21 March 2005 (ITT)

	TREATMENT GROUP		
	TPF (N=177)	PF (N=181)	ALL (N=358)
Number of patients with			
event	122 (68.9%)	146 (80.7%)	268 (74.9%)
censored data	55 (31.1%)	35 (19.3%)	90 (25.1%)
Censoring reasons (Survival)			
Lost to follow-up	8 (4.5%)	9 (5.0%)	17 (4.7%)
Date of last contact before the cut-off date	15 (8.5%)	5 (2.8%)	20 (5.6%)
No event at cutoff date	32 (18.1%)	21 (11.6%)	53 (14.8%)

One patient, ID00047, (randomized to the TPF treatment group) died from progressive disease but date of death is unknown in [redacted], by convention, the date is set to [redacted]
Data source: Study TAX 323 efficacies update.

b(6)

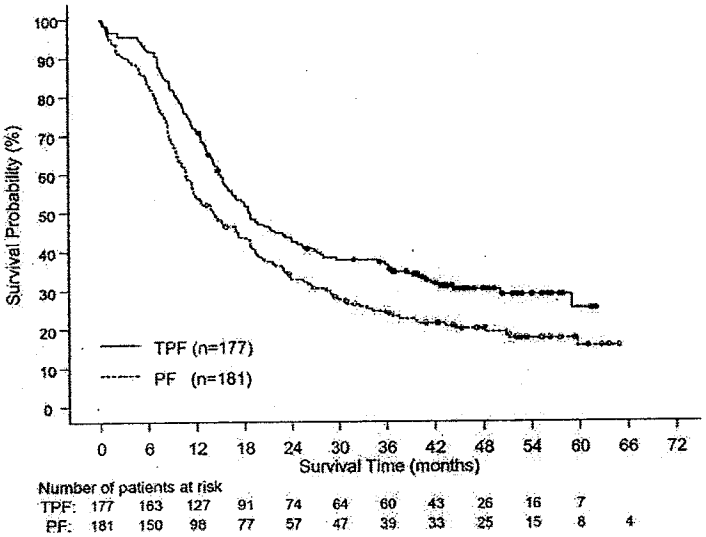
The summary of OS analysis and log-rank test is shown below.

Table 20: Summary of TAX 323 Statistics for OS Up Date (ITT)

	Randomization group	
	TPF (N=177)	PF (N=181)
Median overall survival (months) [95% CI]	18.6 [15.7 - 24.0]	14.2 [11.5 - 18.7]
Kaplan-Meier estimates for overall survival		
1-year estimate [95% CI]	71.8% [65.1 - 78.4]	54.1% [46.9 - 61.4]
2-year estimate [95% CI]	42.9% [35.6 - 50.3]	32.8% [25.9 - 39.6]
3-year estimate [95% CI]	36.5% [29.3 - 43.6]	23.9% [17.6 - 30.3]
Hazard ratio: TPF/PF [95% CI]	0.71 [0.56 - 0.90]	
Log-Rank p value	0.0052	

Data source: Study TAX 323 efficacy up date.

Figure 5: TAX 323 Overall Survival Up Date- Kaplan-Meier (ITT)



Reviewer: Median OS was 4.4 month longer in the TPF arm treatment group than in the PF arm. The difference between the treatment groups was statistically significant (log-rank test, P = 0.0052), with HR 0.71. The 3-year survival rate estimated was 12.6% more for the TPF arm (36.5%) compared to PF arm (23.9%). Beside confirmed previous OS analysis, 74.9% events for this up dated analysis is much more mature than the first cut off analysis using 66.25 events. Verified by the statistical reviewer, the overall survival result supports the primary analysis result.

6.1.4.3 Response Rate

Due to the study TAX 323 design, the response rate can be assessed at multiple stages: response after neoadjuvant chemotherapy, response after radiotherapy, and response on both chemotherapy and radiotherapy period. All responses are summarized in section 10.1.1.3, except response after neoadjuvant therapy are summarized as below.

Table 21: Response after Neoadjuvant Chemotherapy (ITT)

	Randomization group	
	TPF (N=177)	PF (N=181)
Complete response	15 (8.5%)	12 (6.6%)
Partial response	105(59.3%)	85 (47%)
No change	30 (16.9%)	45 (24.9%)
Progression of disease	10 (5.6%)	12 (6.6%)
Not evaluable	17 (9.6%)	27 (14.9%)
Overall RR (CR+PR) 95% CI	67.8% [60.4-74.6]	53.6% [46.0-61.0]
P value	0.006	
Complete RR (CR) 95% CI	8.5% [4.8-13.6]	6.6% [3.5-11.3]
P value	0.509	

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; RR = response rate; CR = complete response; PR = partial response; CI = confidence interval.
Data source: TAX 323 study report.

Reviewer note: The overall response rate observed on TPF arm (67.8%) is 14.2% higher than that of PF arm (53.6%). However, the complete response rate observed on both arms were comparable (8.5% vs. 6.6%). Both the overall response rate and the CR rates for the PF arm were lower than previously reported neoadjuvant combination cisplatin and infusional 5-FU studies in newly diagnosed patients. These may related to number of chemosensitive patient enrolled and excluding patient with operable disease.

Table 22: Response after radiotherapy (radiated patients only)

	Randomization group	
	TPF (N=130)	PF (N=124)
Complete response	52 (40%)	33 (26.6%)
Partial response	24 (18.5%)	21 (16.9%)
No change	0 (0.0%)	1 (0.8%)
Progression of disease	25 (19.2%)	47 (37.9%)
Not evaluable	29 (22.3%)	22 (17.7%)
Overall RR (CR+PR) 95% CI	58.5% [49.5-67.0]	43.5% [34.7-52.7]
P value	0.017	
Complete RR (CR) 95% CI	40% [31.5-49.0]	26.6% [19.1-35.3]
P value	0.024	

CR = complete response; PR = partial response; CI = confidence interval
Data source: TAX 323 study report

Table 23: Response on both chemotherapy and radiotherapy period (ITT)

	Randomization group	
	TPF (N=177)	PF (N=181)
Complete response	59 (33.3%)	36 (19.9%)
Partial response	69 (39%)	70 (38.7%)
No change	24 (13.6%)	39 (21.5%)
Progression of disease	11 (6.2%)	13 (7.2%)
Not evaluable	14 (7.9%)	23 (12.7%)
Overall RR (CR+PR) 95% CI	72.3% [65.1-78.8]	58.6% [51.0-65.8]
P value	0.006	
Complete RR (CR) 95% CI	33.3% [26.4-40.8]	19.9% [14.3-26.5]
P value	0.004	

CR = complete response; PR = partial response; CI = confidence interval; BOR= best overall response
Data source: TAX 323 study report.

Reviewer: The TPF arm had 15% higher response rate (58.5% vs. 43.5%) and 13.4% higher CR rate (40% vs. 26.6%) on the response to radiotherapy, and 11.7% higher response rate (72.3% vs. 58.6%) and 13% higher CR rate on the response to CT/RT therapies. Besides most patients received per protocol radiotherapy sensitive, especially taxane sensitive for the TPF arm, that other factor could be that there were 6% more patients received RT on the TPF arm (74.7 % fro TPF and 68.5% for PF). The RR and CR of PF arm for either radiotherapy or chemotherapy and radiotherapy were lower than previously reported studies for the similar patient population. A possible explanation for this result is that the study TAX 323 selected radiotherapy following neoadjuvant chemotherapy instead of chemoradiotherapy as definitive therapy following neoadjuvant chemotherapy.

6.1.4.4 Patient Reported Outcome (PRO)

b(4)

6.1.5 Efficacy Conclusions

1. The comparative study TAX 323 demonstrated statistically significant advantage of TPF over PF as neoadjuvant therapy for chemotherapy naïve in operable advanced HNSCC patients in primary analysis, PFS, on ITT population (N = 355) after 260 events. The PFS analyses indicated a 3 month advantage in median PFS (11.4 months for TPF [95%CI: 10.1 – 14.0] vs. 8.3 months [95% CI: 7.4 – 9.1] for PF), with an HR of 0.72 (Log rank p = 00.0073).

2. The secondary analyses of overall survival, both at the PFS cut off date (237 event) and at the time of up date (266 events), support the PFS analyses. The overall survival analyses demonstrated a 4 months advantage in median survival on both 237 and 266 events analyses, with an HR of 0.72 (237 events, log-rank p = 0.0128) and 0.71 (266 events, log-rank p = 0.0052).

3. The secondary endpoint of response rate analyses also favoring the TPF arm, with a 14% higher response rate for neoadjuvant chemotherapy (67.8% for TPF vs. 53.6% for PF) and 15% higher overall response rate for both neoadjuvant chemotherapy and radiotherapy. However, the difference on complete response observed was less than 2% for chemotherapy (8.5% for TPF vs. 6.6% for PF) and 14% for both chemotherapy and radiotherapy. Both the overall response rate and the CR rates for the PF arm were lower than previously reported neoadjuvant combination cisplatin and infusional 5-FU studies in newly diagnosed patients. These may relate to available patient pool and excluding patient with operable disease. The other important factor could affect the efficacy result is that the study TAX 323 selected radiotherapy following neoadjuvant chemotherapy instead of chemoradiotherapy as definitive therapy following neoadjuvant chemotherapy.

4. Although it has not been confirmed by the FDA, the sponsor's preliminary result on TAX 324 primary analysis, improvement in overall survival in this study also suggests that TPF is superior to PF.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The TAX323 study report, data sets were reviewed with the emphasis of adverse events and patients exposure to chemotherapy. For chemotherapy, the safety and exposure analysis population (SP) is ITT population. For radiotherapy, the safety and exposure analysis population used is patients who received radiation therapy (RSP). The AE analyses are based on NCI CTC system.

The reviewer confirmed the sponsor's analyses on relative dose intensity; median number of cycles administered, and mean duration of exposure to chemotherapy and conclude that all were similar between the two arms.

Table 24: Overview of exposure to chemotherapy (SP = ITT)

	TPF (N=174)	PF (N=181)
Relative dose intensity	97%	91%
Median no. of cycles administered	4	4
Median duration (week)	12.00	12.14
Patients who received 4 cycles	78.7%	65.2%

SP = safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5- FU; N = number of patients
Data source: TAX323 study report

Confirmed by the reviewer, the dose and duration of locoregional radiotherapy was also comparable between the two arms.

Table 25: Radiation Exposure between the two Arms (RSP < ITT)

	Treatment received	
	TPF (N=130)	PF (N=124)
Total dose of PTVI+PTVII (Gy)		
Number	129[a]	124
Median	70.00	70.00
Mean	68.532	69.160
SEM	0.5860	0.8833
Minimum	28.00	14.40
Maximum	87.60	112.00
Total duration of PTVI+PTVII (weeks)		
Number	130	124
Median	7.14	7.14
Mean	7.041	7.001
SEM	0.1511	0.1143
Minimum	0.00	2.14
Maximum	18.14	10.00

RSP = radiotherapy safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; SEM = Standard error of the mean
a Patient 00135 (TPF) had a missing dose in PTVII.
Data Sourse: TAX 323 study report.

Almost all patients (349, 98.3%, n= 355, ITT) who received chemotherapy experienced at least 1 EA during treatment, regardless of relationship to study medication (treatment emergent AE, TEAE). The sponsor summarized all EAs and conducted safety analyses. The reviewer analyzed and verified TAX323 study safety results provided by the sponsor.

Table 26: Number of patients with TEAEs during chemotherapy with or without radiotherapy (SP = ITT)

	Treatment received	
	TPF (N=174)	PF (N=181)
Number of patients on treatment (chemotherapy or radiotherapy)		
With at least one TEAE	174 (100.0%)	175 (96.7%)
With at least one grade 3/4 TEAE	107 (61.5%)	104 (57.5%)
With at least one grade 4 TEAE	34 (19.5%)	38 (21.0%)
With at least one TEAE related	171 (98.3%)	169 (93.4%)
With at least one grade 3/4 TEAE related	94 (54.0%)	84 (46.4%)
With at least one grade 4 TEAE related	24 (13.8%)	31 (17.1%)

TEAE = treatment-emergent adverse event; SP = safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Data source: Tax 323 study

Patients who received chemotherapy and experienced at least 1 AE were 96.6% (343/355, ITT), regardless the relationship to the treatment (TEAE).

Table 27: Number of patients with TEAEs during chemotherapy (SP = ITT)

	Treatment received	
	TPF (N=174)	PF (N=181)
Number of patients on chemotherapy		
With at least one TEAE	173 (99.4%)	170 (93.9%)
With at least one grade 3/4 TEAE	68 (39.1%)	70 (38.7%)
With at least one grade 4 TEAE	16 (9.2%)	21 (11.6%)
With at least one TEAE related	168 (96.6%)	159 (87.8%)
With at least one grade 3/4 TEAE related	55 (31.6%)	50 (27.6%)
With at least one grade 4 TEAE related	9 (5.2%)	15 (8.3%)

TEAE = treatment-emergent adverse event; SP = safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Data source: TAX 323 study

Reviewer: There is only one patient on TPF arm (0.6%) and 11 patients on PF arm (6.1%) did not experience any AE during chemotherapy.
Patients who received radiotherapy and experienced at least 1 AE were 95.7% (243/254, RSP).

Table 28: Number of patients with TEAEs during radiotherapy (RSP < ITT)

	Treatment received	
	TPF (N=130)	PF (N=124)
Number of patients on radiotherapy		
- With at least one TEAE	124 (95.4%)	119 (96.0%)
- With at least one grade 3/4 TEAE	66 (50.8%)	62 (50.0%)
- With at least one grade 4 TEAE	19 (14.6%)	19 (15.3%)
- With at least one TEAE related	113 (86.9%)	112 (90.3%)
- With at least one grade 3/4 TEAE related	56 (43.1%)	53 (42.7%)
- With at least one grade 4 TEAE related	15 (11.5%)	17 (13.7%)

TEAE = treatment-emergent adverse event; RSP = radiotherapy safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Data source: TAX 323 study

Reviewer: The incidence of AEs observed in both chemotherapy and radiotherapy, or during one of the therapy, are comparable between the two arms. Analyses in specific category are described in the section below.

7.1.1 Deaths

The total number of death at the cut off day (260 PFS events) was 253, 115 and 138 for TPF and PF, respectively. The reviewer verified the sponsor's death analyses and summarized as below:

Table 29: Summary of death (SP = ITT)

Treatment received	TPF (N=174)	PF (N=181)
Total deaths[a]	115 (66.1%)	138 (76.2%)
Within 60 days of first administration of study treatment[b]	6 (3.4%)	12 (6.6%)
Progression of disease	0 (0.0%)	2 (1.1%)
Toxicity	3 (1.7%)	6 (3.3%)
Infection not due to protocol treatment	2 (1.1%)	0 (0.0%)
Intercurrent death not due to malignant disease	0 (0.0%)	1 (0.6%)
Other	1 (0.6%)	3 (1.7%)
Within 30 days of last study treatment	8 (4.6%)	22 (12.2%)
Progression of disease	1 (0.6%)	3 (1.7%)
Toxicity	4 (2.3%)	11 (6.1%)
Infection not due to protocol treatment	1 (0.6%)	0 (0.0%)
Intercurrent death not due to malignant disease	1 (0.6%)	1 (0.6%)
Other	1 (0.6%)	7 (3.9%)
More than 30 days after last study treatment	107 (61.5%)	116 (64.1%)
Progression of disease	88 (50.6%)	103 (56.9%)
Infection not due to protocol treatment	3 (1.7%)	4 (2.2%)
Intercurrent death not due to malignant disease	5 (2.9%)	1 (0.6%)
Other	11 (6.3%)	7 (3.9%)
Missing	0 (0.0%)	1 (0.6%)

SP = safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
a Patient 47 (randomized in TPF group) died from progressive disease but date of death is [redacted] by convention the date is set to [redacted]
b Death within 60 days from first administration of study treatment is also included in any of the other "dead" category (within 30 or more than 30 days from last administration of study treatment) b(6)
Data source : TAX 323 Study

Reviewer: The higher death rated has been noted for PF arm (10.1%) and it is consistent cross all category, within 60 days of first administration of study treatment (3.2%), within 30 days of last study treatment (7.4%), and more than 30 days of last study treatment (2.6%). In addition, there was more death for PF arm due to treatment toxicity (and progression of disease.

7.1.2 Other Serious Adverse Events

All servere adverse events (SAE) occurred within 30 days of last study treatment were recorded, regardless the relationship to the study drug, as treatment emergent AE (TEAE). Over all incidence of SAEs observed during chemotherapy and radiotherapy were summarized by the sponsor and verified by the reviewer. Analyses are based on NCI CTC criteria.

Table 30: Overview of number of patients with serious TEAEs during chemotherapy (SP = ITT)

	Treatment received	
	TPF (N=174)	PF (N=181)
Number of patients under chemotherapy		
With at least one serious TEAE	48 (27.6%)	63 (34.8%)
With at least one serious grade 3/4 TEAE	37 (21.3%)	46 (25.4%)
With at least one serious grade 4 TEAE	21 (12.1%)	25 (13.8%)
With at least one serious TEAE related	38 (21.8%)	50 (27.6%)
With at least one serious grade 3/4 TEAE related	30 (17.2%)	35 (19.3%)
With at least one serious grade 4 TEAE related	15 (8.6%)	21 (11.6%)

TEAE = treatment-emergent adverse event; SP = safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Data source: TAX 323 study.

Table 31: Overview of patients with serious TEAEs during radiotherapy (SP = ITT)

	Treatment received	
	TPF (N=130)	PF (N=124)
Number of patients under radiotherapy		
With at least one serious TEAE	17 (13.1%)	20 (16.1%)
With at least one serious grade 3/4 TEAE	11 (8.5%)	14 (11.3%)
With at least one serious grade 4 TEAE	6 (4.6%)	11 (8.9%)
With at least one serious TEAE related	10 (7.7%)	15 (12.1%)
With at least one serious grade 3/4 TEAE related	6 (4.6%)	10 (8.1%)
With at least one serious grade 4 TEAE related	2 (1.5%)	7 (5.6%)

TEAE = treatment-emergent adverse event; SP = safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Data source: TAX 323 study.

Reviewer: The incidence of SAE observed during either chemotherapy or radiotherapy were comparable for both arms, with slightly higher number of incidence/patients noted on the control arm (PF) which may related to higher dose of cisplatin and 5-FU.

The reviewer summarized SAEs observed in ITT (SP) population and included SAEs occurred in at least 2 patients in the following table.

Clinical Review
Qin Ryan MD, PhD
NDA 20449 S39
Taxotere (Docetaxel)

Table 32: Summary of SAEs occurred in at least two patients regardless of relationship to treatment (chemotherapy with or without radiotherapy, SP = ITT)

Body System / Adverse Events in NCI CTC Trem	TPF (174)				PF (181)			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
Blood Bone Marrow								
White Blood Count	24	13.79	19	10.92	80	44.2	54	29.83
Hemoglobin	15	8.62	6	3.45	18	9.94	7	3.87
Platelets	5	2.87	3	1.72	17	9.39	11	6.08
Granulocytes	2	1.15	2	1.15	21	11.6	14	7.73
Cancer Related Symptoms								
Cancer Pain	54	31.00	25	14.37	40	22.17	23	12.71
Other: Hemorrhage	5	2.87	2	1.15	8	4.42	2	1.1
Cardiovascular								
Edema	31	17.82	2	1.15	29	16.02	1	0.55
Hypertension	8	4.6	3	1.72	8	4.42	6	3.31
Venous	7	4.02	5	2.87	12	6.63	3	1.66
Dysrhythmias	4	2.3	3	1.72	5	2.76	3	1.66
Ischemia Myocardial	4	2.3	4	2.3	1	0.55	0	0
Hypotension	3	1.72	0	0	3	1.66	2	1.1
Cardiac Function	2	1.15	2	1.15	3	1.66	3	1.66
Flu-Like Symptoms								
Lethargy	76	43.69	6	3.45	78	43.09	11	6.08
Myalgia	21	12.07	2	1.15	11	6.08	0	0
Gastrointestinal								
Stomatitis	132	75.91	59	33.91	139	76.78	59	32.6
Esophagitis/Dysphagia/Odynophagia	87	50.01	45	25.86	93	51.42	50	27.62
Nausea	82	47.17	1	0.57	95	51.4	13	7.18
Diarrhea	58	33.32	6	3.45	45	24.92	9	4.97
Vomiting	48	27.61	1	0.57	40	22.13	9	4.97
Anorexia	35	20.13	3	1.72	53	29.28	11	6.08
Taste,Sense Of Smell Altered	33	18.97	3	1.72	22	12.15	3	1.66
Mouth,Nose Dryness	29	16.72	2	1.15	25	13.76	4	2.21

Body System / Adverse Events in NCI CTC Trem	TPF (174)				PF (181)			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
Gastrointestinal Pain/Cramping	14	8.05	1	0.57	17	9.39	1	0.55
Gastrointestinal Bleeding	10	5.75	4	2.3	3	1.66	1	0.55
Gastritis/Ulcer	4	2.3	2	1.15	3	1.66	1	0.55
Other: Dehydration	2	1.15	0	0	9	4.97	2	1.1
Small Bowel Obstruction	1	0.57	1	0.57	2	1.1	1	0.55
Genitourinary								
Creatinine	9	5.17	0	0	18	9.94	2	1.1
Infection								
Infection	77	44.25	21	12.07	83	45.86	22	12.15
Febrile Neutropenia	3	1.72	3	1.72	0	0	0	0
Metabolic								
Hypokalemia	5	2.87	1	0.57	4	2.21	2	1.1
Hyperglycemia	0	0	0	0	2	1.1	2	1.1
Neurologic								
Sensory	45	25.86	1	0.57	24	13.26	1	0.55
Constipation	34	19.54	1	0.57	44	24.31	2	1.1
Altered Hearing	22	12.64	1	0.57	31	17.13	5	2.76
Motor	20	11.49	7	4.02	17	9.39	4	2.21
Neurologic Pain	16	9.2	1	0.57	14	7.73	1	0.55
Mood	8	4.6	1	0.57	16	8.84	1	0.55
Cortical,Somnolence	2	1.15	0	0	3	1.66	3	1.66
Other								
Other: Pain	2	1.15	0	0	5	2.76	2	1.1
Other: Aggravation Reaction	1	0.57	1	0.57	1	0.55	1	0.55
Other: Overdose	1	0.57	1	0.57	1	0.55	1	0.55
Other: Accidental Injury	0	0	0	0	3	1.66	2	1.1
Pulmonary								
Voice Changes	46	26.44	1	0.57	56	30.94	3	1.66
Shortness Of Breath	33	18.97	7	4.02	40	22.1	14	7.73
Pleural Effusion	2	1.15	1	0.57	2	1.1	1	0.55

Body System / Adverse Events in NCI CTC Trem	TPF (174)				PF (181)			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
Pulmonary Edema	2	1.15	1	0.57	2	1.1	2	1.1
Skin								
Alopecia	141	81.03	21	12.07	80	44.24	0	0
Rash/Itch	73	41.95	8	4.6	68	37.57	14	7.73
Local Toxicity	42	24.14	3	1.72	29	16.02	3	1.66
Other: Skin Disorder	32	18.39	13	7.47	28	15.47	8	4.42
Desquamation	19	10.92	2	1.15	23	12.71	0	0
Weight								
Weight Loss	60	34.54	9	5.17	71	39.21	11	6.08
Weight Gain	59	33.91	1	0.57	54	29.83	2	1.1

SP = safety population = ITT; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients.
Data source: TAX323 study.

Reviewer: The reviewer's SAE analyses confirmed the sponsor's SAE analyses. Top 5 SAEs are Stomatitis/Esophagitis, leucopenia, cancer pain, infection and alopecia. Between the two arms, SAEs frequency $\geq$ 5% than the other arm, were Alopecia (12%, 12% TPF vs 0% PF) for TPF arm, Leukopenia (19%, 29.8%PF vs 10.9% TPF) and esophagitis (6%, 7.2% PF vs. 0.6% TPF). Overall, the toxicities between the two arms appear to be comparable during the per protocol treatment.

7.1.3 Dropouts and Other Significant Adverse Events

Verified by the reviewer, drop out or discontinuation of chemotherapy due to AEs occurred in 6.2% of TPF-treated patients and 11.6% of PF-treated patients. Details are shown below.

Table 33: Adverse events regardless of relationship to study medication that led to discontinuation of chemotherapy (SP = ITT)

	RANDOMIZATION GROUP	
NCIC term	TPF (N=177)	PF (N=181)
Number of patients without AE leading to treatment discontinuation	166 (93.8%)	161 (89.0%)
Number of patients with at least one AE leading to treatment discontinuation	11 (6.2%)	20 (11.0%)
Ischemia myocardial	3 (1.7%)	1 (0.6%)
Gastritis/ulcer	1 (0.6%)	
Gastrointestinal bleeding	1 (0.6%)	
Infection	1 (0.6%)	3 (1.7%)
Lethargy	1 (0.6%)	3 (1.7%)
Motor	1 (0.6%)	1 (0.6%)
Other: cirrhosis of liver	1 (0.6%)	
Other: hemorrhage	1 (0.6%)	1 (0.6%)
Stomatitis	1 (0.6%)	2 (1.1%)
Venous	1 (0.6%)	1 (0.6%)
White blood count	1 (0.6%)	1 (0.6%)
Altered hearing		5 (2.8%)
Anorexia		1 (0.6%)
Creatinine		3 (1.7%)
Diarrhea		2 (1.1%)
Esophagitis/dysphagia/odynophagia		1 (0.6%)
Hypokalemia		1 (0.6%)
Other: dehydration		1 (0.6%)
Other: hypophosphatemia		1 (0.6%)
Other: withdrawal syndrome		1 (0.6%)
Platelets		2 (1.1%)
Sensory		1 (0.6%)
Shortness of breath		1 (0.6%)
Weight loss		1 (0.6%)

ITT = intent-to-treat; AE = adverse event; NCIC = National Cancer Institute of Canada; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients A patient may have more than one adverse event leading to treatment discontinuation.
Data source: TAX 323 study.

Reviewer: Drop put on TPF arm is 5% less than that of PF arm, most likely related to the higher does of Cisplatin and 5-FU used on PF arm. The most frequent AE that caused chemotherapy

discontinuation was altered hearing, with all instances in the PF treatment group (2.8%). As for radiotherapy, only 3 (2.3%) patients (3 in TPF arm and 0 in PF arm) who received per protocol radiotherapy dropped out due to AEs. One of this patient discontinued both chemotherapy and then radiotherapy (did not received plan full course therapy for both) due to AEs.

7.1.4 Common Adverse Events

Measured by the NCI CTC criteria, the reviewer analyzed all AEs in the TAX 323 study data set and summarized all grade AEs that occurred in > 5% patients as below.

Clinical Review
Qin Ryan MD, PhD
NDA 20449 S39
Taxotere (Docetaxel)

Table 34: Common toxicity occurred during treatment (chemotherapy with or without radiotherapy), in at least 5% of patients, related to treatment (SP = ITT)

Body System / Adverse Events in NCI CTC Term	TPF				PF			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
Blood Bone Marrow								
White Blood Count	24	13.79	19	10.92	80	44.2	54	29.83
Hemoglobin	15	8.62	6	3.45	18	9.94	7	3.87
Platelets	5	2.87	3	1.72	17	9.39	11	6.08
Granulocytes	2	1.15	2	1.15	21	11.6	14	7.73
Cancer Related Symptoms								
Cancer Pain	54	31.02	25	14.37	40	22.17	23	12.71
Cardiovascular								
Edema	31	17.82	2	1.15	29	16.02	1	0.55
Hypertension	8	4.6	3	1.72	8	4.42	6	3.31
Venous	7	4.02	5	2.87	12	6.63	3	1.66
Flu-Like Symptoms								
Lethargy	76	43.69	6	3.45	78	43.09	11	6.08
Fever In Absence Of Infection	58	33.33	1	0.57	69	38.12	0	0
Myalgia	21	12.07	2	1.15	11	6.08	0	0
Arthralgia	10	5.75	0	0	4	2.21	0	0
Hay Fever	10	5.75	0	0	8	4.42	0	0
Gastrointestinal								
Stomatitis	132	75.91	59	33.91	139	76.78	59	32.6
Esophagitis/Dysphagia/Odynophagia	87	50.01	45	25.86	93	51.42	50	27.62
Nausea	82	47.17	1	0.57	95	51.4	13	7.18
Diarrhea	58	33.32	6	3.45	45	24.92	9	4.97
Vomiting	48	27.61	1	0.57	40	22.13	9	4.97
Anorexia	35	20.13	3	1.72	53	29.28	11	6.08
Taste,Sense Of Smell Altered	33	18.97	3	1.72	22	12.15	3	1.66
Mouth,Nose Dryness	29	16.72	2	1.15	25	13.76	4	2.21
Gastrointestinal Pain/Cramping	14	8.05	1	0.57	17	9.39	1	0.55
Heartburn	14	8.05	0	0	13	7.18	0	0
Gastrointestinal Bleeding	10	5.75	4	2.3	3	1.66	1	0.55
Genitourinary								
Creatinine	9	5.17	0	0	18	9.94	2	1.1
Hypersensitivity								

Body System / Adverse Events in NCI CTC Term	TPF				PF			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
Allergy	13	7.47	0	0	2	1.1	0	0
Infection								
Infection	77	44.25	21	12.07	83	45.86	22	12.15
Neurologic								
Sensory	45	25.86	1	0.57	24	13.26	1	0.55
Constipation	34	19.54	1	0.57	44	24.31	2	1.1
Altered Hearing	22	12.64	1	0.57	31	17.13	5	2.76
Motor	20	11.49	7	4.02	17	9.39	4	2.21
Neurologic Pain	16	9.2	1	0.57	14	7.73	1	0.55
Headache	13	7.47	0	0	14	7.73	0	0
Insomnia	10	5.75	0	0	14	7.73	0	0
Mood	8	4.6	1	0.57	16	8.84	1	0.55
Dizziness	7	4.02	0	0	10	5.52	1	0.55
Pulmonary								
Voice Changes	46	26.44	1	0.57	56	30.94	3	1.66
Shortness Of Breath	33	18.97	7	4.02	40	22.1	14	7.73
Cough	30	17.24	0	0	37	20.44	0	0
Skin								
Alopecia	141	81.03	21	12.07	80	44.24	0	0
Rash/Itch	73	41.95	8	4.6	68	37.57	14	7.73
Local Toxicity	42	24.14	3	1.72	29	16.02	3	1.66
Other: Skin Disorder	32	18.39	13	7.47	28	15.47	8	4.42
Desquamation	19	10.92	2	1.15	23	12.71	0	0
Dry Skin	12	6.9	0	0	5	2.76	0	0
Weight								
Weight Loss	60	34.54	9	5.17	71	39.21	11	6.08
Weight Gain	59	33.91	1	0.57	54	29.83	2	1.1

SP = safety population = ITT; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients.
Data source: TAX323 study.

Reviewer: The reviewer's common AE analyses confirmed the sponsor's common AE analyses. Top 5 common AEs are Stomatitis/Esophagitis, Alopecia, nausea/vomiting and lethargy. For TPF arm, common AEs that ≥ 5% than the PF arm were Alopecia (37.2%, 81% vs 44.2%), and Anorexia (9%, 29.3% vs 20.1%).

The reviewer confirmed sponsor's analyses on common AEs occurred during the chemotherapy and summarized as follows.

Table 35: Common AEs during chemotherapy (by NCIC CTG term in at least 5% of patients) regardless of relationship to study medication (SP = ITT)

NCIC CTG term	TPF (N=181)		PF (N=174)	
	All	Grade 3/4	All	Grade 3/4
Alopecia	141 (81.0%)	19 (10.9%)	78 (43.1%)	
Nausea	82 (47.1%)	1 (0.6%)	93 (51.4%)	13 (7.2%)
Stomatitis	74 (42.5%)	7 (4.0%)	85 (47.0%)	20 (11.0%)
Lethargy	71 (40.8%)	6 (3.4%)	69 (38.1%)	6 (3.3%)
Diarrhea	57 (32.8%)	5 (2.9%)	43 (23.8%)	8 (4.4%)
Fever in absence of infection	55 (31.6%)	1 (0.6%)	66 (36.5%)	
Infection	47 (27.0%)	15 (8.6%)	47 (26.0%)	14 (7.7%)
Vomiting	46 (26.4%)	1 (0.6%)	70 (38.7%)	9 (5.0%)
Weight gain	45 (25.9%)		41 (22.7%)	
Cancer pain	36 (20.7%)	8 (4.6%)	29 (16.0%)	6 (3.3%)
Weight loss	36 (20.7%)	1 (0.6%)	48 (26.5%)	1 (0.6%)
Sensory	31 (17.8%)	1 (0.6%)	19 (10.5%)	1 (0.6%)
Constipation	29 (16.7%)	1 (0.6%)	29 (16.0%)	2 (1.1%)
Anorexia	28 (16.1%)	1 (0.6%)	45 (24.9%)	6 (3.3%)
Edema	26 (14.9%)	1 (0.6%)	25 (13.8%)	1 (0.6%)
Local toxicity	26 (14.9%)	1 (0.6%)	20 (11.0%)	3 (1.7%)
Esophagitis/dysphagia/odynophagia	22 (12.6%)	2 (1.1%)	33 (18.2%)	5 (2.8%)
Rash/itch	20 (11.5%)		11 (6.1%)	
Shortness of breath	19 (10.9%)	5 (2.9%)	18 (9.9%)	8 (4.4%)
Taste, sense of smell altered	18 (10.3%)		9 (5.0%)	
Myalgia	17 (9.8%)	2 (1.1%)	13 (7.2%)	
Gastrointestinal pain/cramping	13 (7.5%)	1 (0.6%)	16 (8.8%)	1 (0.6%)
Cough	12 (6.9%)		16 (8.8%)	
Allergy	11 (6.3%)		5 (2.8%)	
Heartburn	11 (6.3%)		11 (6.1%)	
Altered hearing	10 (5.7%)		18 (9.9%)	5 (2.8%)
Dry skin	10 (5.7%)		3 (1.7%)	
Headache	10 (5.7%)		11 (6.1%)	
Hay fever	9 (5.2%)		7 (3.9%)	
Desquamation	7 (4.0%)	1 (0.6%)	10 (5.5%)	
Venous	6 (3.4%)	4 (2.3%)	10 (5.5%)	3 (1.7%)
Voice changes	6 (3.4%)		12 (6.6%)	1 (0.6%)
Insomnia	5 (2.9%)		11 (6.1%)	
Dizziness	4 (2.3%)		9 (5.0%)	1 (0.6%)

AE = treatment-emergent adverse event; SP = safety population = ITT; NCIC CTG = National Cancer Institute of Canada Clinical Trials Group; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Notes: Percentages have been calculated on the total number of patients. For the number of patients with TEAEs and for each NCIC CTG classification, patients having one or more NCIC CTG term are counted only once. For each patient, only the maximum grade recorded for the same NCIC CTG term is taken into account into the calculations.
Data source: TAX 323 study.

7.1.5 Laboratory Findings

The number of patients that evaluable for laboratory safety (SP) are very from the ITT population depending on a given laboratory test. The definition for patients to be considered evaluable for hematology safety is as follows: A patient is evaluable if having at least 1 cycle evaluable (e.g., with a blood count between Day 2 and next IV during chemotherapy). The reviewer has verified sponsor's laboratory safety analyses and summarized as follows.

7.1.5.1 Hematology

The number of evaluable patients for the hematology safety analyses (SP) is basically identical to the ITT population. The reviewer confirmed sponsor's finding on major hematological toxicities and summarized as below:

Table 36: Summary of hematology findings in TAX 323 study (SP = ITT)

Treatment received	TPF (N=174)			PF (N=181)		
Grade	All (%)	3+4 (%)	4 (%)	All (%)	3+4 (%)	4 (%)
Anemia	155 (89.1)	16 (9.2)	4 (2.3)	159 (87.8)	25 (13.8)	7 (3.9)
Leukopenia	159 (91)	72 (41.4)	13 (7.5)	138 (76.2)	42 (23.2)	11 (6.1)
Neutropenia*	161 (93.1)	132 (76.3)	85 (49.1)	156 (86.7)	95 (52.8)	43 (23.9)
Thrombocytopenia	41 (23.6)	9 (5.2)	4 (2.3)	85 (47.0)	33 (18.2)	14 (7.3)

SP = safety population = ITT; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients.
* The evaluable patient population for nuetropenia is two patients less than the ITT population (TPF = 173, 99.4%; PF = 180, 99.4%).
Data source: TAX323 study.

Reviewer: Anemia and Leukopenia are fairly comparable between the two arms. Whereas neutropenia were significantly higher in the TPF arm, especially grade 4 neotropenia was 25% higher for TPF compared with PF. Of note, thrombocytopenia was significantly lower for TPF arm.

7.1.6.2 Other laboratory test

For liver function and serum chemistry safety analyses, the number of evaluable patients (SP) are slightly less than the ITT population. The reviewer has confirmed sponsor's analyses and summarized results as below.

Table 37: Summary of liver function and serum chemistry findings of study TAX 323 (SP < ITT)

Treatment received	TPF (N=174)				PF (N=181)			
Grade	SP No (%)	All (%)	3+4 (%)	4 (%)	SP No (%)	All (%)	3+4 (%)	4 (%)
Liver function								
AST	163 (93.7)	13 (8.0)	0	0	170 (93.9)	11 (6.5)	0	0
ALT	169 (97.1)	16 (9.5)	0	0	175 (96.7)	7 (4)	0	0
Alkaline Phosphatase	171 (98.3)	26 (15.2)	0	0	175 (96.7)	33 (18.9)	0	0
Total bilirubin	168 (96.6)	12 (7.1)	5 (3)	3 (1.8)	174 (96.1)	12 (6.9)	7 (4)	5 (2.9)
Serum Chemistry								
Creatinine	172 (98.9)	15 (8.7)	1 (0.6)	1 (0.6)	179 (98.9)	33 (20.1)	5 (2.8)	4 (2.2)
Hypokalemia	183 (99.4)	26 (15)	2 (1.2)	0	180 (99.4)	35 (19.4)	1 (0.6)	0
Hypomagnesemia	147 (84.5)	76 (51.7)	6 (4.1)	1 (0.7)	156 (86.2)	61 (39.1)	5 (3.2)	2 (1.3)
Hyponatremia	173 (99.4)	46 (26.6)	2 (1.2)	0	178 (98.3)	56 (31.5)	5 (2.8)	0
Hypocalcemia	167 (98)	33 (19.8)	8 (4.8)	6 (3.6)	176 (97.2)	33 (18.8)	2 (2.3)	2 (1.1)
Hypercalcemia	167 (96)	5 (3)	0	0	176 (97.2)	11 (6.3)	2 (1.1)	2 (1.1)

SP = safety population < ITT; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients.
Data source: TAX323 study.

Reviewer: The number evaluable patient for safety analyses (SP) for liver function and serum chemistry were variablely smaller than the ITT. However, most of the evaluable patients were more than 93% except one is about 85 % of ITT population. The laboratory abnormalities are comparable between the two arms. The grade 3 or 4 laboratory AEs were less then 3% in all category. With the exception of hypomagnesemia, It is 11% more frequent in TPF arm for all grades (51.7% vs.39.1%). The Incidence of grade 3/4 hypomagnesemia was 4.1% for TPF and 3.2% for PF.

7.1.6 Specific Safety Issues

7.1.6.1 Neutropenic infection and febrile neutropenia
Primary prophylaxis with antibiotics was primarily used in the TPF treatment group. A total of 164 patients from the TPF treatment group (94.3%) and 12 patients from the PF treatment group (6.6%) received primary prophylaxis with antibiotics throughout the TPF cycles, as shown in Table below. Secondary infection prophylaxis was required for both treatment groups in the event of a previous febrile neutropenia/infection episode or prolonged neutropenia grade 4 (> 7 days) or in case of delayed neutropenia recovery (>28 days). The number of patients who received secondary prophylaxis with G-CSF was limited. The use of G-CSF in treatment of severe neutropenia was low and similar in both treatment groups.

Table 38: Number of patients experiencing neutropenic infection and febrile neutropenia regardless of prophylactic G-CSF.

TREATMENT RECEIVED	TPF (N=174)	PF (N=181)
Number of evaluable patients for assessing neutropenic infection	173 (99.4%)	180 (99.4%)
Number of evaluable patients for assessing febrile neutropenia[a]	173 (99.4%)	180 (99.4%)
Neutropenic Infection (any relationship)[b]	24 (13.9%)	15 (8.3%)
Deaths due to neutropenic infection	4 (2.3%)	6 (3.3%)
Febrile Neutropenia (any relationship)[c]	9 (5.2%)	4 (2.2%)
Deaths due to febrile neutropenia	0	0

G-CSF = granulocyte colony-stimulating factor; SP = safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
a Number of patients used for the following calculations
A patient is evaluable if having at least one cycle with a blood count between day 2 and the next IV. For each patient, only evaluable cycles regardless of prophylactic G-CSF are taken into account for the analysis.
b Neutropenic infection = Grade =2 infection concomitant with grade 3 or 4 neutropenia.
c Febrile Neutropenia = Grade =2 fever concomitant with grade 4 neutropenia requiring I.V. antibiotics and/or hospitalization.
Data source: Study TAX 323.

Less than 10% of the safety population was evaluable for febrile neutropenia and neutropenic infection while receiving secondary G-CSF prophylaxis. The incidence of febrile neutropenia and neutropenic infection for patients had secondary G-CSF prophylaxis are based on the evaluable cycles that these patients received.

Table 39: Incidence of neutropenic fever or infection after secondary G-CSF prophylaxis (evaluable cycle only)

Total Evaluable Treatment Cycles	TPF (N=617)	PF (N=605)
Number of evaluable cycles on G-CSF for assessing febrile neutropenia[a]	31 (5.0%)	25 (4.1%)
Febrile Neutropenia (any relationship)[b]	1 (3.1%)	2 (7.7%)
Number of evaluable cycles on G-CSF for assessing neutropenic infection[a]	32 (5.2%)	26 (4.3%)
Neutropenic Infection (any relationship)[c]	2 (6.3%)	2 (7.7%)

a Number of cycles used for the following calculations: A patient is evaluable if having at least one cycle with a blood count between Day 2 and the next IV. For each patient, only evaluable cycles with prophylactic G-CSF are taken into account for the analysis.
b Febrile Neutropenia = Grade > 2 fever concomitant with grade 4 neutropenia requiring I.V. antibiotics and/or hospitalization.
c Neutropenic infection = Grade > 2 infection concomitant with grade 3 or 4 neutropenia.
Data source: Study TAX 323.

7.2.6.2: Fluid retention

As per protocol, almost all patients in the TPF treatment group (99.4%) received corticosteroids across cycles, to prevent hypersensitivity reaction and to reduce or delay fluid retention, compared to 77.9% in the PF treatment group. There were more patients with fluid retention in the TPF treatment group (35, 20.1%) than in the PF treatment group (26, 14.4%), as shown in Table below. The most frequent associated symptoms were edema only (22 patients, 12.6%, in the TPF treatment group and 12 patients, 6.6%, in the PF treatment group) and weight gain only (10 patients, 5.7%, in the TPF treatment group and 11 patients, 6.1% in the PF treatment group), with no grade 3 or 4 events.

Table 40: Fluid retention (SP = ITT)

	Treatment received	TPF (N=174)	PF (N=181)
Incedence	Number of patients with fluid retention	35 (20.1%)	26 (14.4%)
	Stop chemotherapy due to fluid retention	0 (0.0%)	2 (1.1%)
Intensity	Mild	21 (12.1%)	15 (8.3%)
	Moderate	13 (7.5%)	9 (5.0%)
	Severe + Life threatening	0 (0.0%)	1 (0.6%)
	Missing	1 (0.6%)	1 (0.6%)
Sign and symptoms	Edema only	22 (12.6%)	12 (6.6%)
	Weight gain only	10 (5.7%)	11 (6.1%)
	Edema + weight gain	2 (1.1%)	2 (1.1%)
	Lung edema	0 (0.0%)	1 (0.6%)
	Edema + lung edema	1 (0.6%)	0 (0.0%)

TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients Edema = all edemas except lung edema and brain edema.
Notes: Fluid retention includes only symptoms related to the study drug
Of note, "weight gain" adverse event should be regarded with caution because validation of this term was discontinued during the course of the study
Data source: Study TAX 323

7.2.6.3: Neurologic events

Baseline neurologic signs and symptoms (< grade 2) were present in 23.7% of TPF patients and 18.8% of PF patients. During the chemotherapy period, neurologic events were observed in 20.7% of patients of the TPF treatment group compared to 13.8% in patients of the PF treatment group (Table below). The majority were of neurosensory origin, and they were more frequent in the TPF treatment group (16.7% versus 7.7%). Discontinuation due to neurologic disorders among other events occurred in 1 patient in the PF treatment group (patient 00199), who presented with coma in the context of multi-organ failure.

Table 41: Neurological toxicity observed in TAX323

Treatment received	TPF (N=174)		PF (N=181)	
Number of patients with at least one NCIC CTG neurologic event	36 (20.7%)		25 (13.8%)	
NCIC CTG term	Grade 3/4	All	Grade 3/4	All
Neurologic	1 (0.6%)	36 (20.7%)	6 (3.3%)	25 (13.8%)
Altered hearing		10 (5.7%)	5 (2.8%)	13 (7.2%)
Cortical, somnolence		1 (0.6%)		
Motor		1 (0.6%)		2 (1.1%)
Sensory	1 (0.6%)	29 (16.7%)	1 (0.6%)	14 (7.7%)
Vision		1 (0.6%)		

NCIC CTG = National Cancer Institute of Canada Clinical Trials Group; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Notes: For each patient, only the maximum grade recorded for the same NCIC CTG term is taken into account in the calculations. Neuro-toxicity includes the following NCIC CTG terms: Altered hearing, Cerebellar, Cortical/somnolence, Extrapyramidal/involuntary movement, Motor, Sensory and vision.
Data source: Study TAX 323.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

1. The exposure of chemotherapy and radiotherapy in terms of intensity and duration are similar between the two study groups. The frequency of adverse events during the chemotherapy with or without radiotherapy are comparable between the two arms.

2. The death rate noted on the control arm (76.2% death for PF) was 10% higher than that of TPF arm (66.1%). Regardless the death is due to disease progression or treatment toxicity, the death rate for PF arm is consistent higher cross all category, within 60 days of first administration of study treatment (3.2%), within 30 days of last study treatment (7.4%), and more than 30 days of last study treatment (2.6%).

3. The incidence of NCI grade 3/4 adverse events during the chemotherapy with or without radiotherapy was comparable between the two arms (21.3 % for TPF vs. 25.4% for PF). Severe adverse events occurred more than 5% on TPF arm subjects were neutropenia (76.3%), alopecia (11%), infection (8.6%), weight lost (6.6%), stomatitis/esophagitis (5.1%). The significant difference between the two arms were 11% more Alopecia (11% TPF vs 0% PF) and 24% more neutropenia (76.3% TPF vs 52.8% PF). Overall, the toxicities between the two arms appear to be comparable during the per protocol treatment.

4. The incidence of any adverse events during the chemotherapy with or without radiotherapy was comparable between the two arms (100% for TPF vs. 96.7% for PF). Top 5 common AEs occurred on TPF arm were neutropenia (93.3%), anemia (89.1%), alopecia (81%), stomatitis/ssophagitis (55.1%), and nausea (47.1%). For TPF arm, common AEs that $\geq$ 5% than the PF arm were alopecia (37.9%, 81% vs 43.1%), neutropenia (6.6%, 93.1% vs. 86.7%), diarrhea (9%, 32.8% vs. 23.8%), neurosensory (7.3%, 17.8 %vs. 10.5%), neutropenic infection

(5.6%, 13.9% vs. 8.3%), fuid retension (5.6%, 20.1% vs. 14.4%) and altered taste or sense of smell (5.3%, 10.3% vs. 5%).

5. Drop out due to adverse events was 6% for the TPF arm and 11% for the PF arm.

8.6 Literature Review

Squamous cell carcinoma of the head and neck (SCCHN) represents 5% of newly diagnosed cancers in adult patients. Worldwide, more than 500 000 new cases are projected annually. It is a potentially curable malignancy when diagnosed at an early stage. Unfortunately, patients often present with advanced locoregional disease and in this group of patients the prognosis is quite poor. Following standard therapy, only 30% will be alive after 3 years. Of these, 60% to 70% will develop locoregional recurrences within 2 years and 20% to 30% will develop distant metastases.

Surgery followed by chemoradiotherapy is the accepted standard for tumors considered to be resectable. Those patients considered unresectable have traditionally been treated with chemoradiotherapy alone.

Integrating chemotherapy in the upfront treatment of locally advanced disease is under investigation. The goal of this treatment strategy is to enhance local control, to decrease local recurrences and distant failures, and ultimately to improve survival. One approach is neoadjuvant, or induction chemotherapy before the definitive local therapies, surgery and/or radiotherapy. The phase II studies neoadjuvant therapy with cisplatin and infusional 5-fluorouracil (5-FU) emerged as one of the most active combinations[1]. Consistent complete response (CR) rates in the range of 20% to 50% were observed after 3 cycles of chemotherapy, with overall response rate of 60-100%, despite differences in the treatment regimens tested[2-10]. Although most of the randomized studies did not demonstrate survival benefit, distant metastasis has been significant reduced. In addition, the responder to neoadjuvant chemotherapy usually predictably response to subsequent radiotherapy and usually live longer than nonresponders[11-21]. These studies also indicated that neoadjuvant chemotherapy did not increase the morbidity of subsequent surgery and/or radiotherapy. Therefore, the combination of cisplatin and infusional 5-FU (PF) has been the best established and arguably most widely used neoadjuvant treatment for patients with potentially curable, advanced, local-regional HNSCC before radiotherapy with or without surgery. However, Taxotere or paclitaxel plus cisplatin and 5-FU (TPF) demonstrated promising antitumor activity in the treatment of SCCHN, high response rates were observed with this triple regimen in single arm studie[22-24]. Recent data from randomized study, as table shown below, suggested that the triple regimen may provide survival benefit as neoadjuvant therapy to definitive therapy[25-27].

Table 42: Neoadjuvant chemotherapy comparative study: taxene/cisplatin/5FU vs. cisplatin/5FU

Regimens	N	Response	Survival
Paclitaxel/PF vs. PF (Hitt 2003[25])	384	$P < 0.0001$	$P = 0.038$
Docetaxel/PF vs. PF (Vermorken 2004[26])	358	$P = 0.007$	$P = 0.016$

The safety of this triple regimen has now been assessed in a number of studies. In one European study[6], patients received Taxotere 75 mg/m^2 with cisplatin 75 mg/m^2 and 5-FU 750 mg/m^2 per day for 5 days together with the prophylactic administration of ciprofloxacin. The following adverse events (AEs) were observed (all grades of AEs, incidence per patient): hematotoxicity: neutropenia (96%), thrombocytopenia (25%); digestive toxicity: nausea (63%), vomiting (38%), diarrhea (46%), stomatitis (46%); and asthenia (67%).

For definitive local therapies, chemoradiotherapy has demonstrated survival advantage over radiotherapy in multiple randomized large clinical studies[28-36]. As indicated by meta-analyses, only chemoraiotherapy has statistically significant survival advantage, neoadjuvant therapy with PF regimen has trend to survival benefit, whereas adjuvant chemotherapy has no survival benefit (see table below)[37-39].

Table 43: Chemotherapy meta-analysis on survival (MACH-NC)[37]

Timing	No. Trials	No.pts.	RR (95% CI)	P value	5 yr benefit
Neoadjuvant	31	5269	0.95 (0.88 - 1.01)	NS	2%
PF subset	15	2487	0.88 (0.79 - 0.97)	.05	
Adjuvant	8	1854	0.98 (0.85 -1.19)	NS	1%
Concurrent	26	3727	0.81 (0.76 - 0.88)	< 0.0001	8%

Further more, addition of neoadjuvant chemotherapy to radiotherapy resulted additional survival advantage, better locoregional and distant control (table below).[35]

Table 44: Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy

Vokes et al. (University of Chicago)	Concurrent	Induct.-- Conc.
	T-FHX	CT--T-FHX
Overall Survival	60%	77%
Locoreg. Control	86%	94%
Distant Control	79%	93%

The study submitted in this sNDA, TAX 323, compared neoadjuvant chemotherapy treatment with TPF to treatment with cisplatin + 5-FU (PF) in a randomized phase III setting, in an effort to improve local control in patients with inoperable locally advanced HNSCC.

9 OVERALL ASSESSMENT

9.1 Conclusions

The study TAX 323 has demonstrated advantage of TPF combination as neoadjuvant therapy in locally advanced HNSCC patients over the existing PF regimen with acceptable risk/benefit ratio.

9.2 Recommendation on Regulatory Action

The reviewer recommend approve Taxotere (75 mg/m2, IV) in combination with Cisplatin and infusional 5-FU for neoadjuvant treatment of patients with locally advanced inoperable squamous cell carcinoma.

9.3 Recommendation on Postmarketing Actions

The reviewer recommend the sponsor submit study TAX 324 as a sNDA for efficacy and safety review.

9.4 Labeling Review

See label.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study TAX 323

10.1.1.1 Protocol Review
Title: A randomized phase III multicenter trial of neoadjuvant docetaxel (Taxotere) plus cisplatin plus 5-fluorouracil (5-FU) versus neoadjuvant cisplatin plus 5-fluorouracil in patients with locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN)

Objectives

Primary: To evaluate the progression-free survival after treatment with docetaxel plus cisplatin plus 5-FU (TPF) in comparison with cisplatin plus 5-FU (PF) in patients with locally advanced inoperable SCC of the head and neck.

Secondary: To evaluate and compare the clinical response rate both before and after radiotherapy, the local symptoms, the duration of response, the time to treatment failure, the survival, the toxicity and the quality of life in the 2 study groups.

Mile Stones

No SPA or EOP2 regarding study TAX 323.
There was a pre-NDA meeting held on 1-15-2006 as described in section 2.5.

Patient Selection Criteria (take as is from the original protocol):

"(1) Tumor type

Histologically or cytologically proven squamous cell carcinoma of the head and neck presenting with locally advanced disease at diagnosis. Primary tumor sites eligible are: oral cavity, oropharynx, hypopharynx and larynx. Although they are admittedly of squarnous cell types, the following tumors will be excluded because their responsiveness to chemotherapy may differ: tumors of the nasopharynx, the nasal and paranasal cavities.

(2) Extent of the disease - Patients are required to have at least one uni or bidimensionally measurable lesion.
- Stage III or IV without evidence of distant metastases, according to the TNM staging system. Absence of metastases must be checked by chest X-ray (with or without CT), abdominal

ultrasound or CT in case of liver function test abnormalities, and bone scan in case of local symptoms.
- Tumor considered as inoperable after evaluation by a multidisciplinary team. Reason for inoperability will be reported in the CRF.

(3) Prior treatment
- No previous chemotherapy or radiotherapy for any reason and no previous surgery for SCCHN are allowed at time of study entry.
- No prior treatment within a therapeutic clinical trial is allowed within 30 days prior to study entry

(4) Concurrent treatment
- No concurrent treatment with any other anticancer therapy.
- No chronic treatment (> 3 months) with corticosteroids at a daily dose > 20 mg methylprednisolone or equivalent,

- No concomitant use of drugs which could interact wtth 5-fluorouracil (e.g. cimetidine, allopurinol, folic or folinic acid)

(5) Patient condition
- Age between 18 and 70 years
- WHO performance status 0 or 1
- Excluding pregnant, lactating women or of childbearing potential unless adequate contraception

(6) Prior and concomitant associated diseases
- No previous or current malignancies at other sites with the exception of adequately treated in situ carcinoma of the cervix uteri, basal or squamous cell carcinorna of the skin or other cancer curatively treated by surgery and with no evidence of disease for at least 5 years
- No symptomatic peripheral neuropathy > grade 2 by NCIC-CTG criteria
- No clinical altered hearing
- No other serious illness or medical condition including but not limited to:
* unstable cardiac disease despite treatment
* myocardial infarction within 6 months prior to study entry
* history of significant neurologic or psychiatric disorders including dementia or seizures * active uncontrolled infection
* active peptic ulcer
* chronic obstructive pulmonary disease requiring hospitalization during the year preceding study entry

(7) Laboratory data
- hermatology:
* neutrophit count > 2.0 x 10^9/L
* platelet count > 100 x 10^9/L
* hemoglobin > 10 g/dl (6.2 mmol/L)
- hepatic function:

* total serum bilirubin < 1 time the upper normal limit (UNL) of the participating center
* ASAT (SGOT) and ALAT (SGPT) < 2.5 x UNL
* alkaline phosphatase < 5 x UNL
* patients with ASAT or ALAT > 1.5 UNL associated with alkaline phosphatase > 2.5 UNL are not eligible for the study
- renal function: serum creatinine < 120 pmol/L (1.4 mg/dl); if values are > 120 prnol/L, creatinine clearance shou1d be > 60 ml/min (actual or calculated by the Cockcroft- Gault method.

(8) Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, those conditions should be discussed with the patient before registration in the trial.

(9) Signed informed consent prior to beginning protocol specific procedures."

Study Design - See section 6.1.3 for details.

Treatments

Chemotherapy – Induction

Table 45: Chemotherapy Regimen

Experimental arm (Arm A)	docetaxel: 75 mg/m^2, one hour IV infusion on day 1 followed by cisplatin 75 mg/m^2 administered as a one-hour IV infusion. The continuous IV infusion of 5-FU 750 rng/m^2/day from day 1 to day 5 will begin after the end of cisplatin administration.
Standard arm (Arm B)	Cisplatin: 100 mg/m^2, administered as one-hour infusion on day 1 followed by the continuous IV infusion of 5-FU 1000 mg/m^2/day from day 1 to day 5.

The cycles will be repeated every three weeks up to a total of 4 cycles.

Premedication:
- Dexamethasone (Docetaxel arm only) 8 mg per os bid for 3 days starting the day before docetaxel infusion.
- Ciprofloxacin (or alternate) 500 mg p.o. bid for lQ days starting on day 5 of each cycle of chemotherapy.
- Antiemetics (5-HT3 antagonist) prior and after cisplatin administration.

Supportive care:
- Tube feeding: Early enteral tube feeding should be considered if difficulty is anticipated.
- GCSF for neutropenia and subsequent cycles.

Duration of administration:

Patients will receive 4 cycles of chemotherapy unless progression, unacceptable toxicity or patient refusal. Patients with progression noted at any time or those who do not respond at the primary tumor site after 2 cycles will be immediately referred to the radiation oncologist.

Locoregional Definitive Treatment

Radiotherapy:

All patients will receive radiotherapy after the end of the chemotherapy with a minimum interval of 3 weeks and a maximum interval of 6 weeks after completion of the last cycle (day 28 to 56 of last cycle). The irradiated volumes will include the primary site and both sides of the neck. Radiation will be delivered using either a conventional fractionation (1.8 Gy - 2.0 Gy, 1x/day, five days per week - total dose of 66 - 70 Gy), or accelerated/hyperfractionated regimens of radiotherapy (2 x/day, with a minimum inter-fraction interval of 6 hours, five days per week, scheme at the discretion of the center - up to a total of maximum 70 Gy for accelerated regimens and of maximum 74 Gy for hyperfractionated schemes). Each institution will commit itself to treat all patients with one of these regimens (conventional or hyperfractionation) prior to study start.

Surgery:

Neck dissection before radiotherapy may be considered for patients with good response at the primary site and poor response at the neck. For patients who will have undergone neck dissection, the interval between the end of chemotherapy and initiation of radiotherapy will be increased by 2 additional weeks. Surgery may be considered following completion of radiotherapy for patients with residual lesion at the primary site and/or the neck 3 months after completion of radiotherapy.

Required Clinical and Radiological Evaluations (taken as is from the original protocol)

"Tumor assessment including CT-scan or MRI and endoscopy (if necessary) was performed at the following times during the study:
Prestudy;
After Cycle 2 of chemotherapy (Day 21);
After completion of chemotherapy (days 21 to 28 of Cycle 4);
12 weeks after completion of radiotherapy;
On follow-up visits; and
At any time if suspicion of disease progression.

One of 3 methods of tumor assessment (measurable, evaluable, or non evaluable) was to be chosen for the entire duration of the study.

Lesion assessments:

1. Assessment of bidimensionally measurable lesions:

i. Physical examination: A skin nodule or superficial lymph node was considered as a measurable lesion if it measured at least 20 x 10 mm;
ii. CAT scan: A lesion was considered measurable if it measured at least 20 x 10 mm.

2. Assessment of unidimensionally measurable lesions - lesions that could be measured with only 1 diameter were assessed by:
i. Physical examination: ≥20 mm;
ii. CAT scan: ≥ 20 mm.

3. Assessment of evaluable not measurable lesions: Lesions that were neither bidimensionally nor unidimensionally measurable as defined above."

Criteria for evaluation of response

Definition of evaluability: All patients receiving ≥ 2 cycles of chemotherapy were considered evaluable for response if all baseline lesions were assessed at least once after the second cycle with the same method of measurement as was used at baseline. Patients with progression earlier than Cycle 2 were evaluable as "early progression."

Response criteria: Response was evaluated with modified WHO criteria. The criteria were modified by removal of the necessity for confirmation of tumor response by a second observation not less than 4 weeks after the initial assessment. In this particular study, given the fact that radiotherapy was started as soon as possible after the end of chemotherapy, some responses (CRs or partial PRs) bidimensionally and unidimensionally measurable disease and evaluable not measurable disease (except bone) are described below.

1. Bidimensionally and unidimensionally measurable disease:
• **CR**: Disappearance of all known disease.

• **PR**: In case of bidimensionally measurable disease, decrease by at least 50% of the sum of the products of the largest perpendicular diameters of all measurable lesions. For unidimensionally measurable disease, decrease by at least 50% in the sum of the largest diameters of all lesions. It was not necessary for all lesions to have regressed to qualify for PR, but no lesion should have progressed and no new lesion should have appeared. Serial evidence of appreciable change documented by radiography or photography was to be obtained and was to be available for subsequent review. The assessment was to be objective.

• **No change** (NC): For bidimensionally measurable disease, <50% decrease and <25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions observed at least 6 weeks after start of treatment. For unidimensionally measurable disease, <50% decrease and <25% increase in the sum of the diameter of all lesions observed at least 6 weeks after start of treatment. No new lesions should have appeared.

• **Progressive disease** (PD): >25% increase in the size of at least 1 bidimensionally or unidimensionally measurable lesion (in comparison with the measurements at nadir) or

appearance of a new lesion. The occurrence of pleural effusion or ascites was also considered as PD if this was substantiated by positive cytology. Pathological fracture or collapse of bone were not necessarily evidence of disease progression. Patients could be assigned to the progression category 6 weeks after entering the study. If progression was observed before this, the patient was considered to have "early progression."

• **PD** after initial response: A 25% or more increase in the size of 1 or more measurable lesion (relative to the smallest [nadir] size measured since the start of the treatment).

2. Evaluable not measurable disease (except bone)

• **CR**: Complete disappearance of all known disease.

• **PR**: Estimated decrease in tumor size of 50%.

• **NC**: NC observed at least 6 weeks after start of treatment. This included stable disease, estimated decrease of less than 50%, and lesions with estimated increase of less than 25%.

• **PD:** Appearance of any new lesions not previously identified or estimated increase of 25% or more in existent lesions.

Overall Response

The table below describes how overall response was determined in the presence of bidimensionally or unidimensionally measurable lesions.

Table 46: Determination of overall response in the presence of bidimensionally or unimensionally measurable lesions

Response in bidimensionally measurable lesions	Response in unidimensionally measurable and evaluable not measurable lesions	Response in non evaluable lesions	Overall response
PD	Any	Any	PD
Any	PD	Any	PD
NC	Any except PD	Any except PD	NC
PR	Any except PD	Any except PD	PR
CR	Any except PD	Any except PD	PR
CR	CR	CR	CR
Any	Any	PD or new lesion	PD

PD = progression of disease, NC = no change, PR = partial response, CR = complete response.

Determination of best overall response

Best overall response was the best response designation recorded from the date of randomization until disease progression. Confirmed and unconfirmed CRs or PRs were considered for determination of best overall response. The clinical response rates were calculated at the end of the neoadjuvant chemotherapy and after the end of the administration of radiation therapy by the study coordinator and were defined as follows:

The overall clinical response rate after neoadjuvant chemotherapy (ORR-CT) is the best response designation recorded from the date of randomization up to disease progression during chemotherapy or end of chemotherapy cycles.

The clinical response rate after radiation therapy (ORR-RT) is the best response recorded at the end of the radiation therapy taking into account all tumor assessments after radiation therapy up to disease progression or further anti-cancer therapy, and is measured using the date of randomization as a reference.

The overall clinical response rate for the whole treatment (ORR-CTRT) is the best response recorded on the whole treatment (chemotherapy + radiotherapy) and is measured taking the best response between the ORR-CT and ORR-RT.

Final evaluation
A patient final evaluation was performed to determine, for every patient, his/her eligibility/evaluability status and his/her main efficacy endpoints. This assessment included the following:
eligibility,
major protocol violations during the study,
best overall response to chemotherapy,
response to radiotherapy,
date of progression,
date and type of subsequent anticancer therapy.

This final evaluation was done using the data entered into the EORTC database by the study coordinator in collaboration with the EORTC data manager and the Sponsor. The Sponsor was usually represented by the clinical study director and/or clinical trial manager. The patient final evaluation was then entered into the EORTC database and transferred to the Sponsor via a SAS dataset (FEVAL dataset) after the EORTC database had been locked (in April 2004). The statistical analysis conducted by the Sponsor and reported in this report has primarily used the FEVAL dataset as long as eligibility, evaluability, and main efficacy variables were concerned."

Safety Evaluation

Recording of toxicities will be graded according to NCIC-CTG expanded toxicity criteria for neoadjuvant chemotherapy and according to RTOG/EORTC late radiation morbidity criteria for radiotherapy. They will be performed every 3 weeks during chemotherapy, at the end of chemotherapy (day 21 of the last cycle) before and during radiotherapy and then at the time of follow up visits.

An **adverse event** was any sign, symptom, illness, or experience that developed or worsened in severity during the course of the study. Intercurrent illnesses were to be regarded as adverse events.

Abnormal results of diagnostic procedures, including abnormal laboratory findings, were considered to be adverse events if:
The abnormality resulted in study withdrawal;
Was associated with a serious adverse event;
Was associated with clinical signs and symptoms;
Was considered by the investigator to be of clinical significance.

The investigators were to decide if adverse events were related to the protocol treatment (i.e., none, unlikely, possibly, or probably related) and the decision was to be recorded on the toxicity forms.

A **serious adverse event** is any event that:
Is fatal;
Is life-threatening;
Requires inpatient hospitalization or prolongs existing hospitalization;
Results in persistent or significant disability or incapacity;
Is a congenital anomaly or birth defect;
Is an important medical event.

Adverse events were to be documented by the investigator as follows:

All adverse events occurring during the study period were to be recorded on the toxicity forms. The study period is defined as being from the date of randomization until the patient's death. However, any adverse event occurring more than 30 days after the end of radiotherapy was reported only if it was considered to be possibly or probably related to study treatment (chemotherapy or radiotherapy) or if the adverse event was ongoing. For patients who received radiotherapy, all adverse events occurring before radiotherapy were reported in the last cycle of chemotherapy. For patients who did not receive radiotherapy, the chemotherapy period ended 30 days at the last chemotherapy infusion.

If the adverse event was serious and occurred during the study period, it had to be reported to the Sponsor within 1 working day by telephone and/or fax and in writing within 2 days using the "Adverse Event Report" form. Any SAEs that occurred >30 days after the end of radiotherapy and that were possibly or probably related to the study treatment were reported in the same manner.

Death during study

Any death occurring during the treatment period (chemotherapy or radiotherapy) or within 30 days following the last day of treatment was to be reported to the Sponsor within 24 hours,

regardless of the relationship to the study treatment. Deaths occurring during the study follow-up period were required to be reported as serious adverse events only if it was believed that the death was possibly related to the study treatment. All deaths were reported on the death report form regardless of the cause.

Laboratory safety data

The following laboratory tests were performed at specified times during and following chemotherapy using standard methods:
Hematology: Total white blood cell count (WBC), neutrophils, platelet count, hemoglobin. Only values at nadir and Day 1 before treatment of each cycle were to be collected. In case of grade 4 neutropenia, a blood cell count was to be performed every 2 days and recorded in the CRF. Relevant data were also recorded at the time of AEs. Laboratory data were not required during the radiotherapy phase of the study.

Blood chemistry: Total bilirubin, alkaline phosphatase, AST, ALT, electrolytes (Na+, K+, Mg2+), SC, CC (measured or calculated; in case SC was >120 µmol/L), total protein, albumin, and calcium. Only values at Day 1 before treatment of each cycle were to be collected. All tests were carried out according to standard laboratory procedures at each study center's locally accredited laboratory, which defined the normal reference range for each assessment.

Other safety data

Complete history of malignant and non-malignant diseases including known hypersensitivity reactions;
Full clinical examination including height, weight, temperature, neurologic examination, assessment of WHO PS;
ECG; and
Chest x-ray.

Statistical Considerations

Endpoints

PFS: Progression-free survival will be calculated from the date of randomization until the date of progression or the date of death (regardless the reason of death), whichever occurred first. If progression or death did not occur before the cut-off date, the patient was censored at the last valid assessment date before the cut-off date.

OS: Survival will be measured from the date of randomization up to the date of death (regardless of the reason for death). If death or last contact did not occur before the cut-off date, the patient was censored at the cut off date, or last contact date if the patient lost follow up before the cut-off date.

RR: Response will be evaluated by modified WHO criteria. In this particular trial given the fact that radiotherapy will be started as soon as possible after the end of chemotherapy. All patients receiving > 2 cycles will be considered evaluable for the response if all baseline lesions have been assessed at least once after the second cycle with the same method of measurement as baseline and if no major protocol violation occurred during the study. However patients with progression earlier than cycle 2, will be evaluable as "early progression".

DOR: The duration of overall response (PR + CR) was calculated from the date of randomization up to the documentation of progression in the responders for the whole treatment (neoadjuvant chemotherapy plus radiotherapy). If progression or death did not occur before the cut-off date/further anti-cancer therapy date (or occurred after the cut-off date), the patient was censored at the last valid assessment date before the cut-off date/further anti-cancer therapy date (at the cut-off date otherwise).

TTF: Time to treatment failure will be calculated from the date of randomization up to the date of failure (progression, relapse, death or withdrawal due to adverse event, patient's refusal, or lost to follow-up).

Local symptoms will be assessed by using the performance status scale for head and neck developed and validated by M. List, Pain intensity will be evaluated by using a visual analogue scale.

Quality of life will be assessed by the EORTC-QLQ-C30 (version 3.0) (1) and the QLQ-H&N35 (6) at baseline (prior to treatment allocation knowledge by the patient), twice during chemotherapy and twice after radiotherapy.

Safety Variables:

The safety analyses are presented overall and by period as defined below:

The baseline (BL) period includes all information recorded up to the randomization date.

The chemotherapy (CT) period starts on the randomization day and ends the day before the start of radiation therapy.

The radiotherapy (RT) period starts on the day the radiation therapy was first given and ends the day of the last administration of radiation therapy treatment plus 30 days (applies only to patients who went on radiation therapy).

The follow-up (FUP) period (applies only to AEs) starts 31 days after the last study treatment period.

Randomization and stratification

Randomization was 1:1. Patients were stratified prior to randomization by primary tumor site and institution.

Populations:

Four study populations were defined: an intent-to-treat (ITT) population, a safety population (SP), a radiotherapy safety population (RSP), and an evaluable for response population.

ITT population (ITT): All randomized patients analyzed in the treatment group to which they were randomized.

Safety population (SP): All treated patients analyzed according to the chemotherapy treatment received in Cycle 1.

Radiotherapy safety population (RSP): All patients evaluable for safety receiving radiotherapy, analyzed according to the chemotherapy treatment received in Cycle 1.

Evaluable for response population: All eligible patients analyzed in the study treatment they received. To be evaluable a patient had to satisfy the following condition: the patient must have received a minimum of 2 cycles of neoadjuvant chemotherapy treatment and have had at least 1 disease assessment with the same imaging procedure for each lesion as at baseline. However, if progression occurred before the second cycle, the patient was considered as evaluable and

reported as early progression. A patient evaluability will be determined by an External Response Review Committee (ERRC) after review of the imaging procedures.

Sample Size and Analyses:
Assuming a median progression-free survival rate of 10 months in the standard arm, it was estimated that 260 events would be needed to ensure a 85% power to detect an improvement of 5 months in median progression free survival with the experimental regimen (from 10 to 15 months, corresponding to HR=1.5) with a 2-sided test performed at the 5% significance level. The size of the target difference was justified by the added costs and toxicity of docetaxel,

Assuming a recruitment period of 24 months and a further follow-up period of 12 months after the last entry, 330 evaluable patients were needed (165 on each arm) to provide the necessary number of events.

Anticipating that about 5% of the patients randomized will not be evaluable or will be lost to follow-up, the sample size had been increased to a total of 348 randomized patients.

An Independent Data Monitoring Committee (IDMC) assessed whether the test arm chemotherapy regimen has an acceptable safety profile after the first 25 patients have been randomized to the TPF arm with a minimum follow-up of 1 cycle (23 days). The IDMC made recommendations to revise the protocol in case there is strong evidence of unacceptable toxicity.

A formal interim analysis of safety and efficacy were performed after 42 progression events observed. The analysis included the first 124 patients accrued over 9 months with a further follow-up period of 3 months (half-way through the total accrual period). The results were submitted to the IDMC. The IDMC consisted of 4 independent experts (a surgeon, an oncologist, a radiotherapist, and a statistician). Their mission was defined as follows:

To provide technical advice on specific issues encountered during the study;
To monitor the efficacy/safety of the test regimen through analysis of deaths, serious adverse events, grade 3 and 4 adverse events, and tumor progressions;
To give recommendations whether or not to pursue accrual based on the results of the interim analysis (this was subsequently canceled);
To give advice on monitoring or analytical issues during the study.

The EORTC data center team reviewed the trial design, primary and secondary endpoints, definition of SAEs, and presented the treatment and toxicity data on 50 patients. The cutoff for this data analysis was 06 December 2000. A total of 205 patients had been randomized, and accrual was expected to be completed in approximately 1 year. The IDMC then met in closed session to consider whether or not any modification of the experimental treatment (TPF) should be recommended for reasons of patient safety. The IDMC did not recommend any modifications to the TPF regimen.

The primary and secondary efficacy analyses were to be performed in the ITT population. Time-to-event data were described using Kaplan-Meier curves and life tables. A non-parametric

confidence interval was calculated for the median survival time. Time-to-event intervals between groups were compared with the log-rank and Wilcoxon linear rank tests and in Cox's proportional hazards model. Hazard ratio (HR) and 95% confidence intervals were obtained from a proportional hazards Cox regression model. Before fitting the Cox model, a substantial evidence for non-proportional treatment hazards in the form of a qualitative change over time was explored. For multivariate analyses, the following baseline items were fitted to the model for each analysis: treatment, oral cavity primary, oropharynx primary, hypopharynx primary, T stage, N stage, and WHO PS. Backwards elimination was then used to drop individual factors from the model with likelihood ratio tests with a 2-sided significance level >10% (primary site was evaluated with a single test).

Chi-square tests were used to compare groups on categorical variables unless the expected cell frequency was <5, in which case Fisher's exact test was used. Logistic or proportional odds models were used to adjust for prognostic factors. Exact confidence intervals were calculated for binary event rates.

Protocol Amendment:

Amendment 1 (13 August 1999)

This amendment modified and clarified some elements regarding patient selection, study design, study treatment, study evaluations, dose adjustment, concomitant medication, response evaluation and interim analysis (to include all data available for the first 25 patients), and updated the pilot study results. This amendment did not include any change regarding the statistical methodology and analysis.

Amendment 2 (25 October 2000)

This amendment made the following modifications:
The timing of follow-up was amended: every 3 months the first year, then every 6 months;
The criteria of inoperability were clarified as all T3-4 patients, all N2-3 stages excluding T1N2, and patients for organ preservation;
A 25% cisplatin dose reduction (from 75 mg/m^2 to 60 mg/m^2) was added in case of National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) expanded toxicity scale grade 4 thrombocytopenia (25 x 10^9);
The external review of responses was cancelled, as majority events has been observed in this study were death and progression-free survival (PFS) was the primary endpoint of this study;
The following aspects of the statistical analysis were amended: the statistical analyses plan were modified by addition of the date of relapse to the date of progression or death for PFS, the definition of time to treatment failure (TTF) was clarified with regard to handling patient's lost-to-follow-up, the duration of the partial response analysis was cancelled, and the calculation of statistical power associated with the overall survival analysis was amended based on the planned sample size (n = 348).

Amendment 3 (05 April 2001)

This amendment modified the criteria for tumor inoperability to exclude patients technically operable who refuse surgery and patients for organ preservation. Also contains minor changes concerning the timing of investigations during chemotherapy and follow-up visits. No changes were made on the statistical methodology and analysis.

Note: The significant amendments were further clarified definition of inoperable disease and excluded candidates for organ preservation, and revised SAP to focus on primary analysis, PFS. These does not affect the outcome of the study.

10.1.1.2 Patient Demography and Disposition

A total of 358 patients randomized between 14 April 1999 and 15 March 2002 from 37 centers in 15 countries. Patients demographics are shown in section 6.1.4

A summary of primary disease characteristics is shown below:

Table 47: Primary disease characteristics

	Randomization group		
	TPF (N=177)	PF (N=181)	All (N=358)
Anatomic site			
Hypopharynx	53 (29.9%)	52 (28.7%)	105 (29.3%)
Larynx	12 (6.8%)	13 (7.2%)	25 (7.0%)
Oral cavity	31 (17.5%)	32 (17.7%)	63 (17.6%)
Oropharynx	81 (45.8%)	84 (46.4%)	165 (46.1%)
Histopathological grade			
Well-differentiated	28 (15.8%)	32 (17.7%)	60 (16.8%)
Moderately differentiated	83 (46.9%)	90 (49.7%)	173 (48.3%)
Poorly differentiated	39 (22.0%)	31 (17.1%)	70 (19.6%)
Undifferentiated	1 (0.6%)	0 (0.0%)	1 (0.3%)
Differentiation cannot be assessed	3 (1.7%)	3 (1.7%)	6 (1.7%)
Missing	23 (13.0%)	25 (13.8%)	48 (13.4%)
Clinical T			
T1	3 (1.7%)	1 (0.6%)	4 (1.1%)
T2	11 (6.2%)	16 (8.8%)	27 (7.5%)
T3	40 (22.6%)	34 (18.8%)	74 (20.7%)
T4	123 (69.5%)	130 (71.8%)	253 (70.7%)
Clinical N			
N0	16 (9.0%)	26 (14.4%)	42 (11.7%)
N1	28 (15.8%)	29 (16.0%)	57 (15.9%)
N2	101 (57.1%)	104 (57.5%)	205 (57.3%)
N3	31 (17.5%)	20 (11.0%)	51 (14.2%)
NX	1 (0.6%)	2 (1.1%)	3 (0.8%)
Time from first diagnosis to randomization (months)			
Median	0.7	0.8	0.7
Minimum	0.0	0.0	0.0
Maximum	8.3	11.3	11.3

ITT = intent-to-treat; TPF= Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Data source: TAX 325 study report

The most frequent clinical TNM stage in both treatment groups was T4/N2/M0 (41.9%). The other TNM stages reported in >10% of patients in any treatment group were T4/N1/M0 (11.2%), and T3/N2/M0 (10.6%). Metastatic disease was found in 2 patients (00235 and 00315) and was as major deviation at inclusion. However, this has no impact to the ITT population.

A summary of tumor characterristics at inclusion is shown below:

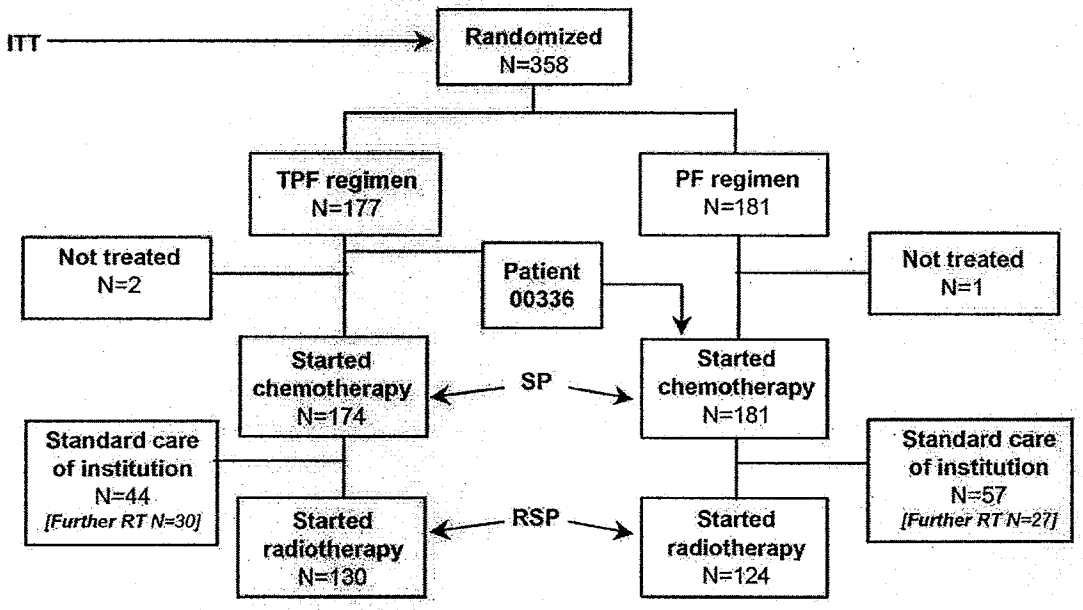
Table 48: Tumor characteristics at inclusion

	Randomization group		
	TPF (N=177)	PF (N=181)	All (N=358)
Number of organs involved			
1	18 (10.2%)	23 (12.7%)	41 (11.5%)
2	153 (86.4%)	143 (79.0%)	296 (82.7%)
3 or more	5 (2.8%)	12 (6.6%)	17 (4.7%)
No tumor assessment at baseline	1 (0.6%)	3 (1.7%)	4 (1.1%)
Measurability of disease			
Bidimensional disease	169 (95.5%)	165 (91.2%)	334 (93.3%)
Unidimensional disease	2 (1.1%)	10 (5.5%)	12 (3.4%)
Evaluable disease	5 (2.8%)	1 (0.6%)	6 (1.7%)
Non evaluable disease	0 (0.0%)	1 (0.6%)	1 (0.3%)
Missing	1 (0.6%)	3 (1.7%)	4 (1.1%)
No tumor assessment at baseline	0 (0.0%)	1 (0.6%)	1 (0.3%)
Organ involved			
Lymph nodes	157 (88.7%)	155 (85.6%)	312 (87.2%)
Hypopharynx	110 (62.1%)	110 (60.8%)	220 (61.5%)
Mouth	27 (15.3%)	29 (16.0%)	56 (15.6%)
Tongue	20 (11.3%)	23 (12.7%)	43 (12.0%)
Larynx	12 (6.8%)	16 (8.8%)	28 (7.8%)
Tonsil	10 (5.6%)	6 (3.3%)	16 (4.5%)
Pharynx	0 (0.0%)	4 (2.2%)	4 (1.1%)
Bone	1 (0.6%)	2 (1.1%)	3 (0.8%)
Connective soft tissue	0 (0.0%)	1 (0.6%)	1 (0.3%)
Head/neck unspecified	1 (0.6%)	0 (0.0%)	1 (0.3%)
Nasopharynx	1 (0.6%)	0 (0.0%)	1 (0.3%)
Thyroid gland	1 (0.6%)	0 (0.0%)	1 (0.3%)

Note: A patient may have several organs involved
Data source: TAX 325 study report

Study TAX 323 patients disposition are as follows:

Figure 6: Patient disposition



TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; ITT = Intent to treat population; SP = Safety population; RSP = Radiotherapy safety population
Note: Patient 00336 was randomized to TPF, but received PF by mistake.

As shown in the figure above, multiple disposition paths resulted due the multi-treatment design of study TAX323. The table below summarized all randomized patients by treatment received.

All randomized patients received CT, but only a fraction of patients received RT. Not all patients who received study treatment were able to complete planned CT, RT or both. The table below table below indicated all randomized patients who did or did not complete treatment and the type of the treatment discontinued.

Table 49: Incidence of treatment completion or discontinuation

DISCONTINUATION PRIOR TO CT/RT COMPLETION (%)	RANDOMIZATION GROUP		
	TPF (N=177)	PF (N=181)	ALL (N=358)
Number of patients without discontinuation	119 (67.2%)	108 (59.7%)	227 (63.4%)
Number of patients with at least one discontinuation prior to CT/RT[a]	58 (32.8%)	73 (40.3%)	131 (36.6%)
Discontinuation prior to CT completion	52 (29.4%)	68 (37.6%)	120 (33.5%)
Discontinuation prior to RT completion	7 (4.0%)	5 (2.8%)	12 (3.4%)

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; AE = adverse event; CT = chemotherapy; RT = radiotherapy
a Prior to completion of chemotherapy or radiotherapy. One patient (00327) discontinued during both CT and RT.
Data source: TAX 323 study report.

As shown above, the majority treatment discontinuation occurred during the chemotherapy and only a very small fraction patients did not complete RT. The reasons for discontinuing chemotherapy are summarized as below:

Table 50: Reason for discontinuation chemotherapy

	Randomization group		
	TPF (N=177)	PF (N=181)	ALL (N=358)
Number of patients			
End of chemotherapy form missing	1 (0.6%)	1 (0.6%)	2 (0.6%)
With treatment discontinuation[a]	176 (99.4%)	180 (99.4%)	356 (99.4%)
Primary reason for discontinuation			
Completion of chemotherapy according to protocol	124 (70.1%)	112 (61.9%)	236 (65.9%)
Adverse event	11 (6.2%)	21 (11.6%)[b]	32 (8.9%)
Death	6 (3.4%)	12 (6.6%)	18 (5.0%)
Progressive disease	24 (13.6%)	20 (11.0%)	44 (12.3%)
Major protocol violation	2 (1.1%)	3 (1.7%)	5 (1.4%)
Lost to follow-up	2 (1.1%)	0 (0.0%)	2 (0.6%)
Consent withdrawn	4 (2.3%)	8 (4.4%)	12 (3.4%)
Other	3 (1.7%)	4 (2.2%)	7 (2.0%)
Discontinuation due to death			
Toxicity from study drug treatment	3 (1.7%)	8 (4.4%)	11 (3.1%)
Infection not due to protocol treatment	2 (1.1%)	0 (0.0%)	2 (0.6%)
Other	1 (0.6%)	4 (2.2%)	5 (1.4%)
Discontinuation due to adverse event			
Only not related AE	3 (1.7%)	3 (1.7%)	6 (1.7%)
Only related AE	6 (3.4%)	16 (8.8%)	22 (6.1%)
Not related and related AE	2 (1.1%)	1 (0.6%)	3 (0.8%)
No AE recorded	0 (0.0%)	1 (0.6%)	1 (0.3%)

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; AE = adverse event
Data source: TAX 323 study report.
a With treatment discontinuation form completed
b For one patient (00158) no AE was reported at chemotherapy discontinuation

Reviewer: The early drops out from chemotherapy due to disease progression were similar between the two arms (13.6% for TPF and 11.0% for PF). Lower chemotherapy drops out rate were noted for TPF arm for adverse event (6.2% for TPF and 11.6% for PF) and death (3.4% for TPF and 6.6% for PF).

The chemotherapy exposure for patients who received per protocol RT is summarized as below:

Table 51: Chemotherapy status in patients who received per protocol RT

	Randomization group		
	TPF (N=130)	PF (N=124)	All (N=254)
Number of patients			
End of chemotherapy form missing	1 (0.8%)	0 (0.0%)	1 (0.4%)
With treatment discontinuation	129 (99.2%)	124 (100.0%)	253 (99.6%)
Primary reason for discontinuation			
Completion of chemotherapy according to protocol	116 (89.2%)	104 (83.9%)	220 (86.6%)
Adverse event	9 (6.9%)	15 (12.1%)	24 (9.4%)
Major protocol violation	1 (0.8%)	2 (1.6%)	3 (1.2%)
Consent withdrawn	1 (0.8%)	2 (1.6%)	3 (1.2%)
Other	2 (1.5%)	1 (0.8%)	3 (1.2%)
Completion of chemotherapy according to protocol			
Completion after 2 cycles	5 (3.8%)	8 (6.5%)	13 (5.1%)
Completion after 4 cycles	111 (85.4%)	96 (77.4%)	207 (81.5%)

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Data source: TAX 323 study report.

The chemotherapy status for patients who did not receive per protocol RT are summarized as below:

Table 52: Chemotherapy status in patients who did not receive per protocol RT

	Randomization group		
	TPF (N=47)	PF (N=57)	All (N=104)
Number of patients			
End of chemotherapy form missing	0 (0.0%)	1 (1.8%)	1 (1.0%)
With treatment discontinuation [a]	47 (100.0%)	56 (98.2%)	103 (99.0%)
Primary reason for discontinuation			
Completion of chemotherapy according to protocol	8 (17.0%)	8 (14.0%)	16 (15.4%)
Adverse event	2 (4.3%)	6 (10.5%)	8 (7.7%)
Death	6 (12.8%)	12 (21.1%)	18 (17.3%)
Progressive disease	24 (51.1%)	20 (35.1%)	44 (42.3%)
Major protocol violation	1 (2.1%)	1 (1.8%)	2 (1.9%)
Lost to follow-up	2 (4.3%)	0 (0.0%)	2 (1.9%)
Consent withdrawn	3 (6.4%)	6 (10.5%)	9 (8.7%)
Other	1 (2.1%)	3 (5.3%)	4 (3.8%)
Completion of chemotherapy according to protocol			
Completion after 2 cycles	0 (0.0%)	2 (3.5%)	2 (1.9%)
Completion after 4 cycles	8 (17.0%)	6 (10.5%)	14 (13.5%)

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
a With treatment discontinuation form completed
Data source: TAX 323 study report.

All surgical interventions, per protocol, in the SCCHN area (cervical nodes and/or primary tumor) were to be performed before PD. After PD, surgery was allowed as further anti-cancer therapy. The incidence of per protocol surgery is summarized as below:

Table 53: Incidence of per protocol surgery

	TREATMENT RECEIVED	
	TPF (N=174)	PF (N=181)
Number of patients		
WITH AT LEAST ONE SURGERY	45 (25.9%)	27 (14.9%)
WITH SURGERY BEFORE PD [a b]	17 (9.8%)	9 (5.0%)
- Between chemotherapy and radiotherapy	7 (4.0%)	4 (2.2%)
- After radiotherapy	10 (5.7%)	5 (2.8%)
WITH SURGERY AFTER PD [b]	28 (16.1%)	18 (9.9%)

SP = safety population; TPF= Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients PD = progressive disease
a One patient (00024) in the TPF treatment group had surgery before PD both between chemotherapy and radiotherapy (occurrence of first surgery) and after radiotherapy.
b Three patients in the TPF treatment group (00014, 000240, 00306) and two patients in the PF treatment group (00027, 00085) had surgery both before PD (occurrence of first surgery) and after PD.
Data source: TAX 323 study report

With various dispositions in this multimodality study TAX 323, several analysis populations, in addition to the ITT population, were used by the applicant for efficacy and safety analyses. They are listed as below:

Table 54: Analysis populations

	Randomization group		
	TPF (N=177)	PF (N=181)	All (N=358)
Number of patients			
Randomized	177 (100.0%)	181 (100.0%)	358 (100.0%)
Eligible	166 (93.8%)	167 (92.3%)	333 (93.0%)
Evaluable for safety	175 (98.9%)	180 (99.4%)	355 (99.2%)
Received chemotherapy	175 (98.9%)	180 (99.4%)	355 (99.2%)
Received radiotherapy	130 (73.4%)	124 (68.5%)	254 (70.9%)
Evaluable for response	163 (92.1%)	155 (85.6%)	318 (88.8%)

ITT = intent to treat; TPF= Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Data source: TAX 323 study report

For safety population, 2 patients of each arm excluded for not receiving any study treatment. One patient, who randomized to TPF arm but treated with PF by mistake, was removed from TPF group and added to the PF group. Therefore, the safety population was 174 for TPF and 180 for PF.

The reasons for excluding patients from the evaluable population are as follows.

Table 55: Reasons of non-evaluability for response by randomization group (ITT)

	Randomization group	
	TPF (N=177)	PF (N=181)
Patients non evaluable for response	14 (7.9%)	26 (14.4%)
Patient did not receive 2 cycles of induction chemotherapy	12 (6.8%)	21 (11.6%)
Tumor assessment methods different from baseline	2 (1.1%)	5 (2.8%)
Reason of chemotherapy discontinuation for patients with <2 cycles		
Adverse event	3 (1.7%)	5 (2.8%)
Completion of chemotherapy according to protocol	0 (0.0%)	1 (0.6%)
Consent withdrawn	1 (0.6%)	3 (1.7%)
Death	5 (2.8%)	9 (5.0%)
Major protocol violation	2 (1.1%)	1 (0.6%)
Other	1 (0.6%)	2 (1.1%)

ITT = intent to treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Data source: TAX 323 study report

10.1.1.3 Efficacy Results

The Primary Analysis: TTP
See section 6.1.4 efficacy findings.

Overall Survival
See section 6.1.4 efficacy findings.

Response Rate
The response rates of chemotherapy, radiotherapy and both are summarized in section 6.1.4.

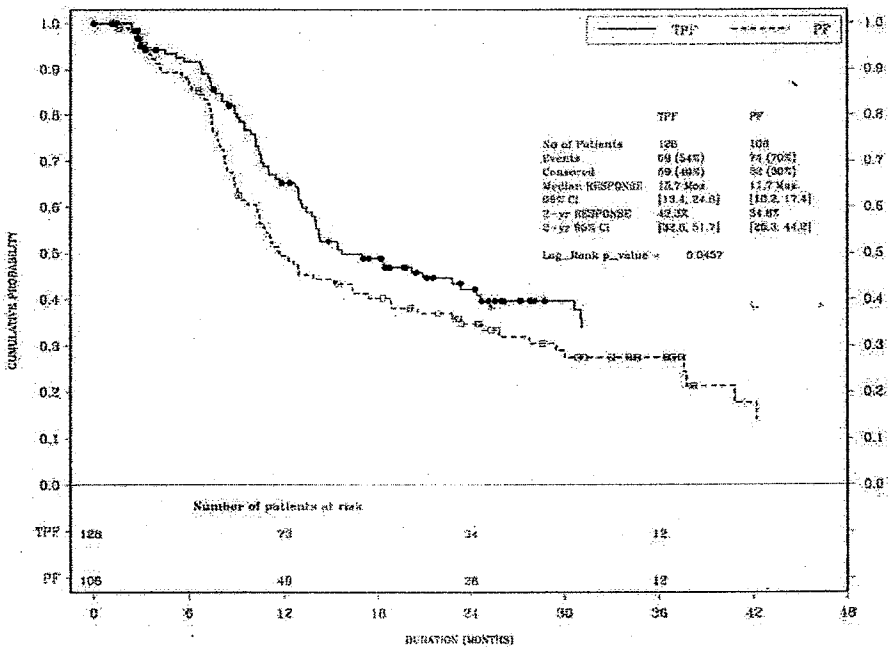
Duration of Response

Table 56: Duration of Response (CR+PR during CT&RT)

	RANDOMIZATION GROUP		
	TPF (N=128)	PF (N=106)	ALL (N=234)
Number of patients with			
event	69 (53.9%)	74 (69.8%)	143 (61.1%)
censored data	59 (46.1%)	32 (30.2%)	91 (38.9%)
Event reasons (Response)			
Progression	65 (50.8%)	69 (65.1%)	134 (57.3%)
Death	4 (3.1%)	5 (4.7%)	9 (3.8%)
Censoring reasons (Response)			
Lost to follow-up	2 (1.6%)	3 (2.8%)	5 (2.1%)
No event at cutoff date	43 (33.6%)	26 (24.5%)	69 (29.5%)
Death more than 100 days after the last valid assessment	12 (9.4%)	3 (2.8%)	15 (6.4%)
Further anti-cancer therapy before event	2 (1.6%)	0 (0.0%)	2 (0.9%)

TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Data source: TAX 323 study report.

Figure 7: Duration of Response-Kaplan-Meier Curve



Event = progression or death
Data source: TAX 323 study report.

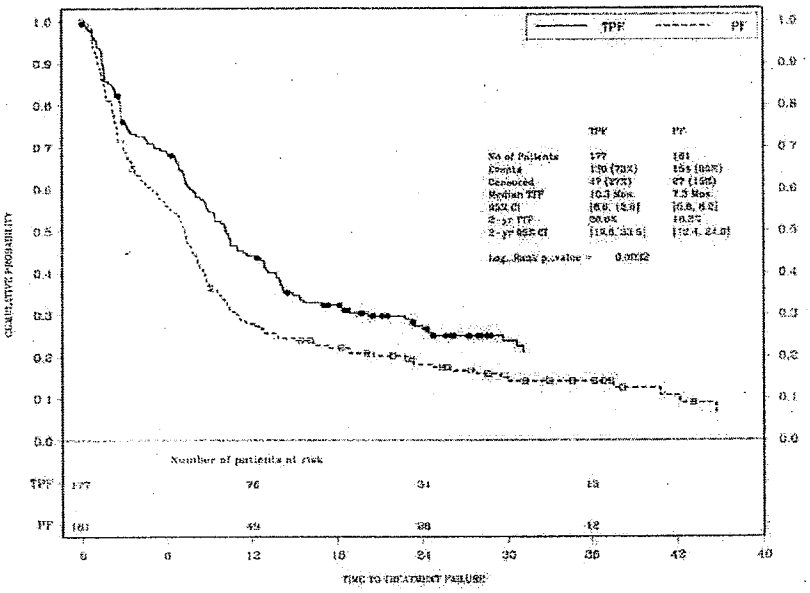
Time to treatment Failure

Table 57: Time to Treatment Failure (ITT)

	RANDOMIZATION GROUP		
	TPF (N=177)	PF (N=181)	ALL (N=358)
Number of patients with			
event	130 (73.4%)	154 (85.1%)	284 (79.3%)
censored data	47 (26.6%)	27 (14.9%)	74 (20.7%)
Event reasons (TTF)			
Progression	89 (50.3%)	99 (54.7%)	188 (52.5%)
Death	21 (11.9%)	25 (13.8%)	46 (12.8%)
CT Withdrawal due to AE	11 (6.2%)	21 (11.6%)	32 (8.9%)
RT Withdrawal due to AE	2 (1.1%) [a]	0 (0.0%)	2 (0.6%)
CT Subject's refusal	4 (2.3%)	8 (4.4%)	12 (3.4%)
RT Subject's refusal	1 (0.6%)	1 (0.6%)	2 (0.6%)
Lost to follow-up before treatment completion	2 (1.1%)	0 (0.0%)	2 (0.6%)
Censoring reasons (TTF)			
Lost to follow-up after treatment completion	4 (2.3%)	1 (0.6%)	5 (1.4%)
No event at cutoff date	43 (24.3%)	26 (14.4%)	69 (19.3%)

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; TTF = time to treatment failure; AE = adverse event
a One patient (00327) discontinued during both CT and RT due to AE and was counted only once during chemotherapy (first failure) in this TTF table
Data source: TAX 323 study report.

Figure 8: Time to treatment failure-Kaplan Meier Curve (ITT)



ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU Event = progression, relapse, death, discontinuation due to adverse event, patient refusal of treatment, or lost to follow-up before the end of treatment (chemotherapy plus radiotherapy).
Data source: TAX 323 study report

Reviewer Note: The TTF analysis also support better efficacy of TPF arm.

Patient Reported Outcome (PRO)

Please see section 6.1.4.4.

10.1.1.4 Safety Results
In addition to the pertinent safety analysis and review in section 7, other relevant safety assessments are described below. All analses are based on NCI CTC criteria.

10.1.1.4.1 Common Toxicity

Table 58: Patients with study drug-related AEs during chemotherapy of all grades, in at least 2 patients (SP)

NCIC CTG term	Treatment received	
	TPF (N=174)	PF (N=181)
Number of patients without serious TEAE	136 (78.2%)	131 (72.4%)
Number of patients with serious TEAE	38 (21.8%)	50 (27.6%)
Infection	12 (6.9%)	11 (6.1%)
Fever in absence of infection	10 (5.7%)	5 (2.8%)
White blood count [a]	8 (4.6%)	8 (4.4%)
Hemoglobin [b]	5 (2.9%)	9 (5.0%)
Diarrhea	3 (1.7%)	5 (2.8%)
Gastrointestinal pain/cramping	3 (1.7%)	1 (0.6%)
Ischemia myocardial	3 (1.7%)	1 (0.6%)
Lethargy	3 (1.7%)	3 (1.7%)
Platelets [c]	3 (1.7%)	4 (2.2%)
Stomatitis	3 (1.7%)	9 (5.0%)
Creatinine	2 (1.1%)	4 (2.2%)
Febrile neutropenia	2 (1.1%)	1 (0.6%)
Granulocytes [d]	2 (1.1%)	5 (2.8%)
Hypokalemia	2 (1.1%)	2 (1.1%)
Cardiac function	1 (0.6%)	3 (1.7%)
Other: dehydration	1 (0.6%)	3 (1.7%)
Altered hearing		3 (1.7%)
Anorexia		3 (1.7%)
Nausea		4 (2.2%)
Vomiting		5 (2.8%)

TEAE = treatment-emergent adverse event; SP = safety population; NCIC CTG = National Cancer Institute of Canada Clinical Trials Group; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
a leucopenia,
b anemia,
c thrombocytopenia,
d neutropenia
Notes: Percentages have been calculated on the total number of patients.
For the number of patients with TEAEs and for each NCIC CTG classification, patients having one or more NCIC CTG term are counted only once.
For each patient, only the maximum grade recorded for the same NCIC CTG term is taken into account into the calculations.
Data source: TAX 323 study

10.1.2. Study TAX 324

Note: The summary of study TAX 324 results were submitted for information purpose only, these results have not been reviewed and analysed by FDA.

10.1.2.1 Protocol Review

Title: A Randomized Phase III Multicenter Trial of Neoadjuvant Docetaxel (Taxotere®) Plus Cisplatin and 5-Fluorouracil (TPF) Versus Neoadjuvant Cisplatin Plus 5 Fluorouracil Followed by Concomitant Chemoradiotherapy to Improve the Overall Survival and Progression Free Survival in Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck.

Mile Stone

10-28-1997, Study TAX 324 protocol was submitted for special protocol assessment.

8-3-1999, Study TAX 324 protocol final version submitted for review.

Objectives

Primary - To compare the overall survival after treatment with the test tri-therapy (TPF: docetaxel plus cisplatin and 5-Fluorauracil (5-FU)) or the control treatment (PF: Cisplatin plus 5 FU) followed by chemoradiotherapy for patients with locally advanced squamous cell carcinoma of head and neck (SCCHN).

Secondary - The main secondary endpoint is progression free survival (PFS). The other secondary endpoints are improvement of local symptoms; time-to-treatment failure; quality of life; clinical complete response rate (CR) and overall response rate (CR +PR) after chemotherapy and after locoregional therapy (chemoradiotherapy); duration of response (CR and CR+PR); toxicity; relationship of tumor markers and response to therapy.

Study Design

TAX324 was a randomized, multicenter, open-label, phase III trial comparing two combination chemotherapy regimens as neoadjuvant (induction) treatment before chemoradiotherapy for locally advanced SCCHN.

Patients were randomized to receive either the test tri-therapy (TPF) or the control treatment (PF), followed by chemoradiotherapy in both groups. Random assignment was carried out centrally using the biased coin minimization technique and stratified at inclusion by the following factors:

1. Primary tumor site (oral cavity versus oropharynx versus hypopharynx versus larynx)
2. N stage (N0-1 versus N2-3)
3. Center

10.1.2.2 Efficacy Summary

The primary endpoint of TAX 324 is overall survival.

Treatment regimen

Table 59: Treatment Arms and Regimens

Arm	Regimen
TPF	Docetaxel 75 mg/m² by 1 hour IV infusion on day 1 followed by cisplatin 100 mg/m² administered as a 30-minute to three hour IV infusion. The continuous IV infusion of 5-FU 1000 mg/m²/day from day 1 to day 4 was to begin after the end of cisplatin infusion on day 1.
PF	Cisplatin 100 mg/m² as a 30-minute to three hour IV infusion on day 1 followed by the continuous IV infusion of 5-FU 1000 mg/m²/ day from day 1 to day 5.

In case of grade 3 or grade 4 hearing loss, carboplatin (at dosage of AUC=5) might be used to replace cisplatin in the remaining chemotherapy cycles. The dose of carboplatin AUC5 was to be calculated based on the Calvert formula (Calvert, A. J Clin Oncol, 1989 7:1748-56; reference available upon request).

Routine premedication was required in the docetaxel arm (arm TPF): dexamethasone 8 mg per os b.i.d. for 3 days starting the day before docetaxel infusion and ciprofloxacin (or alternate) 500 mg per os b.i.d. for 10 days starting on day 5 of each cycle of chemotherapy.

The cycles of chemotherapy were to be repeated every 3 weeks for up to a total of 3 cycles of chemotherapy unless progression, unacceptable toxicity, patient refusal, or NC (no change: less than 25% reduction in tumor size) at primary site after 2 cycles.

All patients who did not have progressive disease were to receive chemoradiotherapy as per protocol. Patients with progression noted at any time were to be referred for locoregional treatment according to the standard of care for the participating center. Patients discontinuing due to toxicity, patient refusal, or NC (less than 25% reduction in tumor size) at primary tumor site after cycle 2 were to be referred for early chemoradiotherapy according to the protocol.

Patients in both treatment arms were to receive 7 weeks of chemoradiotherapy following chemotherapy with a minimum interval of 3 weeks and no later than 8 weeks after start of the last cycle (day 22 to day 56 of last cycle). During radiotherapy, carboplatin was to be given weekly as a one-hour infusion for a maximum of 7 doses. The irradiated volumes included the primary site and both sides of the neck. Radiation was to be delivered with megavoltage equipment using once daily fractionation (2 Gy x 1/day, 5 days per week for 7 weeks).

Surgery on the primary site of disease and/or neck was to be considered at anytime following completion of chemoradiotherapy for resectable recurrent primary and/or nodal metastatic disease in an operable individual.

Statistics Methods

Table 60: Study TAX 324 Patient Population

Population	
Intent-to-treat population (ITT)	all randomized subjects, except the 38 subjects*, analyzed in the treatment arm to which they were randomly assigned.
Safety population (SP & CRSP)	Patients that received chemotherapy are evaluable for safety for the chemotherapy period (SP). Patients that received chemoradiotherapy are evaluable for safety for the chemoradiotherapy period (CRSP). In both populations, patients are analyzed in the chemotherapy treatment group they actually received in cycle 1.

* Patients excluded from statistical analyses: Following an agreement with FDA on March 6, 2002, 37 patients incorrectly randomized between April 30, 2001 and September 12, 2001 due to an error in the randomization system, are excluded from all analyses. All available data received on these 37 subjects will be summarized separately (as is) in an appendix of the study report (documentation including correspondence with the FDA is available).

Similarly, upon FDA's recommendation on April 3, 2003, one patient randomized by the Albany VA medical center has been excluded from all analyses due to GCP compliance issues. Data for this subject will be summarized separately (as is) in an appendix of the study report (correspondence with the FDA on this issue is available).

Primary Endpoint
Overall survival (OS) is the primary efficacy parameter and is measured from the date of randomization up to the date of death. Survival is censored at the cut-off date for patients known to have lived beyond this date. For patients lost to follow-up prior to the cut-off date, survival is censored at the date last known alive.

The overall survival is calculated using a Kaplan-Meier method in the intent-to-treat population. The cut-off date used for the analysis is defined on the basis of at least two years follow-up and at least 227 events. The two treatment arms are compared with an unadjusted logrank test.

Sample Size Calculation Assumptions
For overall survival, the primary endpoint for the trial, a hazard ratio of 0.65 (assumed median OS of 43 months in TPF and 28 months in PF) can be detected with a 91% power using a 2-sided logrank test at a 5% significance level with 436 patients (218 per arm) recruited in 30 months. To achieve this statistical hypothesis, the minimum follow-up will be 24 months and a total of 227 events are needed. A maximum of 500 patients were to be recruited (250 per arm) assuming that approximately 15% of the patients would be lost to follow-up or early drop outs in this study.

10.1.2.2 TAX 324 Patient Demographic
Patients for the analysis populations were recruited in the US (67%), Argentina (17%), Russia (8%), Canada (3%), France (2%) and Portugal (2%), percentages are provided on the ITT population. The ITT population excludes 37 patients incorrectly randomized and 1 patient with GCP compliance problems. Of the 501 remaining randomized patients, 494 patients (98.6%)

were treated with the study chemotherapy. No error in the treatment allocation was recorded. A total of 387 patients (77.2%) received chemoradiotherapy following chemotherapy.

Table 61: Analysis populations by randomization group

Number of patients	RANDOMIZATION GROUP		
	TPF	PF	ALL
All Randomized	280	259	539
ITT population*	**255**	**246**	**501**
Evaluable for safety (SP)	251 (98.4%)	243 (98.8%)	494 (98.6%)
Evaluable for safety for chemoradiotherapy period (CRSP)	203 (79.6%)	184 (74.8%)	387 (77.2%)

ITT = Intent to treat, TPF = docetaxel + cisplatin + 5-FU, PF = cisplatin + 5-FU, N = number of patients
* ITT population excludes the 37 incorrectly randomized and 1 patient with GCP compliance problem, percentages are based on the ITT population
Data source: TAX 324 Study Summary

Base line characteristics of the ITT population are summarized as below.

Table 62: Baseline Characteristics (ITT)

	RANDOMIZATION GROUP		
	TPF (N=255)	PF (N=246)	ALL (N=501)
Sex			
Male	215 (84.3%)	204 (82.9%)	419 (83.6%)
Female	40 (15.7%)	42 (17.1%)	82 (16.4%)
Age (Years)			
Median	55	56	56
≥ 65 years	34 (13.3%)	36 (14.6%)	70 (14.0%)
PS WHO			
0	142 (55.7%)	126 (51.2%)	268 (53.5%)
1	113 (44.3%)	117 (47.6%)	230 (45.9%)
Missing	0 (0.0%)	3 (1.2%)	3 (0.6%)
Anatomic site of cancer			
Hypopharynx	42 (16.5%)	35 (14.2%)	77 (15.4%)
Larynx	48 (18.8%)	42 (17.1%)	90 (18.0%)
Oral cavity	33 (12.9%)	38 (15.4%)	71 (14.2%)
Oropharynx	132 (51.8%)	130 (52.8%)	262 (52.3%)
Other	0 (0.0%)	1 (0.4%)	1 (0.2%)
Reason for inoperability			
Technical unresectability	92 (36.1%)	84 (34.1%)	176 (35.1%)
Selection based on low surgical curability	78 (30.6%)	75 (30.5%)	153 (30.5%)
Organ preservation	85 (33.3%)	87 (35.4%)	172 (34.3%)
Clinical stage			
III	41 (16.1%)	45 (18.3%)	86 (17.2%)
IV	214 (83.9%)	200 (81.3%)	414 (82.6%)
Missing	0 (0.0%)	1 (0.4%)	1 (0.2%)
Time from 1st diagnosis to randomization (months)			
Median	0.9	0.9	0.9

ITT = Intent to treat, TPF = docetaxel + cisplatin + 5-FU, PF = cisplatin + 5-FU, N = number of patients
Data source: TAX 324 study summary

10.1.2.3 TAX 324 Efficacy Results – Overall Survival

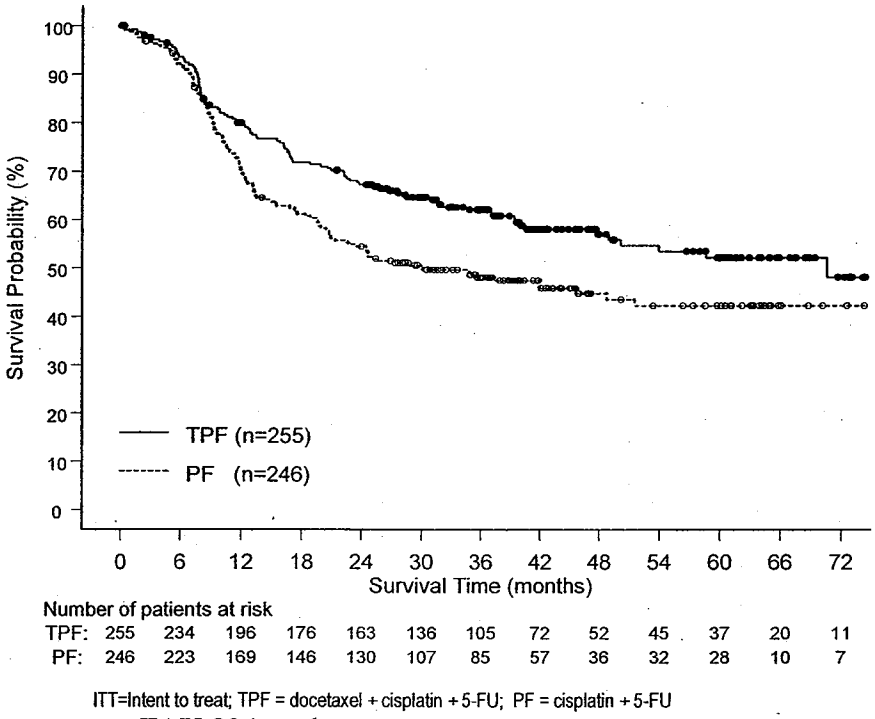
The final analysis on primary endpoint, overall survival of study TAX 324 was also included in this NDA review. All TAX 324 patients were randomized between May 21, 1999 and December 3, 2003. The cutoff date for analysis of overall survival was December 3, 2005, corresponding to 2 years follow-up of the last patient randomized in the study. At the cut-off date, median follow-up was 41.9 months, 69% of patients were followed for 3 years. At the cut-off date of December 3, 2005, 234 of 501 (46.7%) patients had died (40.8% in TPF and 52.8% in PF). The proportion of patient lost-to follow-up was 5.9% in TPF and 5.7% in PF.

Table 63: TAX 324 Primary Analysis: Overall Survival (ITT)

	RANDOMIZATION GROUP	
	TPF (N=255)	PF (N=246)
Median overall survival (months) [95% CI]	70.6 [49.0 - NA]	30.1 [20.9 - 51.5]
Kaplan-Meier estimates for overall survival		
1-year estimate [95% CI]	80.0% [75.0 - 84.9]	69.9% [64.1 - 75.7]
2-year estimate [95% CI]	67.3% [61.5 - 73.2]	54.5% [48.2 - 60.8]
3-year estimate [95% CI]	62.1% [55.9 - 68.2]	48.1% [41.7 - 54.5]
Hazard ratio: TPF/PF [95% CI]	0.70 [0.54 - 0.90]	
Log-Rank p value	0.0058	

ITT=Intent to treat, TPF=Taxotere+cisplatin+5-FU, PF=cisplatin+5FU, CI=confidence interval, NA=Not applicable, N=Number of patients
Hazard ratio <1 favors TPF.
Data source: TAX 324 study summary

Figure 9: TAX 324 primary Analysis: Overall Survival – Kaplan-Meier Curve



ITT=Intent to treat; TPF = docetaxel + cisplatin + 5-FU; PF = cisplatin + 5-FU

Data source: TAX 324 study summary

The sensitivity analysis for overall survival were performed by the applicant. The OS sensitivity analysis performed on all randomized patients are as below.

Table 64: OS Sensitivity Analysis on All Randomized Patients (N = 538)*

	RANDOMIZATION GROUP	
	TPF (N=279)	PF (N=259)
Overall Survival (OS):		
Hazard ratio: TPF/PF [95% CI]	0.72 [0.56 - 0.92]	
p value	0.008	

ITT=Intent to treat, TPF=Docetaxel+cisplatin+5-FU, PF=cisplatin+5FU, CI=confidence interval, N=Number of patients.
*Patient 06601 from Albany VA center is not included due to GCP compliance problems (detail see NDA 20449 S35 review).
Hazard ratio <1 favors TPF.
Data source: TAX 324 study summary.

In order to explore the potential impact of the incidence of patients lost to follow-up in the study (TPF: 5.9%, PF: 5.7%), the sponsor performed a sensitivity analysis counting the patients lost to follow-up as events.

Table 65: OS Sensitivity Analysis on Patients Lost to Follow-up Counted as Events

	RANDOMIZATION GROUP	
	TPF (N=255)	PF (N=246)
Overall Survival (OS):		
Hazard ratio: TPF/PF [95% CI]	0.72 [0.56 - 0.91]	
p value	0.0067	

ITT=Intent to treat, TPF=Docetaxel+cisplatin+5-FU, PF=cisplatin+5FU, CI=confidence interval, N=Number of patients.
Hazard ratio <1 favors TPF.
Data source: eff_gt0_osltfupev

Reviewer: TAX 324 study design mimic US standard care, using chemoradiothrapy as definitive treatment after induction chemotherapy. Also, the Taxotere was added to the full dose PF regimen. One can anticipate that superior efficacy and worse toxicity observed on TAX 324 TPF arm.

10.1.3 TAX322 Study

The TAX 322 efficacy report was submitted per reviewer request. Breifly, TAX322 was a randomized, multicenter, open-label, phase II/III trial. The phase III compared one docetaxel-based combination chemotherapy regimens (docetaxel plus cisplatin - TP) to the control regimen (cisplatin plus 5-fluorouracil - PF) in the first line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). The randomization was balanced within country and by extent of disease using permuted blocks in a ratio 1:1 (A, B arms respectively). At study entry, the patients were classified by the following categories:

1. Extent of disease (locoregional recurrence versus metastatic disease versus both),
2. Prior chemotherapy with cisplatin and/or 5-FU (yes/no),
3. Prior radiotherapy (=6 months versus >6 months prior to study entry versus no prior radiotherapy)

The primary objective of the study was to compare time to progression in 2 groups of patients after treatment with docetaxel plus cisplatin (TP) vs. cisplatin plus 5-fluorouracil (PF) with recurrent and/or metastatic squamous cell carcinoma of the head and neck. The secondary objectives of the study were to evaluate and compare overall survival, overall response rate, duration of response, time to treatment failure and toxicity between the test group and the control group.

The study TAX 322 failed to show advantage of TP over PF in PFS and OS in patients with recurrent or metastatic HNSCC.

Reviewer: TAX 322 study population has poorer prognosis than studies TAX 323 and 324. The TAX 322 combination regimen (TP) was also different from studies TAX 322 and 324 (TPF) In addition, the study sample sized for phase 3 portion was too small (102evaluable patients, total phase II-III enrollment was 236) to detect a difference, if any, in both TTP and more important,

overall survival. Therefore, the efficacy result of TAX 322 has little influent on the proposed label.

10.1.4 TAX 017 Study

This is a single arm study to determine MTD and DLT of the TPF combination. Two dose levels were tested in patients with locally advanced previously untreated SCCHN:

Table 66: TAX 017 study dose levels

Level	Taxotere mg/m^2	Cisplatin mg/^{2}	5-FU mg/^{2}
I	75	75	3750
II	75	100	3750

The treatment was administered every 3 weeks for 4 cycles. A total of 25 patients were treated in dose level I and 23 patients in dose level II. More than 90% of patients received post-study radiotherapy.

The 3-drug combination proved to be active, with an ORR of 71%. Response rates were comparable at the 2 dose levels evaluated in the study. One-year survival in dose level I was 56% and was not reached in dose level II. The overall one-year survival rate was 69%.

The incidence of adverse events was higher in dose level II compared to dose level I, in particular nephrotoxicity (26% versus 4%), asthenia (87% versus 68%), diarrhea (70% versus 48%), stomatitis (65% versus 48%), and vomiting (70% versus 36%).

The dose level I was recomended for further evaluation in the phase III trial TAX 323, as the efficacy was comparable and the safety profile better compared to dose level II. In that setting the prophylactic use of ciprofloxacin was recommended, as it reduced the incidence of infectious complications in the phase I-II study.

10.1.5 TAX 708 Study

This is a single arm study to explore safety and efficacy. Two dose levels were tested in patients with locally advanced previously untreated SCCHN:

Table 67: TAX 708 study dose levels

Level	Taxotere mg/m^2	Cisplatin mg/^{2}	5-FU mg/^{2}
I	75	75	4000
II	75	100	4000

The treatment was administered every 3 weeks for 3 cycles. A total of 13 patients were treated in dose level I and 30 patients in dose level II. More than 90% of patients received post-study radiotherapy.

The 3-drug combination proved to be active, with an ORR of 93% and an overall CR rate of 39.5%. Specifically, the response rate was 85% for dose level I and 97% for dose level II. One-year survival was 100% in dose level I and 96.5% in dose level II (for both dose levels combined, 97.6%).

Patients treated in dose level I had a higher incidence of the following events possibly or probably related to treatment: asthenia (100.0% vs. 80.0%), headache (38.5% vs. 20.0%), anorexia (69.2% vs. 46.7%), constipation (46.2% vs. 13.3%), epistaxis (23.1% vs. 3.3%), dysphagia (15.4% vs. 3.3%), pain (15.4% vs. 6.7%), tinnitus (23.1% vs. 6.7%), deafness (15.4% vs. 6.7%), fever in the absence of infection (38.5% vs. 23.3%), neuro-motor (23.1% vs. 10.0%), neuro-sensory (30.8% vs. 16.7%), pulmonary (15.4% vs. 0%), vomiting (61.5% vs. 53.3%), and stomatitis (100% vs. 90.0%). Because the sample size was small in this study, it is difficult to reach a conclusion.

Because the efficacy and safety profiles of dose level II were better than those of dose level I, dose level II was recomended for evaluation in the randomized comparative phase III trial TAX 324.

11 REFERENCES

1. Al-Sarraf M. Head and neck cancer - chemotherapy concepts. Sem Oncol 1988; 15: 70-85.

2. Rooney M, Kish J, Jacobs J, et al. Improved complete response rate and survival in advanced head and neck cancer after three-course induction therapy with l20-hour 5-FU infusion and cisplatin. Cancer 55: 1123-1128, 1985.

3. Toohil RJ, Anderson T, Byhardt RW, et al. Cisplatin and fluorouracil as neoadjuvant therapy in head and neck cancer. Arch Otolaryngol Head Neck Surg 113:758-761,1987.

4. Cognetti F, Pinnarò P, Carlíni P, et al. Neoadjuvant chemotherapy in previously untreated patients with advanced head and neck squamous cell cancer. Cancer 62:251- 261, 1988.

5. Vokes EE, Schilsky RL, Weichselbaum RR, et a1. Induction chemotherapy with cisplatin, fluorouracil and high-dose leucovorin for locally advanced head and neck cancer: A clinical and pharmacologic analysis. J Clin Oncol 8:241-247, 1990.

6. Mazeron 11, Martin M, Brun B, et al. Induction chemotherapy in head and neck cancer: Results of a phase II trial. Head and Neck 14:85-9 I, 1992.

7. Tejedor M, Murias A, Soria P, et al. Induction chemotherapy with carboplatin and ftorafur in advanced head and neck cancer. Am J Clin Oncol 15:417-421, 1992.

8. Depondt J, Gehanno P, Martin M, et a. ,Neoadjuvant chemotherapy with carboplatin/5-fluorouracil in head and neck cancer. Oncology 50 (suppl 2):23-27, 1993.

9. HasegawaY, Matsuura H, Fukushima M, et al. A randomized trial of neoadjuvant chemotherapy with cisplatin and 5-FU in advanced head and neck cancer. Proc ASCO 13:286, 1994 (Abstr).

10. Dalley D, Beller E, Aroney R, et aL. The value of chemotherapy (CT) pri,or to definitive local therapy (DL T) inpatients with locally advanced squamous cell carcinoma (SCC) of the head and neck (HN). Proc ASCO 14:297, 1995 (Abstr).

11. Taylor SG, Murthy AK, Vannetzel JM, Colin P, Dray M, Caldarelli DD, et al. Randomized comparison of neoadjuvant cisplatin and fluorouracil infusion followed by radiation versus concomitant treatment in advanced head and neck cancer. J Clin Oncol 1994; 12: 385-395.

12. Paccagnella A, Orlando A, Marchiori C, Zorat PL, Cavaniglia G, Sileni VC, et al. phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by Gruppo di Studio sui Tumori della Testa et del Colho. J Natl Cancer Inst 1994; 86: 265-272.

13. Pinnaro P, Cercato MC, Giannarelli D, Carlini P, Del Vecchio MR, Impiombato FA, et al. A randomized phase II study comparing sequential versus simultaneous chemotherapy in patients with unresectable locally advanced squamous cell carcinoma of the head and neck. Annals Oncology 1994; 5: 513-519.

14. Merlano M, Vitale V, Rosso R, Benasso M, Corvo R, Cavallari M, et al. Treatment of advanced squamous cell carcinoma of the head and neck with alternative chemotherapy and radiotherapy. New Eng J Med 1992; 16: 1115-1121.

15. Martin M, Hazan A, Vergnes L, et al. Randomized study of 5- fluorouracil and cisplatin as neoadjuvant therapy in head and neck cancer: A preliminary report. Int J Radiat Oncol BioI Phys 19:973-975, 1990.

16. Paccagnella A, Orlando A, Marchiori C, et al. Phase III trial of initial chemotherapy in stage II or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori delIa Testa e del Collo. J Natl Cancer Inst 86:265-272, 1994.

17. Ervin TJ, Clark JR, Weichselbaum RR, et al. An analysis of induction and adjuvant chemotherapy in the multidisciplinary treatment of squamous-cell carcinoma of the head and neck. J Clin Oncol 5:10-20, 1987.

18. Adelstein DJ. Induction chemotherapy in head and neck cancer. Hematol/Oncol Clinics of North Amer 13:689-698, 1999.

19. Jaulerry C, Rodriguez J, Brunin F, et al. Induction chemotherapy in advanced head and neck tumors: Results of two randomized trials. Int J Radiat Oncol BioI Phys 23:483- 489, 1992.

20. Volling P, Schroeder M, Eckel H, et al. Results of a prospective randomized trial with induction chemotherapy in cancer of the oral' cavity and the pharynx (abstract 484). In Proceedings of the Fourth International Conference on Head and Neck Cancer, Toronto, Canada, 1996, p 179.

21. Domenge C, Hil C, Lefebvre JL, et aL. Randomized trial ofneoadjuvant chemdtherapy in oropharyngeal carcinoma. British J Cancer 83: 1594-1598, 2000.

22. Schrijvers D, Van Herpen C, Kerger J, Joosens E, Van Laer C, Awada A, et al. Docetaxel, cisplatin and 5-fluorouracil in patients with locally advanced unresectable head and neck cancer: a phase I–II feasibility study. Ann Oncol 2004; 15: 638-645.

23. Hitt R, Paz-Ares L, Brandariz A, et al. Induction chemotherapy with paclitaxel, cisplatin and 5-fluorouracil for squamous cell carcinoma of the head and neck: Long-term results of a phase II trial. Ann Oncol 13:1665-1673,2002.

24. Dunphy FR, Dunleavy TL, Harrison BR, et al. Induction paclitaxel and carboplatin for patients with head and neck carcinoma. Cancer 91 :940-948, 2001.

25. Hitt R, Lopez-Pousa A, Rodriguez M, et al. Phase III study comparing cisplatin (P) & 5-fluorouracil (F) versus P, F and paclitaxel (T) as induction therapy in locally advanced i head and neck cancer. Proc ASCO 22: 496, 2003 (Abstr).

26. Vermorken JB, Remenar E, Van Herpen C, et al. Standard cisplatinlinfusional 5- fluorouracil (PF) vs docetaxel (T) plus PF (TPF) as neoadjuvant chemotherapy for nomesectable locally advanced squamous cell carcinoma of the head and neck: A phase II trial of the EORTC Head and Neck Cancer Group (EORTC #24971). J Clin Oncol 22:490, 2004 (suppl; abstr 5508).

27. Posner MR, Wirth L, Tishler RB, et al. The evolution of induction chemotherapy in locally advanced squamous cell cancer of the head and neck. From: Adelstein DJ.(ed.) Current Clinical Oncology: Squamous Cell Head and Neck Cancer. Humana Press Inc., Totowa, NJ, pp. 171-185, 2005.

28. Ensley JF, Jacobs JR, Weaver A, et al: Correlation between response to cisplatinum-combination chemotherapy and subseque¡t radiotherapy in previously untreated patients with advanced squamous cell cancers of the head and neck. Cancer 54:811 – 814, 1984.

29. Merlano M, Corvo R, Margarino G, et al. Combined chemotherapy and radiation therapy in advanced inoperable squamous cell carcinoma of the head and neck. Cancer 67:915- 921, I 991.

30. Merlano M, Benasso M, Corvó R, et al. Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma ofthe head and neck. J Natl Cancer 1nst 88:583-589, 1996.

31. Lo TCM, Wiley AL, Ansfield FJ, et al. Combined radiation therapy and 5-fluorouracil for advanced squamous cell carcinoma of the oral cavity and oropharynx: A randomized study. Am J Roentgenol 126:229-235, 1976.

32. Sanchiz F, Milá A, Tomer J, et al. Single fraction per day versus two fractions per day versus radiochemotherapy in the treatment of head and neck cancer. 1nt J Radiat Oncol Biol Phys 19:1347-1350,1990.

33. Browman GP, Cripps C, Hodson DI, et al. Placebo-controlled randomized trial of infusional fluorouracil during standard radiotherapy in locally advanced head and neck cancer. J Clin Oncol 12:2648-2653, 1994.

34. Adelstein DJ, Kalish LA, Adams GL, et al. Concurrent radiation therapy and chemotherapy for locally unresectable squamous cell head and neck cancer: An Eastern Cooperative Oncology Group pilot study. J Clin Oncol 11 :2136-2142, 1993.

35.Vokes EE, Kies MS, Haraf DJ, et al. Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. J Clin Oncol 18: I 652 - 1661, 2000.

36. Adelstein DJ, Saxton JP, Lavertu P, et al. Maximizing local control and organ preservation in stage IV squamous cell head and neck cancer with hyperfractionated radiation and concurrent chemotherapy. J Clin Oncol 20:1405-1410, 2002.

37. Pignon JP,Bourhis J, Domengè C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 355:949-955, 2000.

38. Browman GP. Evidence-based recommendations against neoadjuvant chemotherapy for routine management of patients with squamous cell head and neck cancer. Cancer Investigation 12:662-67 I, 1994.

39. EI-Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management .of. squamous cell carcinoma of the head and neck region: A meta-analysis of prospective and randomized trials. J Clin Oncol 14:838-847, 1996.

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

/s/

Qin Ryan
10/6/2006 12:23:47 PM
MEDICAL OFFICER

Amna Ibrahim
10/6/2006 12:32:16 PM
MEDICAL OFFICER

Team Leader's Memo
For A New Drug Application
Division of Drugs Oncology Products

NDA Number:	20,449
Drug Name:	Taxotere™ (docetaxel)
Sponsor:	Sanofi-aventis US, Inc.
Indication:	TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.
Date of Submission:	4/17/2006
Team Leader:	Amna Ibrahim MD
Primary Reviewer:	Qin Ryan MD, PhD

Recommendation:
This Taxotere supplemental NDA should be approved based on the improvement in Progression-free Survival and Overall Survival for the following indication:

"TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck"

Background:
Taxotere is a cytotoxic agent belonging to the class "Taxanes". It acts by disrupting the microtubular network in cells essential for mitotic and interphase cellular functions. By binding to free tubulin it promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells.

Taxotere was first approved in 1996 for patients with locally advanced or metastatic breast cancer after failure of adjuvant therapy with anthracyclines-based therapy. Since that time, it has also been approved for adjuvant treatment of operable node-positive breast cancer in combination with cyclophosphamide, non-small cancer after failure of platinum compounds, androgen independent prostate cancer in combination with prednisone and for previously untreated gastric adenocarcinoma in combination with cisplatin and fluorouracil. It has been used extensively, with a well-known safety profile.

This sNDA was submitted on April, 17, 2006. One major clinical study (TAX 323) was submitted to support this application. The results from TAX 324 will also be discussed briefly in this memo. Only the Clinical Study Report (CSR) of this recently concluded trial was submitted by the sponsor on request by the FDA. A priority review was requested and granted based on an improvement in overall survival.

Study design of TAX 323
TAX 323 was a prospective, multicenter, open-label, two-arm randomized trial conducted in patients with previously untreated, locally advanced, inoperable Head and Neck Cancer of the squamous cell etiology. The treatment arms were as below:

Table 1: Treatment regimens in study TAX 323

Treatments Arms		Schedule
TPF N=177	Taxotere (T) 75 mg/m^2 day 1 Cisplatin (P) 75 mg/m^2 day 1 Fluorouracil (F) 750 mg/m^2 day1	Administered IV every 3 weeks for 4 cycles
PF N=181	Cisplatin (P) 100 mg/m^2 day 1 Fluorouracil (F) 1000 mg/m^2 day 1-5	Administered IV every 3 weeks for 4 cycles

The dose of cisplatin was higher on the control arm, and the addition of Taxotere to a lower dose of cisplatin should be sufficient to demonstrate the efficacy of Taxotere in combination with cisplatin and fluorouracil in the chemotherapy stage of the trial.

Chemotherapy was followed by radiation for patients who did not have progressive disease. Radiation was delivered either with a conventional fraction, or an accelerated/hyperfractionated regimen. Surgery was allowed between chemotherapy and radiation, and following radiation therapy at the discretion of the investigator. Neck dissection before radiotherapy could be considered for patients with a good response at the primary site and poor response at the neck. The primary endpoint was Progression-Free Survival (PFS) defined as time from randomization to progression or survival, which ever came first. Overall Survival (OS) was a secondary endpoint. This was defined as time from randomization to death. According to the original SAP, a total of 260 progression events would be required for the primary analysis which can be expected from a total accrual of 330 patients (165 /arm).

Efficacy Results:
The efficacy and safety of this NDA is based on the 358 patients enrolled to this study. One hundred and eighty one patients were randomized to the control arm (PF) and 177 were enrolled to the investigational arm (TPF). Almost 90% of the patients were male and 90% were of age less than 65years. The median age of patients on study was 53 years. Half of the patients had a WHO performance status of 0 and half had PS of 1. These factors were evenly balanced. A similar number of patients received radiation on both arms. Fewer patients on the control arm had surgery, probably related to increased number progression events on this arm (71% on TPF and 81% on PF).

Table 2: All randomized patients and treatment received (ITT)

Number of patients (%)	Randomized population in the treatment received		
	TPF (N=174)	PF (N=181)	All (N=358)
Received chemotherapy	174 (100.0%)	181 (100.0%)	355 (99.2%)
Received radiotherapy	130 (74.7%)	124 (68.5%)	254 (70.9%)
Received surgery	45 (25.9)	27 (14.9%)	72 (20.4%)

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients
Source: TAX 323 study report

Table 3: Progression-free Survival (ITT)

	RANDOMIZATION GROUP		
	TPF (N=177)	PF (N=181)	ALL (N=358)
Number of patients with			
event	126 (71.2%)	147 (81.2%)	273 (76.3%)
censored data	51 (28.8%)	34 (18.8%)	85 (23.7%)
Event reasons (PFS)			
Progression	101 (57.1%)	117 (64.6%)	218 (60.9%)
Death	25 (14.1%)	30 (16.6%)	55 (15.4%)
Censoring reasons (PFS)			
Lost to follow-up	5 (2.8%)	4 (2.2%)	9 (2.5%)
No event at cutoff date	46 (26.0%)	30 (16.6%)	76 (21.2%)

ITT= intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients;
Source: TAX323 CSR

The primary endpoint progression-free survival (PFS) was significantly longer in the TPF arm compared to the PF arm, p=0.0077 (median PFS: 11.4 vs. 8.3 months respectively) with an overall median follow up time of 33.7 months. Median overall survival with a median follow-up of 51.2 months was also significantly longer in favor of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.2 months respectively) with hazard ratio of 0.71, (0.56, 0.90).

Table 4: Efficacy of TAXOTERE in the induction treatment of patients with inoperable locally advanced SCCHN (Intent-to-Treat Analysis)

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

A Hazard ratio of less than 1 favors Taxotere+Cisplatin+5-FU
* Stratified log-rank test based on primary tumor site

Figure 1 - TAX323 Progression-Free Survival K-M Curve

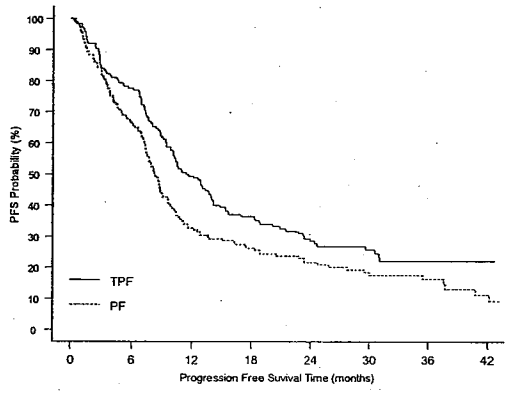
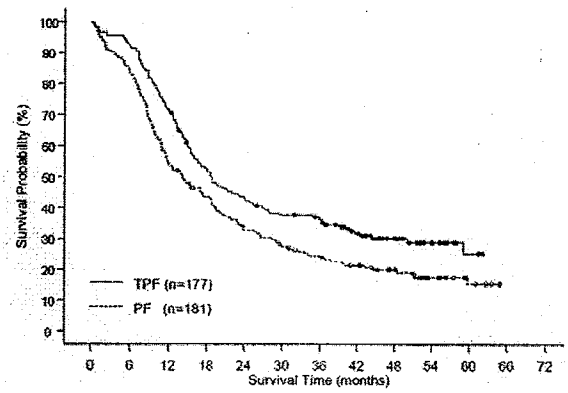


Figure 2 - TAX323 Overall Survival K-M Curve



b(4)

Safety Results:
One hundred and seventy four patients on the TPF arm and 181 patients on the PF arm received chemotherapy. The median number of cycles was 4 in both treatment arms, and the median duration was approximately 12 weeks in both arms. However, 79% on TPF arm and 65% on the PF arm received 4 cycles of chemotherapy.

Ninety nine percent patients on the TPF arm and 94% patients on the PF arm had at least one treatment-emergent adverse event (TEAE) during chemotherapy. The number of deaths was

similar at 8% within 60 days of first administration of study drug or within 30 days of the last study treatment.

The most frequent adverse events on the TPF arm were neutropenia (93%), anemia (89%), alopecia (81%), stomatitis/esophagitis (55%), and nausea (47%). Grade 3 or 4 adverse events with a greater than 5% frequency in patients on the TPF arm were neutropenia (76%), alopecia (11%), infection (9%), weight loss (7%), stomatitis/esophagitis (5%) and thrombocytopenia (5%). Approximately 5% of the TPF arm patients had febrile neutropenia and 14% had neutropenic infection. Compared to patients receiving PF, patients receiving TPF had more alopecia, neutropenia, diarrhea, neurosensory abnormality, neutropenic infection, fluid retention, and altered taste or sense of smell.

There were too few women or patients older than 65 years to comment on the safety or efficacy in these subgroups. Age was not recorded in this trial.

No clinical pharmacology and toxicology reviews were required for this sNDA.

Study TAX324:
Only the CSR of this study was submitted for informational purposes only on FDA's request. It is expected that the NDA for this study will be submitted in a few months. TAX324 was a randomized, multicenter, open-label, phase III trial comparing two combination chemotherapy regimens as neoadjuvant (induction) treatment before chemoradiotherapy for locally advanced SCCHN. The treatment regimen in this study (table 4) isolates the contribution of Taxotere to cisplatin and fluorouracil and is more in line with the US standard of practice.

Table 4: Treatment Arms and Regimens in TAX 324

Arm	Regimen
TPF	Docetaxel 75 mg/m² by 1 hour IV infusion on day 1 followed by Cisplatin 100 mg/m² administered as a 30-minute to three hour IV infusion. CIV 5-FU 1000 mg/m²/day from day 1 to day 4.
PF	Cisplatin 100 mg/m² as a 30-minute to three hour IV infusion on day 1 followed by CIV 5-FU 1000 mg/m²/ day from day 1 to day 5.

CIV: continuous intravenous infusion.

The Taxotere-containing arm demonstrated an improvement in the primary endpoint of overall survival. This study although not reviewed by this division, supports the results of TAX 323.

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

/s/

Amna Ibrahim
10/6/2006 01:11:42 PM
MEDICAL OFFICER

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2006.002.A.00066
APPLICATION TYPE	NDA
SUBMISSION NUMBER	20-449/S-039
SUBMISSION CODE	
IND SUBMISSION EPOCH	
LETTER DATE	April 14, 2006
STAMP DATE	April 14, 2006
REQUESTED COMPLETION DATE	October 14, 2006
DATE OF CONSULT REQUEST	June 13, 2006
REVIEW DIVISION	DODP
MEDICAL TEAM LEADER	
REVIEW DIVISION PM	Ann Staten
SEALD REVIEWER(S)	Melissa Furness
REVIEW COMPLETION DATE	September 26, 2006
ESTABLISHED NAME	(docetaxel)
TRADE NAME	Taxotere
THERAPEUTIC CLASS	Cytotoxic
APPLICANT	Sanofi Aventis
PRIORITY DESIGNATION	Moderate
ENDPOINT(S) CONCEPT(S)	EORTC QLQ-C30
INSTRUMENT(S)	
FORMULATION	Injection
DOSING REGIMEN	
INDICATION	Head and Neck Cancer
INTENDED POPULATION(S)	Patients with Head and Neck Cancer

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

/s/

Melissa Furness
9/29/2006 10:24:27 AM
CSO

Laurie Burke
10/2/2006 06:46:44 PM
INTERDISCIPLINARY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-449/S-039

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1	1. ORGANIZATION ONDQA Division IV Branch VIII	2. NDA NUMBER 20-449
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Sanofi-Aventis Pharmaceuticals P.O Box 9720 Kansas City, MO 64134-0720 Attention: Dhiren N. Shah Director, Regulatory CMC Tel: (816)-966-5100		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)
6. NAME OF DRUG Taxotere®	7. NONPROPRIETARY NAME docetaxel	SE1-039 | 4-14-06
8. SUPPLEMENT PROVIDES FOR: Taxotere in combination with cisplatin and 5-fluorouracil indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN)		9. AMENDMENTS DATES
10. PHARMACOLOGICAL CATEGORY antineoplastic	11. HOW DISPENSED RX x OTC ___	12. RELATED IND/NDA/DMF None
13. DOSAGE FORM(S) injection concentrate	14. POTENCY 20 mg and 80 mg vials	
15. CHEMICAL NAME AND STRUCTURE See PDR		16. RECORDS AND REPORTS CURRENT YES___NO___ REVIEWED YES___NO___

17. COMMENTS

This sNDA was submitted to the FDA on April 14, 2006, and contained efficacy and safety data to support approval for Taxotere in combination with cisplatin and 5-fluorouracil indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (S Sanofi-Aventis Pharmaceuticals Inc. claims Categorical Exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b). Based on the justification provided, it is found to be acceptable. There is no additional CMC change from the original NDA for the DP lots used for these studies.

cc:
NDA 20-449
HFD-150/Div. File
HFD-150/ LZhou
HFD-150/HPatel
HFD-150/FCross
R/D Init. by:

18. CONCLUSIONS AND RECOMMENDATIONS

Approval is recommended.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Liang Zhou, Ph.D.		10/10/06

DISTRIBUTION ORIGINAL JACKET DIVISION FILE REVIEWER LZ
Branch Chief H. Patel, Ph.D.

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

/s/

Liang Zhou
10/10/2006 03:27:23 PM
CHEMIST

Hasmukh Patel
10/11/2006 08:16:37 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449 / S-039

STATISTICAL REVIEW(S)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	20-449/S-039
Drug Name:	Taxotere® (Neoadjuvant Docetaxel)
Indication:	Locally Advanced Inoperable Squamous Cell Carcinoma of the Head and Neck
Applicant:	Sanofi-Aventis
Date:	4/14/2006
Review Priority:	Priority
Biometrics Division:	V (HFD 711)
Statistical Reviewer:	Kun He
Concurring Reviewers:	Rajeshwari Sridhara, Ph.D., Team Leader Aloka Chakravarty, Ph.D., Director
Medical Division:	Oncology Drug Products (HFD 150)
Clinical Team:	Qin Ryan, M.D., Clinical Reviewer Amna Ibrahim, M.D., Acting Team Leader
Project Manager:	Ann Staten, MPH.

Keywords: Stratified log-rank test

TABLE OF CONTENTS

Statistical Review and Evaluation

1. Executive Summary

1.1 Conclusions and Recommendations

The applicant is seeking an approval for Taxotere in combination with cisplatin and 5-fluorouracil for the induction treatment of patients with locally advanced inoperable squamous cell carcinoma of head and neck (SCCHN).

The data and analyses from the current submission demonstrated that patients with locally advanced inoperable squamous cell carcinoma of head and neck in the Taxotere plus cisplatin and 5-FU (TPF) group had a larger median progression-free survival time (11.4 months, 95% CI: 10.1-14.0) than in the cisplatin and 5-FU (PF) group (8.3 months, 95% CI: 7.4-9.1). The difference was approximately 3.1 months, had a nominal p-value .0077 based on a stratified log-rank test with the primary tumor site as stratification factor, and had a 29% progression risk reduction (HR 0.71, 95% CI: 0.56-0.91).

The updated overall survival data and analyses also demonstrated that patients in the Taxotere plus cisplatin and 5-FU (TPF) group had a larger median overall survival time (18.6 months, 95% CI: 15.7-24.0) than in the cisplatin and 5-FU (PF) group (14.2 months, 95% CI: 11.5-18.7). The difference was approximately 4.4 months, had a p-value .0055 based on a stratified log-rank test with the primary tumor site as stratification factor, and had a 29% progression risk reduction (HR 0.71, 95% CI: 0.56-0.90).

1.2 Brief Overview of Clinical Studies

The pivotal study in this submission is Study 323, which was a multinational, open-label, randomized, stratified, phase III study comparing 2 therapy regimens as neoadjuvant (induction) treatment before radiotherapy for locally advanced inoperable Squamous Cell Carcinoma of the Head and Neck (SCCHN). Patients were randomized to receive either Taxotere plus cisplatin plus 5-FU (TPF) or control treatment plus cisplatin plus 5-FU (PF). Patients were stratified at inclusion according to primary tumor site (oral cavity versus oropharynx versus hypopharynx versus larynx) and institution. Patients received 4 cycles of chemotherapy at 3 week intervals unless disease progression/relapse (hereafter, progression), or unacceptable toxicity occurred, or the patient refused treatment. Chemotherapy was to be followed by radiotherapy for patients who did not have progressive disease. All patients were to be followed until death. Patients with progression noted at any time were immediately referred to the radiation oncologist according to the institution's policy and were followed for survival only. The main inclusion criteria included patients between 18 to 70 years old, with histologically or cytologically proven SCCHN presenting with locally advanced, inoperable disease at diagnosis, with at least 1 uni- or bidimensionally measurable lesion, and TNM

stage III or IV disease without metastases. Patients with tumors of the nasopharynx and the nasal and paranasal cavities were excluded.

The primary efficacy endpoint was progression-free survival (PFS), which was calculated from the date of randomization until the date of progression or death (regardless of the reason for death), whichever occurred first. If progression or death did not occur before the cut-off date (or occurred after the cut-off date), the patient was censored at the last valid assessment date before the cut-off date (at the cut-off date otherwise). The primary analysis at the end of the study was a comparison of PFS in the intent-to-treat (ITT) population, which included all randomized patients analyzed in the treatment group to which they were randomized. A Cox proportional hazards model would initially be fit with the following factors: a) treatment (control vs. test); b) oral cavity primary (yes vs. no); c) oropharynx primary (yes vs. no); d) hypopharynx primary (yes vs. no); e) T stage (T4 vs. T2-3); f) N stage (N2-3 vs. N0-1); and g) WHO performance score (PS0 vs. PS≥1). Backwards elimination would then be used to drop individual factors from the model with likelihood ratio tests with a 2-sided significance level > 10% (primary site would be evaluated with a single test). A 2-sided 5% significance level would be applied to the estimate of the treatment hazard ratio from the final model. *(Reviewer's Comments: a stratified log-rank test will be performed and reported. See more discussions in Section 1.3.)*

There were 358 patients randomized, 177 in the TPF group, and 181 in the PF group, respectively.

1.3 Statistical Issues and Findings

Statistical Issues

There are two issues in the submission.

1. The applicant's primary analysis was based on a Cox proportional hazards model, which was specified in the protocol. However, factors (WHO performance score, N stage, and T stage) were not used as the stratification factors during the randomization, hence, they shouldn't be included in the analysis. In addition, because assumptions for Cox proportional hazards model are usually very difficult to verify, instead, a log-rank test is commonly used in the Division of Drug Oncology Products (DDOP) for analyzing endpoints based on time to events because it is a nonparametric test. In this review, a stratified log-rank test based on the stratification factor during the randomization, the primary tumor site, will be performed for both PFS and OS analyses. The other stratification factor, institution, will not be included in the analysis because there were a large number of small institutions.

2. There was an imbalance in radiotherapy between two treatment groups, 73.4% in TPF, and 68.5% in PF groups, respectively. The difference was approximately 4.9%. After a detailed evaluation, the difference in patients who received radiotherapy using 3.4 months as cut-off is 2.6%, which doesn't have big impact on the analyses and conclusions.

Findings

The protocol specified primary analysis was based on a Cox proportional hazards model. As defined in the SAP, the cut-off date was chosen to include at least 260 PFS events. The occurrence of the 260th event was reported to the EORTC data center on 21 September 2003.

The applicant's results of the PFS based on ITT population are presented in Table 1. The full model included adjustment of treatment effect for the following factors: treatment (1 = TPF, 0 = PF), oral cavity primary (0 = no, 1 = yes), oropharynx primary (0 = no, 1 = yes), hypopharynx primary (0 = no, 1 = yes), T stage (0 = T1-2-3, 1 = T4), N stage (0 = NX-0-1, 1 = N2-3), and WHO performance status (0 = PS ≥1, 1 = PS0). The primary sites (oral cavity primary, oropharynx primary, hypopharynx, or larynx) were evaluated with a single test.

Table 1 Cox proportional hazards model (full model) on PFS (ITT)

	Adjusted treatment effect on prospectively selected covariates			
			95% CI	
Covariate	**P value**	**Hazard ratio**	**Lower**	**Upper**
Randomization group: TPF / PF	0.0042	0.70	0.55	0.89
WHO performance score: PS null/ PS ≥ 1	0.0322	0.77	0.61	0.98
N stage: N2-3/N0-N1-NX	0.0360	1.34	1.02	1.77
Hypopharynx primary: yes/no [a]	0.0616	1.01	0.60	1.72
Oropharynx primary: yes/no [a]		0.77	0.46	1.29
Oral cavity primary: yes/no [a]		1.17	0.67	2.06
T stage: T4/T2-T3-T1	0.7495	1.05	0.78	1.41

ITT = intent-to-treat; CI = confidence interval; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; WHO = World Health Organization; PS = performance status

[a] The reference for each primary site variable is the larynx primary site. Then, these variables were evaluated with a single test.

Table 2 presents the result of a stratified log-rank test with the primary tumor site, which was used as a stratification factor during the randomization, as stratification factor on PFS.

Table 2 Stratified Log-rank Test on PFS (ITT)

	TPF (N=177)	PF (N=181)	p-value
Event - Progression - Death	126 (71.2%) 101 (57.1%) 25 (14.1%)	147 (81.2%) 117 (64.6%) 30 (16.6%)	.0077
Censored - Lost to follow-up - No event at cutoff data	51 (28.8%) 5 (2.8%) 46 (26.0%)	34 (18.8%) 4 (2.2%) 30 (16.6%)	
Median PFS (months) [95% CI]	11.4 [10.1 – 14.0]	8.3 [7.4 – 9.1]	
Hazard ratio: TPF/PF [95% CI]	.71 [.56 - .91]		

Patients in the TPF group had a larger median progression-free survival time (11.4 months, 95% CI: 10.1-14.0) than in the PF group (8.3 months, 95% CI: 7.4-9.1). The difference was approximately 3.1 months, had a nominal p-value .0077 based on a stratified log-rank test with the primary tumor site as stratification factor, and had a 29% progression risk reduction (HR 0.71, 95% CI: 0.56-0.91).

Table 3 presents the result of a stratified log-rank test with the primary tumor site, which was used as a stratification factor during the randomization, as stratification factor on updated OS.

Table 3 Stratified Log-rank Test on Updated OS (ITT)

	TPF (N=177)	PF (N=181)	p-value
Event	122 (68.9%)	146 (80.7%)	.0055
Censored - Lost to follow-up -Date of last contact before the cut-off date - No event at cutoff data	55 (31.1%) 8 (4.5%) 15 (8.5%) 32 (18.1%)	35 (19.3%) 9 (2.8%) 5 (2.8%) 21 (11.6%)	
Median PFS (months) [95% CI]	18.6 [15.7 – 24.0]	14.2 [11.5 – 18.7]	
Hazard ratio: TPF/PF [95% CI]	.71 [.56 - .90]		

The updated overall survival data and analyses also demonstrated that patients in the Taxotere plus cisplatin and 5-FU (TPF) group had a larger median overall survival time (18.6 months, 95% CI: 15.7-24.0) than in the cisplatin and 5-FU (PF) group (14.2 months, 95% CI: 11.5-18.7). The difference was approximately 4.4 months, had a p-value .0055 based on a stratified log-rank test with the primary tumor site as stratification factor, and had a 29% progression risk reduction (HR 0.71, 95% CI: 0.56-0.90).

2. Introduction

2.1 Overview

The applicant is seeking an approval for Taxotere in combination with cisplatin and 5-fluorouracil for the induction treatment of patients with locally advanced inoperable SCCHN.

2.1.1 Background

Squamous cell carcinoma of the head and neck (SCCHN) represents 5% of newly diagnosed cancers in adult patients. Worldwide, more than 500 000 new cases are projected annually. It is a potentially curable malignancy when diagnosed at an early stage. Unfortunately, patients often present with advanced locoregional disease and in this group of patients the prognosis is quite poor. Following standard therapy, only 30% will be alive after 3 years. Of these, 60% to 70% will develop locoregional recurrences within 2 years and 20% to 30% will develop distant metastases.

Surgery followed by radiotherapy is the accepted standard for tumors considered to be resectable. Those patients considered unresectable have traditionally been treated with radiotherapy alone.

Integrating chemotherapy in the upfront treatment of locally advanced disease is now under investigation. The goal of this treatment strategy is to enhance local control, to decrease local recurrences and distant failures, and ultimately to improve survival. One approach is neoadjuvant (hereafter, induction) chemotherapy before standard surgery and/or radiotherapy. This approach has yielded promising results, and in phase II studies, induction therapy with cisplatin and infusional 5-fluorouracil (5-FU) emerged as one of the most active combinations.

The pivotal study in this submission is Study 323, which was a multinational, open-label, randomized, stratified, phase III study comparing 2 therapy regimens as neoadjuvant (induction) treatment before radiotherapy for locally advanced inoperable Squamous Cell Carcinoma of the Head and Neck (SCCHN). Patients were randomized to receive either Taxotere plus cisplatin plus 5-FU (TPF) or control treatment plus cisplatin plus 5-FU (PF). Patients were stratified at inclusion according to primary tumor site (oral cavity versus oropharynx versus hypopharynx versus larynx) and institution. Patients received 4 cycles of chemotherapy at 3 week intervals unless disease progression/relapse (hereafter, progression) or unacceptable toxicity occurred, or the patient refused treatment. Chemotherapy was to be followed by radiotherapy for patients who did not have progressive disease. All patients were to be followed up until death. Patients with progression noted at any time were immediately referred to the radiation oncologist according to the institution's policy and were followed for survival only. The main inclusion criteria included patients between 18 to 70 years old, with histologically or cytologically proven SCCHN presenting with locally advanced, inoperable disease at diagnosis, with at least 1 uni- or bidimensionally measurable lesion, and TNM

stage III or IV disease without metastases. Patients with tumors of the nasopharynx and the nasal and paranasal cavities were excluded.

The primary efficacy endpoint was progression-free survival (PFS), which was calculated from the date of randomization until the date of progression or death (regardless of the reason for death), whichever occurred first. If progression or death did not occur before the cut-off date (or occurred after the cut-off date), the patient was censored at the last valid assessment date before the cut-off date (at the cut-off date otherwise). The primary analysis at the end of the study was a comparison of PFS in the intent-to-treat (ITT) population, which included all randomized patients analyzed in the treatment group to which they were randomized. A Cox proportional hazards model would initially be fit with the following factors: a) treatment (control vs. test); b) oral cavity primary (yes vs. no); c) oropharynx primary (yes vs. no); d) hypopharynx primary (yes vs. no); e) T stage (T4 vs. T2-3); f) N stage (N2-3 vs. N0-1); and g) WHO performance score (0 vs. ≥1). Backwards elimination would then be used to drop individual factors from the model with likelihood ratio tests with a 2-sided significance level > 10% (primary site would be evaluated with a single test). A 2-sided 5% significance level would be applied to the estimate of the treatment hazard ratio from the final model. There were 358 patients randomized, 177 in the TPF group, and 181 in the PF group, respectively.

2.1.2 Statistical Issues

There are two issues in the submission.

1. The applicant's primary analysis was based on a Cox proportional hazards model, which was specified in the protocol. However, factors (WHO performance score, N stage, and T stage) were not used as the stratification factors during the randomization, hence, they shouldn't be included in the analysis. In addition, because assumptions for Cox proportional hazards model are usually very difficult to verify, instead, a log-rank test is commonly used in the Division of Drug Oncology Products (DDOP) for analyzing endpoints based on time to events because it is a nonparametric test. In this review, a stratified log-rank test based on the stratification factor during the randomization, the primary tumor site, will be performed for both PFS and OS analyses. The other stratification factor, institution, will not be included in the analysis because there were a large number of small institutions.

2. There was an imbalance in radiotherapy between two treatment groups, 73.4% in TPF, and 68.5% in PF groups, respectively. The difference was approximately 4.9%. After a detailed evaluation, the difference in patients who received radiotherapy using 3.4 months as cut-off is 2.6%, which doesn't have big impact on the analyses and conclusions.

2.2 Data Sources

The path to the CDER Electronic Document Room (EDR) is:

\\Cdsesub1\n20449\S_039\2006-04-14 and \\Cdsesub1\n20449\S_039\2006-06-15

3. Statistical Evaluation

3.1 Evaluation of Efficacy

Part of the text, tables and figures presented in this section are adapted from the applicant's Study Report.

3.1.1 Objective of Study 323

The primary objective of this study was to compare progression-free survival (PFS) in 2 groups of patients with locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN) when treated with either Taxotere + cisplatin + 5-fluorouracil (5-FU) (TPF, test group) followed by locoregional radiotherapy or cisplatin + 5-FU (PF, control group) followed by locoregional radiotherapy.

The secondary objective of this study was to evaluate and compare OS, RR before and after radiotherapy, local symptoms, duration of response, time to treatment failure (TTF), toxicity, and quality of life (QoL) between the test group and the control group.

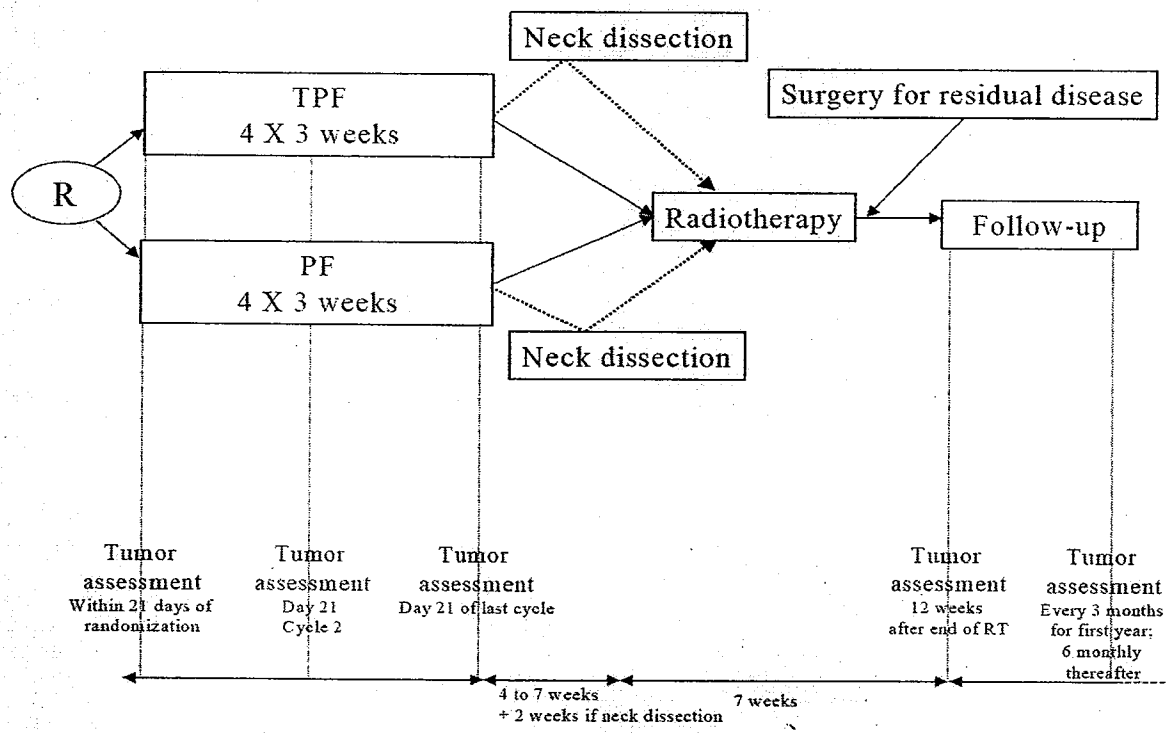
3.1.2 Study Design

This was a multinational, open-label, randomized, stratified, phase III study comparing 2 therapy regimens as neoadjuvant (induction) treatment before radiotherapy in previously untreated patients with locally advanced inoperable SCCHN. Patients were randomized to receive either Taxotere plus cisplatin plus 5-FU (TPF) or control treatment plus cisplatin plus 5-FU (PF). Patients were stratified at inclusion according to primary tumor site (oral cavity versus oropharynx versus hypopharynx versus larynx) and institution. Patients received 4 cycles of chemotherapy at 3 week intervals unless disease progression/relapse (hereafter, progression) or unacceptable toxicity occurred, or the patient refused treatment. Chemotherapy was to be followed by radiotherapy for patients who did not have progressive disease. All patients were to be followed until death. Patients with progression noted at any time were immediately referred to the radiation oncologist according to the institution's policy and were followed for survival only.

Chemotherapy treatment schedules were as follows: for test group:Taxotere 75 mg/m^2, as a one-hour intravenous (i.v.) infusion, followed by cisplatin 75 mg/m^2, administered as a one-hour i.v. infusion on Day 1. 5-FU was administered after cisplatin as a continuous i.v. infusion at 750 mg/m2 per day for 5 days; and for control group: cisplatin 100 mg/m^2, administered as a one-hour i.v. infusion on Day 1, followed by continuous i.v. infusion of 5-FU 1000 mg/m^2 per day for 5 days.

Figure 3.1.2.1 (adapted from the study report page 85) presents the study design.

Figure 3.1.2.1 Study Design



R = Randomization; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; RT = Radiotherapy

The main inclusion criteria included patients between 18 to 70 years old, with histologically or cytologically proven SCCHN presenting with locally advanced, inoperable disease at diagnosis, with at least 1 uni- or bidimensionally measurable lesion, and TNM stage III or IV disease without metastases. Patients with tumors of the nasopharynx and the nasal and paranasal cavities were excluded.

3.1.3 Efficacy Measures

The primary efficacy endpoint was progression-free survival (PFS), which was calculated from the date of randomization until the date of progression or death (regardless of the reason for death), whichever occurred first. If progression or death did not occur before the cut-off date (or occurred after the cut-off date), the patient was censored at the last valid assessment date before the cut-off date (at the cut-off date otherwise).

Secondary endpoints included: (1) overall survival (OS), which was measured from the date of randomization until death (regardless of the reason for death). If death or last contact did not occur before the cut-off date, the patient was censored at the cut-off date, or the last contact date if the patient was lost to follow-up before the cut-off date; (2) overall response (RR), which was defined for each treatment group as the percentage of patients in the group who achieve a complete response (CR) or a partial response (PR) according to WHO criteria. Responses calculated by the study coordinator at the end of the induction chemotherapy and after the administration of radiation therapy were used in the analyses; (3) duration of response, which was calculated from the date of randomization up to the documentation of progression in the responders for the whole treatment (induction chemotherapy plus radiotherapy). If progression or death did not occur before the cut-off date/further anti-cancer therapy date (or occurred after the cut-off date), the patient was censored at the last valid assessment date before the cut-off date/further anti-cancer therapy date (at the cut-off date otherwise); and (4) time to treatment failure (TTF), which was calculated from the date of randomization up to the date of failure (progression, relapse, death, discontinuation of study treatment [chemotherapy or radiotherapy] due to AE, patient refusal of chemotherapy treatment, or lost to follow-up before the end of treatment [chemotherapy plus radiotherapy]). If none of these events occurred before the cut-off date or occurred after the cut-off date, the patient was censored at the date of last valid assessment before cut-off date; at the cut-off date otherwise. Patients lost to follow-up after the end of the treatment (as defined above) were censored at the date of last contact if it occurred before the cut-off date; at the cut-off date otherwise. Patients not treated were censored at their randomization date.

3.1.4 Sample Size Considerations

The primary endpoint for the trial was progression-free survival (PFS) analyzed in the ITT population. The null hypothesis to be tested (H_0) was that there was no difference in PFS between test and control treatment groups. The goal was to have 85% power to reject H_0 at a 2-sided 5% significance level under the alternative hypothesis (H_a) that the test treatment group increased the median PFS by 50%; a control treatment group median of 10 versus 15 months for the test treatment group or a hazard ratio (control/test) of 1.5. Assuming a 24 month accrual period with a further follow-up of 12 months, it was estimated that 260 events were needed to achieve this goal, which could be expected from a total accrual of 330 patients (165/treatment group). Anticipating a 5% lost to follow-up rate, 348 patients were to be recruited (174/treatment group).

A 2-stage design was initially planned to minimize the number of patients treated with the test regimen under H_0, as the test regimen was anticipated to be more toxic. The stage 1 analysis was planned to be performed half-way through the total accrual period when 42 events would have been observed. Due to the cancellation of the interim analysis (i.e., stage 1), only the final analysis (stage 2) was performed.

This study was also powered to detect a difference in survival between the treatment groups. The targeted survival improvement was 15% at 1 year (1-year survival of 85% for the test treatment

group versus 70% for the control). The total number of patients (N=348) was adequate to detect this difference in survival at 1 year with 90% power using a 2-sided significance level of 5%.

3.1.5 Interim Analysis

An interim analysis was planned, but not performed.

3.1.6 Statistical Analysis Plan

Primary efficacy analysis:
The primary analysis at the end of the study was a comparison of PFS in the intent-to-treat (ITT) population, which included all randomized patients analyzed in the treatment group to which they were randomized. A Cox proportional hazards model would initially be fit with the following factors: a) treatment (control vs. test); b) oral cavity primary (yes vs. no); c) oropharynx primary (yes vs. no); d) hypopharynx primary (yes vs. no); e) T stage (T4 vs. T1-3); f) N stage (N2-3 vs. N0-1); and g) Who performance score (PS0 vs. PS≥1). Backwards elimination would then be used to drop individual factors from the model with likelihood ratio tests with a 2-sided significance level > 10% (primary site would be evaluated with a single test). A 2-sided 5% significance level would be applied to the estimate of the treatment hazard ratio from the final model.

Secondary analyses:
The overall response rate and complete response rate between treatment groups was planned to be compared using an unadjusted χ^2 test in the ITT population. In the analysis, there would be no distinction between confirmed and unconfirmed responses. Logistic regression with backwards elimination would be used to explore the influence of the prognostic factors included in the PFS analysis. The response rates would be compared at two time points: after tumor assessment of the last cycle of chemotherapy and before locoregional therapy; and after locoregional therapy. Kaplan-Meier curves and life tables would be calculated in the ITT population for duration of response (CR+PR), duration of partial response, and duration of complete remission.

The Wilcoxon and logrank linear rank tests would be used to compare the time to treatment failure and survival between treatments in the ITT population, respectively. Both endpoints would also be analyzed with a Cox proportional hazards model with backwards elimination to explore the influence of the prognostic factors in the PFS analysis.

Reviewer's Comments:

The applicant's primary analysis was based on a Cox proportional hazards model, which was specified in the protocol. However, factors (WHO performance score, N stage, and T stage) were not used as the stratification factors during the randomization, hence, they shouldn't be included in the analysis. In addition, because assumptions for Cox proportional hazards model are usually very difficult to verify, instead, a log-rank test is commonly used in the Division of Drug

Oncology Products (DDOP) for analyzing endpoints based on time to events because it is a nonparametric test. In this review, a stratified log-rank test based on the stratification factor during the randomization, the primary tumor site, will be performed for both PFS and OS analyses. The other stratification factor, institution, will not be included in the analysis because there were a large number of small institutions.

3.1.7 Applicant's Results and Statistical Reviewer's Findings/ Comments

3.1.7.1 Study Population

Table 3.1.7.1.1 (adapted from the study report page 149) presents the study populations.

Table 3.1.7.1.1 Analysis populations by randomization group (ITT)

	Randomization group		
	TPF (N=177)	PF (N=181)	All (N=358)
Number of patients			
Randomized	177 (100.0%)	181 (100.0%)	358 (100.0%)
Eligible	166 (93.8%)	167 (92.3%)	333 (93.0%)
Evaluable for safety	175 (98.9%)	180 (99.4%)	355 (99.2%)
Received chemotherapy	175 (98.9%)	180 (99.4%)	355 (99.2%)
Received radiotherapy	130 (73.4%)	124 (68.5%)	254 (70.9%)
Evaluable for response	163 (92.1%)	155 (85.6%)	318 (88.8%)

ITT = intent to treat; TPF= Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients

Reviewer's Comments:

There is a slight imbalance in "received radiotherapy" between two treatment groups: 73.4% for TPF, and 68.5% for PF, respectively. Detailed evaluation of this imbalance is discussed in Section 3.1.7.3.

3.1.7.2 Baseline Characteristics

Table 3.1.7.2.1 (adapted from the study report page 151) presents demographics and baseline characteristics for the ITT population.

Table 3.1.7.2.1 Demographics and Baseline, Patients by Group (ITT)

	Randomization group		
	TPF (N=177)	PF (N=181)	All (N=358)
Sex			
Male	159 (89.8%)	162 (89.5%)	321 (89.7%)
Female	18 (10.2%)	19 (10.5%)	37 (10.3%)
Age (Years)			
Median	53	52	53
Minimum	30	30	30
Maximum	69	70	70
Age (Years)			
< 35	2 (1.1%)	4 (2.2%)	6 (1.7%)
[35-50[	53 (29.9%)	59 (32.6%)	112 (31.3%)
[50-65[	104 (58.8%)	100 (55.2%)	204 (57.0%)
[65-75[	18 (10.2%)	18 (9.9%)	36 (10.1%)
Height (cm)			
Median	170	170	170
Minimum	149	147	147
Maximum	194	192	194
Weight at Cycle 1 (kg)			
Median	64.30	65.00	65.00
Minimum	43.00	34.00	34.00
Maximum	108.00	101.00	108.00
PS WHO			
0	90 (50.8%)	91 (50.3%)	181 (50.6%)
1	86 (48.6%)	90 (49.7%)	176 (49.2%)
2	1 (0.6%)	0 (0.0%)	1 (0.3%)

TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; PS = performance status; WHO = World Health Organization

Note: [x-y[refers to a range including x and excluding y

Reviewer's Comments:

1. In the overall patient population the baseline characteristics appear to be balanced between the two treatment groups.
2. Data on race were not recorded in this study.

3.1.7.3 Primary Efficacy Analyses

Primary efficacy analysis was based on a Cox proportional hazards model. As defined in the SAP, the cut-off date was chosen to include at least 260 PFS events. The occurrence of the 260th event was reported to the EORTC data center on 21 September 2003.

The results of the PFS based on ITT population are presented in Table 3.1.7.3.1 (adapted from the study report page 161). The full model included adjustment of treatment effect for the following factors: treatment (1 = TPF, 0 = PF), oral cavity primary (0 = no, 1 = yes), oropharynx primary (0 = no, 1 = yes), hypopharynx primary (0 = no, 1 = yes), T stage (0 = T1-2-3, 1 = T4), N stage (0 = NX-0-1, 1 = N2-3), and WHO performance status (0 = PS ≥1, 1 = PS0). The primary sites (oral cavity primary, oropharynx primary, hypopharynx, or larynx) were evaluated with a single test.

The results of the Cox model adjusted for the potential effect of the prognostic factors on PFS are presented in Table 3.1.7.3.1 (adapted from the study report page 161).

Table 3.1.7.3.1 Cox proportional hazards model (full model) on PFS (ITT)

	Adjusted treatment effect on prospectively selected covariates			
			95% CI	
Covariate	P value	Hazard ratio	Lower	Upper
Randomization group: TPF / PF	0.0042	0.70	0.55	0.89
WHO performance score: PS null/ PS ≥ 1	0.0322	0.77	0.61	0.98
N stage: N2-3/N0-N1-NX	0.0360	1.34	1.02	1.77
Hypopharynx primary: yes/no [a]	0.0616	1.01	0.60	1.72
Oropharynx primary: yes/no [a]	.	0.77	0.46	1.29
Oral cavity primary: yes/no [a]	.	1.17	0.67	2.06
T stage: T4/T2-T3-T1	0.7495	1.05	0.78	1.41

ITT = intent-to-treat; CI = confidence interval; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; WHO = World Health Organization; PS = performance status

[a] The reference for each primary site variable is the larynx primary site. Then, these variables were evaluated with a single test.

Reviewer's Comments:

1. Stratified log-rank test

The applicant's primary analysis was based on a Cox proportional hazards model, which was specified in the protocol. However, factors (WHO performance score, N stage, and T stage) were not used as the stratification factors during the randomization, hence, they shouldn't be included in the analysis. In addition, because assumptions for Cox proportional hazards model are usually very difficult to verify, instead, a log-rank test is commonly used in the Division of Drug Oncology Products (DDOP) for analyzing endpoints based on time to events because it is a nonparametric test. In this review, a stratified log-rank test based on the stratification factor during the randomization, the primary tumor site, will be performed for both PFS and OS analyses. The other stratification factor, institution, will not be included in the analysis because there were a large number of small institutions.

Table 3.1.7.3.2 presents the result of a stratified log-rank test with the primary tumor site as stratification factor on PFS.

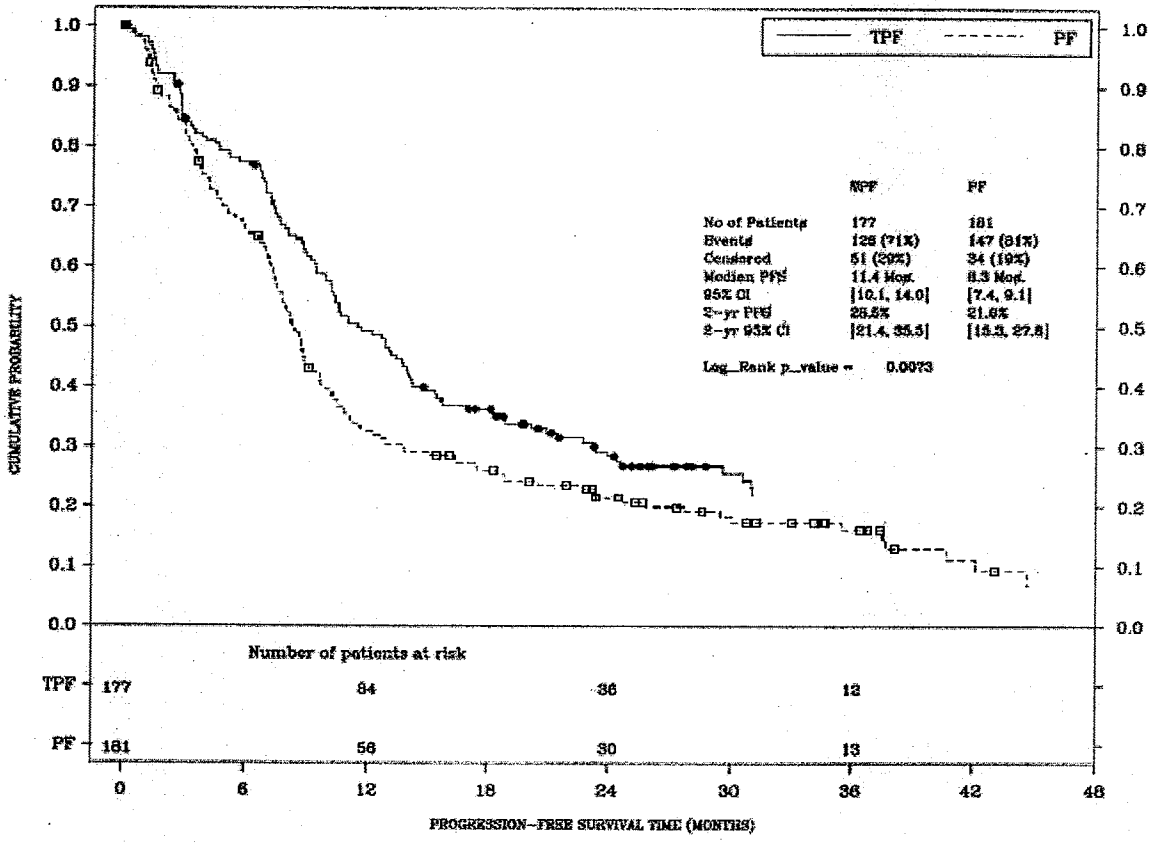
Table 3.1.7.3.2 Stratified Log-rank Test on PFS (ITT)

	TPF (N=177)	PF (N=181)	p-value
Event - Progression - Death	126 (71.2%) 101 (57.1%) 25 (14.1%)	147 (81.2%) 117 (64.6%) 30 (16.6%)	.0077
Censored - Lost to follow-up - No event at cutoff data	51 (28.8%) 5 (2.8%) 46 (26.0%)	34 (18.8%) 4 (2.2%) 30 (16.6%)	
Median PFS (months) [95% CI]	11.4 [10.1 – 14.0]	8.3 [7.4 – 9.1]	
Hazard ratio: TPF/PF [95% CI]	.71 [.56 - .91]		

Patients in the TPF group had a larger median progression-free survival time (11.4 months, 95% CI: 10.1-14.0) than in the PF group (8.3 months, 95% CI: 7.4-9.1). The difference was approximately 3.1 months, had a nominal p-value .0077 based on a stratified log-rank test with the primary tumor site as stratification factor, and had a 29% progression risk reduction (HR 0.71, 95% CI: 0.56-0.91).

Figure 3.1.7.3.1 presents the Kaplan-Meier curve (adapted from the study report page 163).

Figure 3.1.7.3.1 PFS – Kaplan-Meier Curve (ITT)



2. Radiotherapy

Table 3.1.7.3.3 presents the number of patients who had radiotherapy.

Table 3.1.7.3.3 Radiotherapy (ITT)

	TPF (N=177)	PF (N=181)
Radiotherapy	130 (73.4%)	124 (68.5%)
No Radiotherapy	47 (26.6%)	57 (31.5%)
Radiotherapy	130	124
- Event	83 (63.8%)	92 (74.2%)
- Censored	47 (36.2%)	32 (25.8%)
No Radiotherapy	47	57
- Event	43 (91.5%)	55 (96.5%)
- Censored	4 (8.5%)	2 (3.5%)

The mean months for the starting radiotherapy were 3.47 and 3.43 for TPF and PF, respectively. According to the protocol, the radiotherapy starting time was 3 months. Using 3.4 months as a cut-off time, patients whose PFS times were less than 3.4 months shouldn't receive radiotherapy. There were 14/177 (7.9%) in TPF and 19/181 (10.5%) in PF, respectively, whose PFS were greater than 3.4 months and didn't receive radiotherapy. The difference in patients who received radiotherapy using 3.4 months as cut-off is 2.6%, which has no big impact on the analyses and conclusions.

Table 3.1.7.3.4 No Radiotherapy (ITT)

	TPF (N=177)	PF (N=181)
No Radiotherapy	47	57
- Event	43 (91.5%)	55 (96.5%)
- Censored	4 (8.5%)	2 (3.5%)
- PFS Time < 3.4 Months	33 (70.2%)	38 (66.7%)
- PFS Time ≥ 3.4 Months	14 (29.8%)	19 (33.3%)
PFS Time ≥ 3.4 Months	14	19
- Event	13 (92.9%)	19 (100%)
- Censored	1 (7.1%)	0 (0%)

3. Analysis by Country

The trial was conducted in fifteen countries. The randomization was stratified by institution. The number and percentage of events by country, instead of institution, is presented in Table 3.1.7.3.5 due to large number of institutions.

Table 3.1.7.3.5 Number and Percentage of Events by Country (ITT)

Country	Total	TPF Event/Number (%)	PF Event/Number (%)
Austria	21	6/10 (60.0)	9/11 (81.8%)
Belgium	41	12/20 (60.0%)	17/21 (81.0%)
Czech Republic	19	5/8 (62.5%)	8/11 (72.7%)
France	67	28/33 (84.9%)	26/34 (76.5%)
Germany	25	6/12 (50.0%)	10/13 (76.9%)
Hungary	45	19/22 (86.4%)	22/23 (95.7%)
Italy	5	1/1 (100%)	4/4 (100%)
Poland	8	5/5 (100%)	3/3 (100%)
Slovakia	8	2/3 (66.7%)	3/5 (60.0%)
Spain	32	11/17 (64.7%)	11/15 (73.3%)
Switzerland	9	4/6 (66.7%)	2/3 (66.7%)
The Netherlands	30	10/15 (66.7%)	13/15 (86.7%)
Turkey	8	3/4 (75.0%)	3/4 (75.0%)
United Kingdom	23	7/13 (53.9%)	10/10 (100%)
Yugoslavia	17	7/8 (87.5%)	6/9 (66.7%)

Based on the number of events, the difference between two treatment groups in the United Kingdom is larger than the rest. After removing the United Kingdom, the stratified log-rank test with the primary tumor site as stratification factor gives p-value .0099 which is still nominally significant.

Based on the number of events, the trend in France and Yugoslavia is in opposite direction. The following table presents detailed information in France by site.

Table 3.1.7.3.6 Number and Percentage of Events in France by Site (ITT)

Country	Site	Total	TPF Event/Number (%)	PF Event/Number (%)
France		67	28/33 (84.9%)	26/34 (76.5%)
	227	1	0	0/1
	234	21	10/10 (100%)	10/11 (90.9%)
	235	9	4/4 (100%)	4/5 (80.0%)
	282	7	3/3 (100%)	3/4 (75.0%)
	292	5	2/3 (66.7%)	1/2 (50.0%)
	422	5	3/3 (100%)	2/2 (100%)
	429	12	2/6 (33.3%)	4/6 (66.7%)
	469	7	4/4 (100%)	2/3 (66.7%)

Among 8 sites in France, there were 5 sites where the number of events in TPF group is greater than in PF group. Since the number of patients in each site was small, this might not suggest a definite trend.

Yugoslavia had only one site.

3.1.7.4 Secondary Efficacy Analyses

Reviewer's Comments:

Because tests are not adjusted for multiple endpoints, p-values for secondary endpoints serve as descriptive statistics only.

3.1.7.4.1 Overall Survival

Overall survival (OS), analyzed in the ITT population was the main secondary efficacy endpoint for this study. OS is measured from the date of randomization up to the date of death (any cause). At the cut off date, 237 of 358 (66.2%) patients had died (61.0% and 71.3% in the TPF and PF treatment groups, respectively). The proportion of patients lost to follow-up was similar in the 2 treatment groups (3.9% overall).

Tables 3.1.7.4.1.1 and 3.1.7.4.1.2 (adapted from the study report pages171 and 173) present statistics of OS on ITT population.

Table 3.1.7.4.1.1 OS (ITT)

	RANDOMIZATION GROUP		
	TPF (N=177)	PF (N=181)	ALL (N=358)
Number of patients with			
event	108 (61.0%)	129 (71.3%)	237 (66.2%)
censored data	69 (39.0%)	52 (28.7%)	121 (33.8%)
Censoring reasons (Survival)			
Lost to follow-up [a]	6 (3.4%)	8 (4.4%)	14 (3.9%)
No event at cutoff date	63 (35.6%)	44 (24.3%)	107 (29.9%)

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU
Patient 00047 (randomized in TPF group) died from progressive disease but date of death is UKFEB2001, by convention the date is set to 01FEB2001

[a] Includes one patient (PF) not declared as lost to follow-up, for whom date of last contact was before cutoff date.

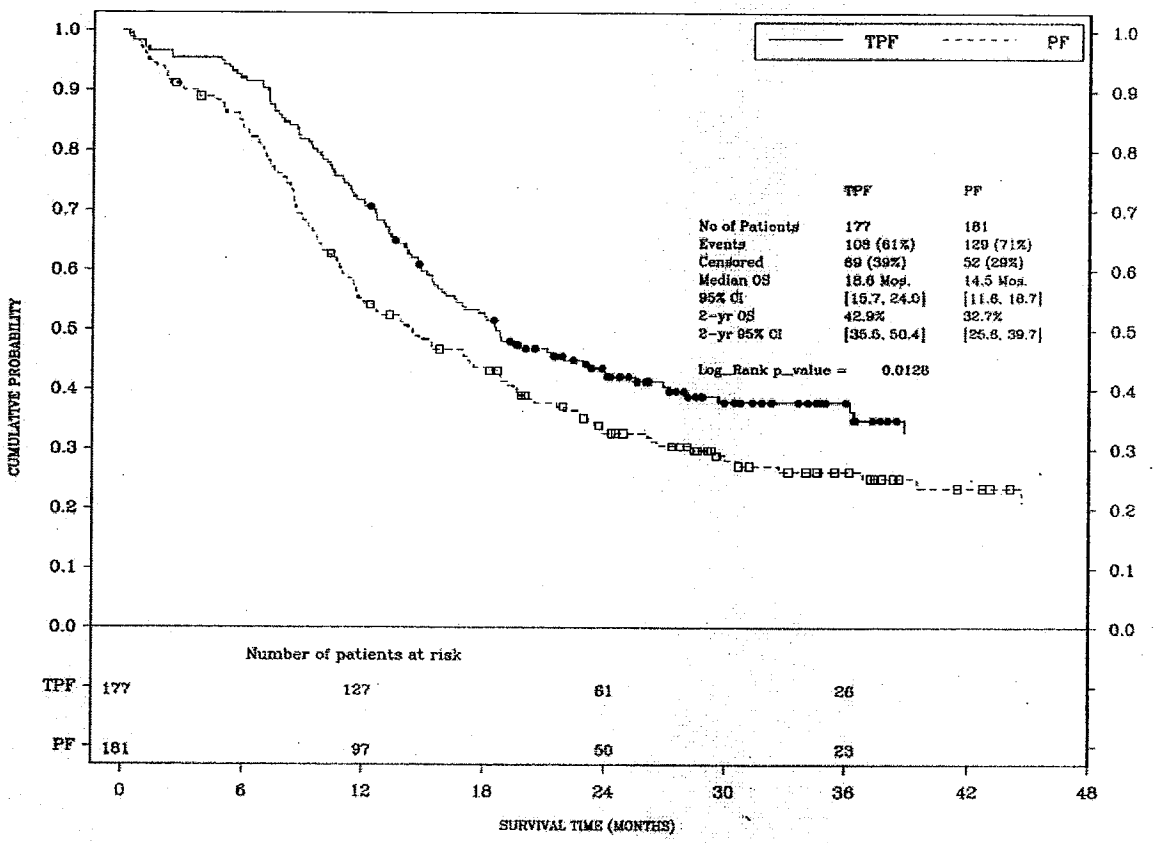
Table 3.1.7.4.1.2 Summary Statistics for OS (ITT)

	Randomization group	
	TPF (N=177)	PF (N=181)
Median overall survival (months) [95% CI]	18.6 [15.7 - 24.0]	14.5 [11.6 - 18.7]
Kaplan-Meier estimates for overall survival		
1-year estimate [95% CI]	71.8% [65.1 - 78.4]	54.7% [47.4 - 62.0]
2-year estimate [95% CI]	42.9% [35.5 - 50.4]	32.7% [25.6 - 39.7]
3-year estimate [95% CI]	37.9% [30.3 - 45.5]	26.3% [19.4 - 33.3]
Hazard ratio: TPF/PF [95% CI]	0.72 [0.56 - 0.93]	
Log-Rank p value	0.0128	

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; CI = confidence interval

Figure 3.1.7.4.1.1 presents the Kaplan-Meier curve (adapted from the study report page 172).

Figure 3.1.7.4.1.1 OS – Kaplan-Meier Curve (ITT)



ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU
Event = death

Reviewer's Comments:

The analysis on OS based on a stratified log-rank test with the primary tumor site as stratification factor has a p-value .0178, with the hazard ratio .72 and 95% CI .56 - .93.

Updated Overall Survival

A total of 358 patients were randomized between 14 April 1999 and 15 March 2002. The cut-off date of 21 September 2003 was used in all efficacy analyses included in the clinical study report (dated February 9, 2006). Median follow-up time was 33.7 months. The current updated analysis of OS extended the follow-up period by 18 additional months. The cut-off date for the present report was March 21, 2005, which corresponded to an overall follow-up of 53 months with an overall median follow-up 51.2 months. PFS was mature at the cut-off date for the clinical study report (September 21, 2003) and was not updated in this report.

Table 3.1.7.4.1.3 (adapted from the study report submitted on June 15, 2006 page 5) presents statistics of updated OS on ITT population.

Table 3.1.7.4.1.3 Updated OS (ITT)

	TREATMENT GROUP		
	TPF (N=177)	PF (N=181)	ALL (N=358)
Number of patients with			
event	122 (68.9%)	146 (80.7%)	268 (74.9%)
censored data	55 (31.1%)	35 (19.3%)	90 (25.1%)
Censoring reasons (Survival)			
Lost to follow-up	8 (4.5%)	9 (5.0%)	17 (4.7%)
Date of last contact before the cut-off date	15 (8.5%)	5 (2.8%)	20 (5.6%)
No event at cutoff date	32 (18.1%)	21 (11.6%)	53 (14.8%)

Patient 00047 (randomized to the TPF treatment group) died from progressive disease but date of death is UKFEB2001, by convention the date is set to 01FEB2001

Figure 3.1.7.4.1.2 presents the Kaplan-Meier curve (adapted from the study report submitted on June 15, 2006 page 6).

Figure 3.1.7.4.1.2 Updated OS – Kaplan-Meier Curve (ITT)

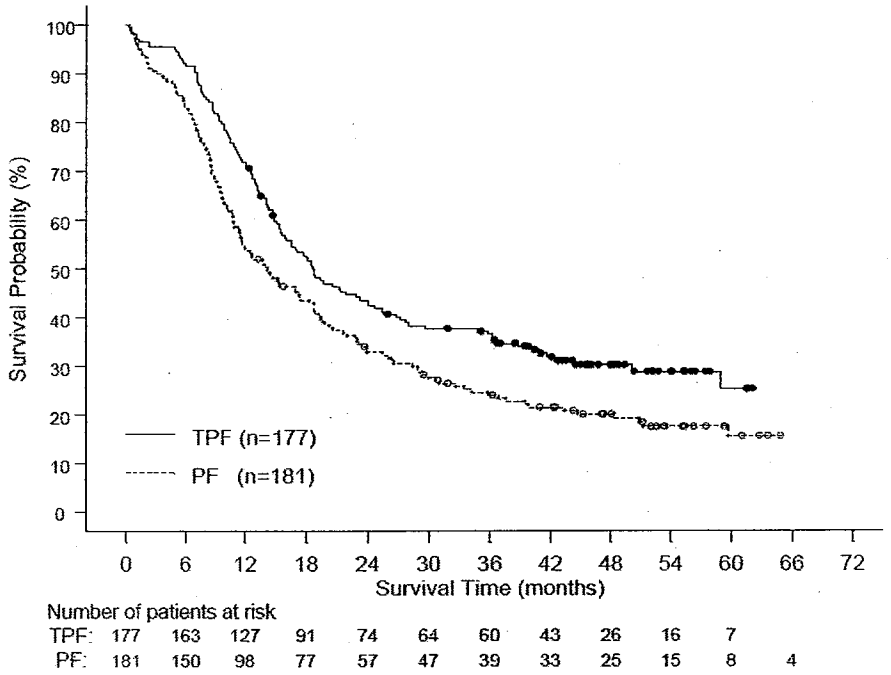


Table 3.1.7.4.1.4 (adapted from the study report submitted on June 15, 2006 page 7) presents statistics of updated OS on ITT population. Median OS was longer in the TPF treatment group (18.6 months, 95% CI: 15.7-24.0) than in the PF treatment group (14.2 months, 95% CI: 11.5-18.7), representing a 4.4-month increase. The difference between the treatment groups was statistically significant (log-rank test, P =.0052), with a 29% risk reduction in mortality for the TPF treatment group compared to the PF treatment group (HR 0.71, 95% CI: 0.56-0.90).

Table 3.1.7.4.1.4 Summary Statistics for Updated OS (ITT)

	Randomization group	
	TPF	PF
	(N=177)	(N=181)
Median overall survival (months) [95% CI]	18.6 [15.7 - 24.0]	14.2 [11.5 - 18.7]
Kaplan-Meier estimates for overall survival		
1-year estimate [95% CI]	71.8% [65.1 - 78.4]	54.1% [46.9 - 61.4]
2-year estimate [95% CI]	42.9% [35.6 - 50.3]	32.8% [25.9 - 39.6]
3-year estimate [95% CI]	36.5% [29.3 - 43.6]	23.9% [17.6 - 30.3]
Hazard ratio: TPF/PF [95% CI]	0.71 [0.56 - 0.90]	
Log-Rank p value	0.0052	

Reviewer's Comments:

The analysis on updated OS based on a stratified log-rank test with the primary tumor site as stratification factor has a p-value .0055, with the hazard ratio .71 and 95% CI .56 - .90.

Table 3.1.7.4.1.5 presents the summary result on updated OS.

Table 3.1.7.4.1.5 Stratified Log-rank Test on Updated OS (ITT)

	TPF (N=177)	PF (N=181)	p-value
Event	122 (68.9%)	146 (80.7%)	.0055
Censored - Lost to follow-up -Date of last contact before the cut-off date - No event at cutoff data	55 (31.1%) 8 (4.5%) 15 (8.5%) 32 (18.1%)	35 (19.3%) 9 (2.8%) 5 (2.8%) 21 (11.6%)	
Median PFS (months) [95% CI]	18.6 [15.7 – 24.0]	14.2 [11.5 – 18.7]	
Hazard ratio: TPF/PF [95% CI]	.71 [.56 - .90]		

3.1.7.4.2 Response to Treatment

Response rates were evaluated at the end of chemotherapy and after locoregional radiotherapy.

3.1.7.4.2.1 Best Overall Response to Chemotherapy

Best overall response to chemotherapy in the ITT population is summarized in Table 3.1.7.4.2.1(adapted from the study report page 174). The overall clinical response rate after induction chemotherapy (ORR-CT) was the best response designation recorded from the date of randomization up to disease progression during chemotherapy or end of chemotherapy cycles. The ORR (i.e., percentage of patients with CR or PR) was higher in the TPF treatment group (67.8%, 95% CI: 60.4-74.6%) than in the PF treatment group (53.6%; 95% CI: 46.0-61.0%). The difference between the two treatment groups was statistically significant (Chi square test, $P = .006$). Overall, the CR rate was low (8.5% versus 6.6% for TPF and PF treatment groups, respectively), and no statistical difference between the treatment groups was observed.

Best overall response was NC in 16.9% of patients in the TPF treatment group and 24.9% in the PF treatment group, and the proportion of outright progressors (best response of PD) during chemotherapy was similar in both treatment groups (6.1% overall). The incidence of patients not evaluable (NE) was 9.6% in the TPF treatment group and 14.9% in the PF treatment group, respectively.

Table 3.1.7.4.2.1 Best Overall Response to Chemotherapy (ITT)

	Randomization group	
	TPF (N=177)	PF (N=181)
Complete response	15 (8.5%)	12 (6.6%)
Partial response	105(59.3%)	85 (47%)
No change	30 (16.9%)	45 (24.9%)
Progression of disease	10 (5.6%)	12 (6.6%)
Not evaluable	17 (9.6%)	27 (14.9%)
Overall RR (CR+PR) 95% CI	67.8% [60.4-74.6]	53.6% [46.0-61.0]
P value	0.006	
Complete RR (CR) 95% CI	8.5% [4.8-13.6]	6.6% [3.5-11.3]
P value	0.509	

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; RR = response rate; CR = complete response; PR = partial response; CI = confidence interval

3.1.7.4.2.2 Best Overall Response to Radiotherapy

Best overall response to radiotherapy in the ITT population is summarized in Table 3.1.7.4.2.2 (adapted from the study report page 175). The overall clinical response rate after radiation therapy (ORR-RT) was the best response recorded at the end of the radiation therapy taking into account all tumor assessments after radiotherapy up to disease progression or further anti-cancer therapy and was measured taking as reference the date of randomization. Both the overall response rate (CR + PR) and the CR rate after radiotherapy were higher in the TPF treatment group than in the PF treatment group, and both differences were statistically significant ($P = .017$ for overall response rate, $P = .024$ for CR rate).

Although the overall response rate after radiotherapy was about 10% lower than that after chemotherapy, in both treatment groups the majority of responders to radiotherapy had a CR. Best overall responses of PD after radiotherapy were found in approximately twice as many patients in the PF treatment group than in the TPF treatment group (37.9% and 19.2%, respectively).

Table 3.1.7.4.2.2 Best Overall Response to Radiotherapy (ITT)

	Randomization group	
	TPF (N=130)	PF (N=124)
Complete response	52 (40%)	33 (26.6%)
Partial response	24 (18.5%)	21 (16.9%)
No change	0 (0.0%)	1 (0.8%)
Progression of disease	25 (19.2%)	47 (37.9%)
Not evaluable	29 (22.3%)	22 (17.7%)
Overall RR (CR+PR) 95% CI	58.5% [49.5-67.0]	43.5% [34.7-52.7]
P value	0.017	
Complete RR (CR) 95% CI	40% [31.5-49.0]	26.6% [19.1-35.3]
P value	0.024	

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; RR = response rate; CR = complete response; PR = partial response; CI = confidence interval

3.1.7.4.2.3 Best Overall Response to Chemotherapy and Radiotherapy

Best overall response (BOR) taking into accounts both chemotherapy and radiotherapy periods is summarized for the ITT population in Table 3.1.7.4.2.3 (adapted from the study report page 176).

When taking into account chemotherapy and radiotherapy periods, both the overall response rate (CR + PR) and the CR rate were higher in the TPF treatment group than in the PF treatment group (CR + PR: 72.3% TPF, 58.6% PF; CR: 33.3% TPF, 19.9% PF). Both differences were statistically significant ($P = .006$ for overall response rate, $P = .004$ for CR rate).

In both treatment groups, the overall response rate taking into account chemotherapy and radiotherapy periods was approximately 7% higher than after chemotherapy alone. Notably, the percentage of patients with CR increased by a factor 4 in the TPF treatment group and by a factor 3 in the PF treatment group compared to after chemotherapy alone.

Table 3.1.7.4.2.3 Best Overall Response to Chemotherapy and Radiotherapy (ITT)

	Randomization group	
	TPF (N=177)	PF (N=181)
Complete response	59 (33.3%)	36 (19.9%)
Partial response	69 (39%)	70 (38.7%)
No change	24 (13.6%)	39 (21.5%)
Progression of disease	11 (6.2%)	13 (7.2%)
Not evaluable	14 (7.9%)	23 (12.7%)
Overall RR (CR+PR) 95% CI	72.3% [65.1-78.8]	58.6% [51.0-65.8]
P value	0.006	
Complete RR (CR) 95% CI	33.3% [26.4-40.8]	19.9% [14.3-26.5]
P value	0.004	

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; RR = response rate; CR = complete response; PR = partial response; CI = confidence interval; BOR= best overall response

Reviewer's Comments:

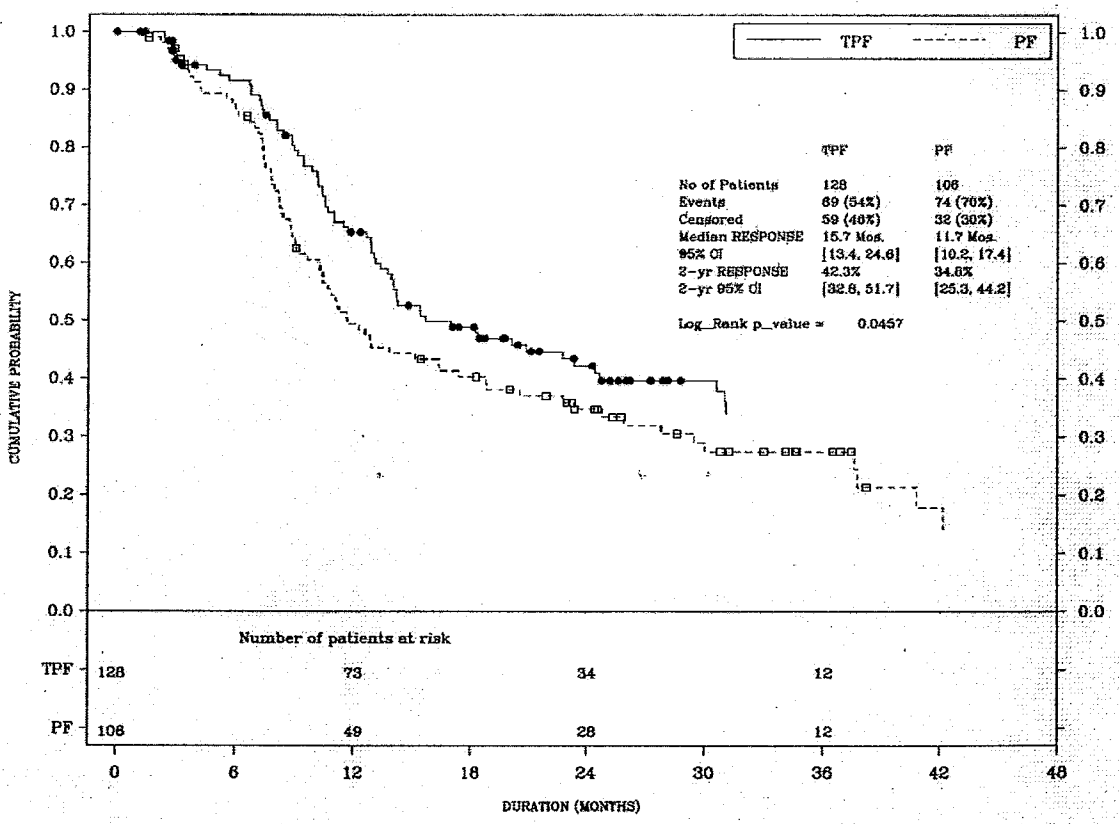
Best overall response rates were higher in the TPF treatment group than in the PF treatment group after chemotherapy with a difference of approximately 14%, and a p-value .006 based on a chi-square test, after radiotherapy with a difference of approximately 15%, and a p-value .017 based on a chi-square test, and overall, taking into account the chemotherapy and radiotherapy periods with a difference of approximately 13%, and a p-value .006 based on a chi-square test. The CR rate after chemotherapy and radiotherapy was higher than in the TPF treatment group with a difference of approximately 12%, and a p-value .004 based on a chi-square test.

3.1.7.4.3 Duration of Response

Duration of response (CR + PR) was calculated from time of randomization until documentation of progression in responders to chemotherapy and radiotherapy.

A Kaplan-Meier plot and summary statistics for duration of response are presented in Figure 3.1.7.4.3.1 (from the study report page 179) and Table 3.1.7.4.3.1 (adapted from the study report page 180), respectively. Median duration of response was higher in the TPF treatment group (15.7 months; 95% CI: 13.4-24.6) than in the PF treatment group (11.7 months; 95% CI: 10.2-17.4), representing a 4 month increase. This difference was statistically significant (log-rank test, P = .0457). The hazard ratio (0.72, 95% CI: 0.52-0.99) favors TPF. Approximately 16% fewer responders in the TPF treatment group than in the PF treatment group had a duration of response event (PD or death) at cut-off, with PD accounting for the majority of this difference.

Figure 3.1.7.4.3.1 Duration of Response – Kaplan-Meier Curve (Responders)



Event = progression or death

Table 3.1.7.4.3.1 Summary Statistics for Duration of Response (Responders to Chemotherapy and Radiotherapy) (ITT)

	RANDOMIZATION GROUP		
	TPF (N=128)	PF (N=106)	ALL (N=234)
Number of patients with			
event	69 (53.9%)	74 (69.8%)	143 (61.1%)
censored data	59 (46.1%)	32 (30.2%)	91 (38.9%)
Event reasons (Response)			
Progression	65 (50.8%)	69 (65.1%)	134 (57.3%)
Death	4 (3.1%)	5 (4.7%)	9 (3.8%)
Censoring reasons (Response)			
Lost to follow-up	2 (1.6%)	3 (2.8%)	5 (2.1%)
No event at cutoff date	43 (33.6%)	26 (24.5%)	69 (29.5%)
Death more than 100 days after the last valid assessment	12 (9.4%)	3 (2.8%)	15 (6.4%)
Further anti-cancer therapy before event	2 (1.6%)	0 (0.0%)	2 (0.9%)

TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients

Reviewer's Comments:

Median duration of response was higher in the TPF treatment group than in the PF treatment group with a difference of approximately 4 months, and a p-value .0457 based on a log-rank test. However, it should be noted that no inference can be drawn since this is considered only in the subset of responders.

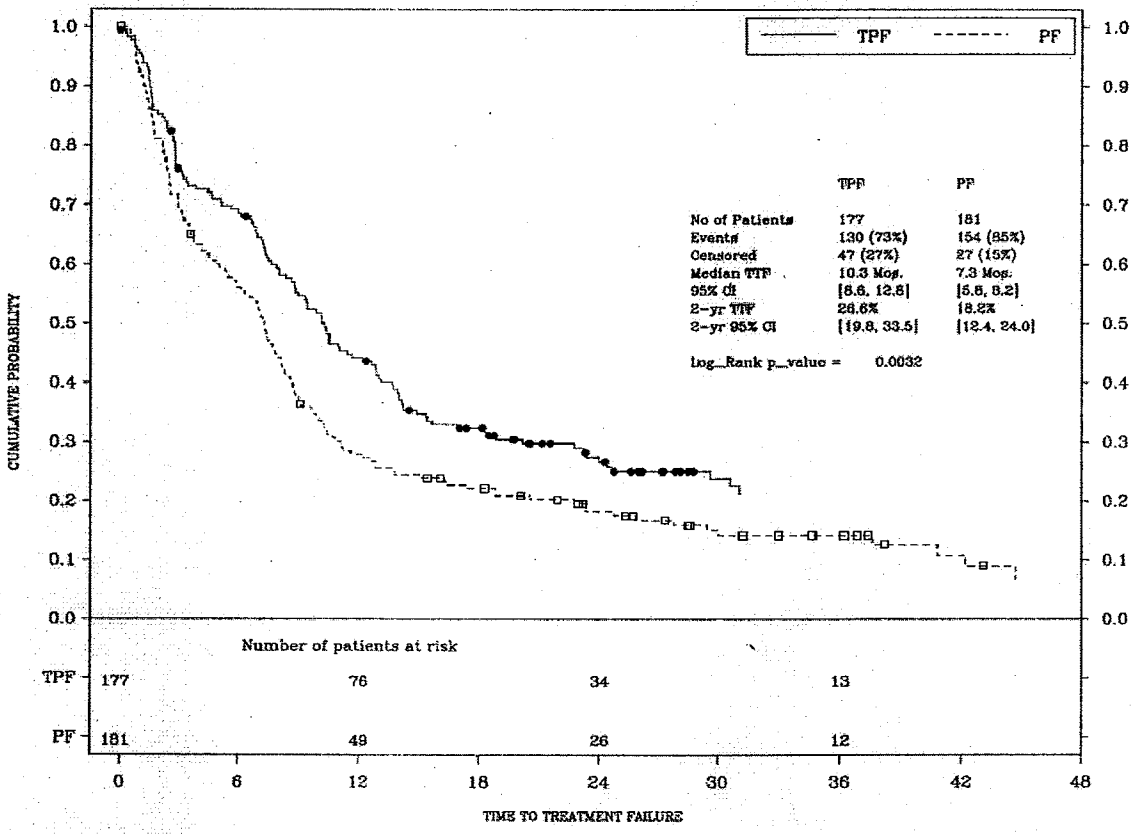
3.1.7.4.4 Time to Treatment Failure

Time to treatment failure (TTF) was calculated from the date of randomization to the date of treatment failure (i.e., progression, relapse, death, discontinuation due to adverse event, patient refusal of treatment, or lost to follow-up before the end of treatment [induction chemotherapy plus radiotherapy]). Observations of lost to follow-up after the end of treatment were censored.

A Kaplan-Meier plot and summary statistics for TTF are presented in Figure 3.1.7.4.4.1 (adapted from the study report page 181) and Table 3.1.7.4.4.1(adapted from the study report page 182), respectively. Median TTF was longer in the TPF treatment group (10.3 months; 95% CI: 8.6-12.8 months) than in the PF treatment group (7.3 months; 95% CI: 5.8-8.2), and this difference was statistically significant (log rank test, $P = .0032$). The hazard ratio (0.71, 95% CI: 056-089) favors treatment with TPF, and treatment with TPF led to higher estimates for this endpoint with no events

at 1, 2, and 3 years. Approximately 12% fewer patients in the TPF treatment group than in the PF treatment group had a TTF event at cut-off, with PD and AEs accounting for the majority of this difference.

Figure 3.1.7.4.4.1 TTF – Kaplan-Meier Curve (ITT)



ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU
Event = progression, relapse, death, discontinuation due to adverse event, patient refusal of treatment, or lost to follow-up before the end of treatment (chemotherapy plus radiotherapy).

Table 3.1.7.4.4.1 Summary Statistics for TTF (ITT)

	RANDOMIZATION GROUP		
	TPF (N=177)	PF (N=181)	ALL (N=358)
Number of patients with			
event	130 (73.4%)	154 (85.1%)	284 (79.3%)
censored data	47 (26.6%)	27 (14.9%)	74 (20.7%)
Event reasons (TTF)			
Progression	89 (50.3%)	99 (54.7%)	188 (52.5%)
Death	21 (11.9%)	25 (13.8%)	46 (12.8%)
CT Withdrawal due to AE	11 (6.2%)	21 (11.6%)	32 (8.9%)
RT Withdrawal due to AE	2 (1.1%) [a]	0 (0.0%)	2 (0.6%)
CT Subject's refusal	4 (2.3%)	8 (4.4%)	12 (3.4%)
RT Subject's refusal	1 (0.6%)	1 (0.6%)	2 (0.6%)
Lost to follow-up before treatment completion	2 (1.1%)	0 (0.0%)	2 (0.6%)
Censoring reasons (TTF)			
Lost to follow-up after treatment completion	4 (2.3%)	1 (0.6%)	5 (1.4%)
No event at cutoff date	43 (24.3%)	26 (14.4%)	69 (19.3%)

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; TTF = time to treatment failure; AE = adverse event

[a] One patient (00327) discontinued during both CT and RT due to AE and was counted only once during chemotherapy (first failure) in this TTF table

Reviewer's Comments:

Median TTF was longer in the TPF treatment group than in the PF treatment group with a difference of approximately 3 months, and a p-value .0032 based on a log rank test. However, this endpoint is not considered for regulatory purposes.

3.2 Evaluation of Safety

Please refer to Clinical Review of this application for safety evaluation.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Since data on race were not recorded in this study, no information is available for the subgroup of

race.

Table 4.1.1 presents PFS by gender and age. Descriptive statistics are presented. Median Months are from the K- M estimates.

Table 4.1.1 PFS by Subgroup (ITT)

Subgroup	Characteristics	Number/N (%) Months [95% CI]	TPF (N=177)	PF (N=181)
Gender	Male	Event Median	115/159 (72.3%) 11.0 [9.4 – 14.0]	131/162 (80.9%) 8.2 [7.4 – 9.0]
	Female	Event Median	11/18 (61.1%) 13.7 [10.4 - .]	16/19 (75%) 10.2 [6.6 – 22.8]
Age	< 65	Event Median	112/159 (70.4%) 11.7 [9.9 – 14.0]	132/163 (81.0%) 8.6 [7.5 – 9.9]
	≥ 65	Event Median	14/18 (77.7%) 10.6 [7.2 – 14.9]	15/18 (83.3%) 7.1 [3.7 – 9.0]

In all subgroups listed above, TPF group has smaller percentage of events and larger median PFS months than PF group.

4.2 Other Special/Subgroup Populations

The analysis by country is presented in Section 3.1.7.3.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

There are two issues in the submission.

1. The applicant's primary analysis was based on a Cox proportional hazards model, which was specified in the protocol. However, factors (WHO performance score, N stage, and T stage) were not used as the stratification factors during the randomization, hence, they shouldn't be included in the analysis. In addition, because assumptions for Cox proportional hazards model are usually very difficult to verify, instead, a log-rank test is commonly used in the Division of Drug Oncology Products (DDOP) for analyzing endpoints based on time to events because it is a nonparametric test. In this review, a stratified log-rank test based on the stratification factor during the randomization, the primary tumor site, is performed for both PFS and OS analyses. The other stratification factor, institution, isn't included in the analysis because there were a large number of small institutions.

2. There was an imbalance in radiotherapy between two treatment groups, 73.4% in TPF, and 68.5% in PF groups, respectively. The difference was approximately 4.9%. After a detailed evaluation, the difference in patients who received radiotherapy using 3.4 months as cut-off is 2.6%, which doesn't have big impact on the analyses and conclusions.

The protocol specified primary analysis was based on a Cox proportional hazards model. As defined in the SAP, the cut-off date was chosen to include at least 260 PFS events. The occurrence of the 260th event was reported to the EORTC data center on 21 September 2003.

The results of the PFS based on ITT population are presented in Table 5.1.1. The full model included adjustment of treatment effect for the following factors: treatment (1 = TPF, 0 = PF), oral cavity primary (0 = no, 1 = yes), oropharynx primary (0 = no, 1 = yes), hypopharynx primary (0 = no, 1 = yes), T stage (0 = T1-2-3, 1 = T4), N stage (0 = NX-0-1, 1 = N2-3), and WHO performance status (0 = PS ≥1, 1 = PS0). The primary sites (oral cavity primary, oropharynx primary, hypopharynx, or larynx) were evaluated with a single test.

Table 5.1.1 Cox proportional hazards model (full model) on PFS (ITT)

	Adjusted treatment effect on prospectively selected covariates			
			95% CI	
Covariate	P value	Hazard ratio	Lower	Upper
Randomization group: TPF / PF	0.0042	0.70	0.55	0.89
WHO performance score: PS null/ PS ≥ 1	0.0322	0.77	0.61	0.98
N stage: N2-3/N0-N1-NX	0.0360	1.34	1.02	1.77
Hypopharynx primary: yes/no [a]	0.0616	1.01	0.60	1.72
Oropharynx primary: yes/no [a]		0.77	0.46	1.29
Oral cavity primary: yes/no [a]		1.17	0.67	2.06
T stage: T4/T2-T3-T1	0.7495	1.05	0.78	1.41

ITT = intent-to-treat; CI = confidence interval; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; WHO = World Health Organization; PS = performance status

[a] The reference for each primary site variable is the larynx primary site. Then, these variables were evaluated with a single test.

Table 5.1.2 presents the result of a stratified log-rank test with the primary tumor site, which was used as a stratification factor during the randomization, as stratification factor on PFS.

Table 5.1.2 Stratified Log-rank Test on PFS (ITT)

	TPF (N=177)	PF (N=181)	p-value
Event - Progression - Death	126 (71.2%) 101 (57.1%) 25 (14.1%)	147 (81.2%) 117 (64.6%) 30 (16.6%)	.0077
Censored - Lost to follow-up - No event at cutoff data	51 (28.8%) 5 (2.8%) 46 (26.0%)	34 (18.8%) 4 (2.2%) 30 (16.6%)	
Median PFS (months) [95% CI]	11.4 [10.1 – 14.0]	8.3 [7.4 – 9.1]	
Hazard ratio: TPF/PF [95% CI]	.71 [.56 - .91]		

Patients in the TPF group had a larger median progression-free survival time (11.4 months, 95% CI: 10.1-14.0) than in the PF group (8.3 months, 95% CI: 7.4-9.1). The difference was approximately 3.1 months, had a nominal p-value .0077 based on a stratified log-rank test with the primary tumor site as stratification factor, and had a 29% progression risk reduction (HR 0.71, 95% CI: 0.56-0.91).

Table 5.1.3 presents the result of a stratified log-rank test with the primary tumor site, which was used as a stratification factor during the randomization, as stratification factor on updated OS.

Table 5.1.3 Stratified Log-rank Test on Updated OS (ITT)

	TPF (N=177)	PF (N=181)	p-value
Event	122 (68.9%)	146 (80.7%)	.0055
Censored - Lost to follow-up -Date of last contact before the cut-off date - No event at cutoff data	55 (31.1%) 8 (4.5%) 15 (8.5%) 32 (18.1%)	35 (19.3%) 9 (2.8%) 5 (2.8%) 21 (11.6%)	
Median PFS (months) [95% CI]	18.6 [15.7 – 24.0]	14.2 [11.5 – 18.7]	
Hazard ratio: TPF/PF [95% CI]	.71 [.56 - .90]		

The updated overall survival data and analyses also demonstrated that patients in the Taxotere plus cisplatin and 5-FU (TPF) group had a larger median overall survival time (18.6 months, 95% CI: 15.7-24.0) than in the cisplatin and 5-FU (PF) group (14.2 months, 95% CI: 11.5-18.7). The difference was approximately 4.4 months, had a p-value .0055 based on a stratified log-rank test with the primary tumor site as stratification factor, and had a 29% progression risk reduction (HR 0.71, 95% CI: 0.56-0.90).

5.2 Conclusions and Recommendations

The data and analyses from the current submission demonstrated that patients with locally advanced inoperable squamous cell carcinoma of head and neck in the Taxotere plus cisplatin and 5-FU (TPF) group had a larger median progression-free survival time (11.4 months, 95% CI: 10.1-14.0) than in the cisplatin and 5-FU (PF) group (8.3 months, 95% CI: 7.4-9.1). The difference was approximately 3.1 months, had a nominal p-value .0077 based on a stratified log-rank test with the primary tumor site as stratification factor, and had a 29% progression risk reduction (HR 0.71, 95% CI: 0.56-0.91).

The updated overall survival data and analyses also demonstrated that patients in the Taxotere plus cisplatin and 5-FU (TPF) group had a larger median overall survival time (18.6 months, 95% CI: 15.7-24.0) than in the cisplatin and 5-FU (PF) group (14.2 months, 95% CI: 11.5-18.7). The difference was approximately 4.4 months, had a p-value .0055 based on a stratified log-rank test with the primary tumor site as stratification factor, and had a 29% progression risk reduction (HR 0.71, 95% CI: 0.56-0.90).

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

/s/

Kun He
9/15/2006 09:20:41 AM
BIOMETRICS

Rajeshwari Sridhara
9/15/2006 10:10:21 AM
BIOMETRICS

Aloka Chakravarty
9/18/2006 08:43:48 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449 / S-039

OTHER REVIEW(S)

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: July 17, 2006

TO: Ann Staten, Regulatory Project Manager
Qin Ryan, M.D., Clinical Reviewer
Division of Oncology Drug Products, HFD-150

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Lauren Iacono-Connors, Ph.D.
Reviewer, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Preliminary Evaluation of Clinical Inspections, Pending Receipt of EIR

NDA: 20449/039

NME: No

APPLICANT: Aventis Pharmaceuticals, Inc.

DRUG: Docetaxel (Taxotere®)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Induction treatment in patients with locally advanced inoperable squamous cell carcinoma of the head and neck.

CONSULTATION REQUEST DATE: May 16, 2006

DIVISION ACTION GOAL DATE: October 14, 2006

PDUFA DATE: October 14, 2006

I. BACKGROUND:

Drug Product:

Docetaxel (Taxotere®) is an antineoplastic agent that is currently approved for the treatment of breast cancer, non-small cell lung cancer, prostate cancer and advanced gastric adenocarcinoma. This agent of the toxoid family corrupts cellular function by disrupting macromolecular/microtubular networks essential to cell division phases of mitosis and interphase.

The sponsor seeks to add to the current indication of Taxotere® to include induction treatment in patients with locally advanced inoperable squamous cell carcinoma of the head and neck.

The clinical investigator, Dr. Eva Remenar, participated as one of the many international clinical investigators on the protocol TAX323 selected for audit. Dr. Remenar's study center represents 1 of 37 study sites, all of which were outside the United States. The study was a multicenter, non-blinded, stratified, phase III study comparing 2 therapy regimens as neoadjuvant (induction) treatment before radiotherapy for locally advanced inoperable Squamous Cell Carcinoma of the Head and Neck. TAX323 had an originally planned enrollment target of 348 subjects. Dr. Remenar's study center screened and randomized 38 subjects, representing approximately 10% of the total study population, into study TAX323. A total of 358 subjects were randomized into this study with 177 in the test treatment arm and 181 into the standard treatment arm.

The clinical investigator, Dr. Eva Remenar, is not listed in the CDER Clinical Investigator System (CIS). However, study TAX323 was conducted under an IND.

PROTOCOL: XRP6976F-323/EORTC (TAX323), "A Randomized Phase III Multicenter Trial of Neoadjuvant Docetaxel (Taxotere ®) Plus Cisplatin Plus 5-Fluorouracil Versus Neoadjuvant Cisplatin Plus 5-Fluorouracil in Patients With Locally Advanced Inoperable Squamous Cell Carcinoma of the Head and Neck."

II. RESULTS:

Inspected Entity	City, State\Country	Protocol(s)	Inspection Dates	EIR Received Date	Final Classification
Eva Remenar, M.D.	Budapest, Hungary	TAX323	June 2006	Pending DAL-DO	Pending

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

1. Eva Remenar M.D.
Orszagos Onkologiai Intezet,
H-1122 Budapest,
Rath Gyorgy u. 7-9
Hungary

a. What was inspected?

The study records of 15 of the 38 subjects enrolled into the study, and under the responsible care of Eva Remenar M.D., were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these 15 subjects the record audit included comparison of source documentation, CRFs and sponsor-provided data line-listings with particular attention paid to inclusion/exclusion criteria compliance, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed the date and cause of death and informed consent forms for all randomized subjects.

Study subjects reviewed during the inspection are listed below.

53/
79/
85/
134/
142/
171/
172/
198/

201/
205/
220/
250/
300/
318/
358/

b(6)

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. Also, the majority of the audited documents were in the native language of Hungarian. Field investigator Mr. Patrick Stone had the benefit of an interpreter who was present for the inspection. However, the language barrier required that Mr. Stone accept the interpretation support and products provided in support of the CI inspection and the outcome.

c. General observations/commentary:

The site was found to be adequate in the execution of the study TAX323. The study was well controlled and documented. No FDA Form 483 was issued. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. Records were audited for 15 subjects. IRB/EC compliance was verified and all 38 randomized subjects had a signed informed consent form. AEs were reported and followed up in accordance with the protocol. Of the 38 subjects randomized into study 19 completed the study according to protocol.

Eva Remenar was fully engaged in the execution of this study. This investigator personally performed all subjects suitability determinations, conducted physical exams, infused study medications, performed follow-up study visits and completed all of the case report form entries. Eva Remenar also performed head and neck tumor dissections when necessary. Eva Remenar did not have the services of a research nurse for this study.

The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on communication from the field investigator, Mr. Patrick Stone. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data from Eva Remenar's site, associated with protocol TAX323, submitted to the agency in support of NDA 20449/039, are reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The study data collected by Eva Remenar appear reliable. The FDA investigator, Mr. Patrick Stone reported in preliminary communications to DSI that he audited 15 of 38 randomized subjects' records under the responsible care of Eva Remenar in the execution of study TAX323. Each of 15 subject's records, source documents, CRFs and sponsor-submitted data listings, were reconciled. Adverse events were recorded and reported in accordance with the protocol. No notable objectionable observations were made. An FDA Form 483 was not issued.

Observations noted above are based on the preliminary communications provided the field investigator Mr. Patrick Stone. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIR and the supporting inspection evidence and exhibits.

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

/s/

Lauren Iacono-Connors
7/17/2006 05:25:47 PM
UNKNOWN

Leslie Ball
7/18/2006 08:59:56 PM
MEDICAL OFFICER

PROJECT MANAGER REVIEW OF LABELING

NDA 20-449/S-039

Drug:	**Taxotere (docetaxel) Concentrate for Injection, 20 mg and 80 mg**
Applicant:	**Sanofi-Aventis**
Submission Date:	**April 14 and June 21, 2006**
Receipt Date:	**April 17 and June 22, 2006**

BACKGROUND:

On September 23, 2005, Aventis submitted supplement 035. This supplement (S-035) provided for the following new proposed indication: "Taxotere in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced gastric cancer". This supplement (S-035) was approved on March 22, 2006. The FPL for this supplement has not been submitted.

On December 21, 2005, Aventis submitted supplement 036. This new CBE supplement (S-036) provides for changes to the package insert Black Box Warning and WARNINGS, Hypersensitivity Reactions subsection to include a new warning for severe hypersensitivity reactions, "fatal anaphylaxis", and to add 4 new sections to the ADVERSE REACTIONS, Post-marketing Experiences subsection. This supplement (S-036) was approved on June 7, 2006. It contained FPL which did not include the new gastric indication.

On April 14, 2006, the sponsor submitted a new supplement S-039. This new supplement (S-039) provides for the following new indication: TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

The April 14, 2006 proposed package insert did not show the tracked changes and did not contain the recent approved gastric indication (S-035) or the CBE (S-036) changes. The sponsor submitted a revised package insert on June 21, 2006 to contain tracked changes for S-039, the CBE changes from S-036 and the gastric indication (S-035).

DOCUMENTS REVIEWED:

I compared the electronic Word version of the proposed package insert text submitted June 21, 2006 for S-039 against the electronic version of the package insert attached to the March 22, 2006 approval letter for S-035.

REVIEW:

The new version correctly highlights (through tracked changes) the changes that the sponsor proposes for this supplement. It also correctly added the gastric and CBE changes from S-035 and S-036 as well as updating the sponsor name and address.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

The proposed draft package insert text submitted on June 21, 2006 with tracked changes is attached.

With the concurrence of the Medical and Statistical reviewers, this labeling may be approved (see their reviews).

___ *{See appended electronic signature page}*_
Ann Staten, Regulatory Health Project Manager
___*{See appended electronic signature page}*_
Dotti Pease, Chief, Project Manager Staff

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

/s/

Ann Staten
6/26/2006 11:38:41 AM
CSO

Dotti Pease
6/26/2006 11:42:26 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449 / S-039

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-449 (Supplemental - Head & Neck)

NAME OF APPLICANT / NDA HOLDER
sanofi-aventis U.S. LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
TAXOTERE®

ACTIVE INGREDIENT(S)	STRENGTH(S)
docetaxel	Single dose vials containing 20 mg (0.5 ml) or 80 mg (2.0 ml) EQ 40 mg Base/ml

DOSAGE FORM
Injection concentrate

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
4,814,470

b. Issue Date of Patent
03/21/1989

c. Expiration Date of Patent
05/14/2010

d. Name of Patent Owner
Aventis Pharma S.A.

Address *(of Patent Owner)*
20 avenue Raymond Aron

City/State
Antony, F-92160 FRANCE

ZIP Code

FAX Number *(if available)*

Telephone Number
331-5571-6892

E-Mail Address *(if available)*
Gerald.Dahling@sanofi-aventis.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Carolyn D. Moon, Esq.

Address *(of agent or representative named in 1.e.)*
1041 Route 202/206

City/State
Bridgewater, NJ

ZIP Code
08807

FAX Number *(if available)*
(908) 231-2840

Telephone Number
(908) 231-2356

E-Mail Address *(if available)*
carolyn.moon@sanofi-aventis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
4.2 Claim Number (*as listed in the patent*) Not applicable	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53, I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	3/24/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Ross J. Oehler, Esq.	
Address 1041 Route 202/206	City/State Bridgewater, NJ
ZIP Code 08807	Telephone Number (908) 231-2972
FAX Number *(if available)* (908) 231-2626	E-Mail Address *(if available)* Ross.Oehler@sanofi-aventis.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtml/fdalist.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S, indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-449 (Supplemental - Head & Neck)

NAME OF APPLICANT / NDA HOLDER
sanofi-aventis U.S. LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
TAXOTERE®

ACTIVE INGREDIENT(S)	STRENGTH(S)
docetaxel	Single dose vials containing 20 mg (0.5 ml) or 80 mg (2.0 ml) EQ 40 mg Base/ml

DOSAGE FORM
Injection concentrate

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,438,072	08/01/1995	11/22/2013

d. Name of Patent Owner
Aventis Pharma S.A.

Address *(of Patent Owner)*
20 avenue Raymond Aron

City/State
Antony, F-92160 FRANCE

ZIP Code

FAX Number *(if available)*

Telephone Number
331-5571-6892

E-Mail Address *(if available)*
Gerald.Dahling@sanofi-aventis.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Carolyn D. Moon, Esq.

Address *(of agent or representative named in 1.e.)*
1041 Route 202/206

City/State
Bridgewater, NJ

ZIP Code
08807

FAX Number *(if available)*
(908) 231-2840

Telephone Number
(908) 231-2356

E-Mail Address *(if available)*
carolyn.moon@sanofi-aventis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
4.2 Claim Number (*as listed in the patent*) Not applicable	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	3/24/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Ross J. Oehler, Esq.	
Address 1041 Route 202/206	City/State Bridgewater, NJ
ZIP Code 08807	Telephone Number (908) 231-2972
FAX Number *(if available)* (908) 231-2626	E-Mail Address *(if available)* Ross.Oehler@sanofi-aventis.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtml/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Patent Information and Certification

Form FDA 3542a for United States Patent No. 5,714,512

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-449 (Supplemental - Head & Neck)

NAME OF APPLICANT / NDA HOLDER
sanofi-aventis U.S. LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
TAXOTERE®

ACTIVE INGREDIENT(S)	STRENGTH(S)
docetaxel	Single dose vials containing 20 mg (0.5 ml) or 80 mg (2.0 ml) EQ 40 mg Base/ml

DOSAGE FORM
Injection concentrate

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

4. GENERAL

a. United States Patent Number 5,714,512	b. Issue Date of Patent 02/03/1998	c. Expiration Date of Patent 07/03/2012
d. Name of Patent Owner Aventis Pharma S.A.	Address *(of Patent Owner)* 20 avenue Raymond Aron	
	City/State Antony, F-92160 FRANCE	
	ZIP Code	FAX Number *(if available)*
	Telephone Number 331-5571-6892	E-Mail Address *(if available)* Gerald.Dahling@sanofi-aventis.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Carolyn D. Moon, Esq.	Address *(of agent or representative named in 1.e.)* 1041 Route 202/206	
	City/State Bridgewater, NJ	
	ZIP Code 08807	FAX Number *(if available)* (908) 231-2840
	Telephone Number (908) 231-2356	E-Mail Address *(if available)* carolyn.moon@sanofi-aventis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
4.2 Claim Number (*as listed in the patent*) Not applicable	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

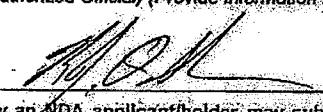
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	3/24/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Ross J. Oehler, Esq.	
Address 1041 Route 202/206	City/State Bridgewater, NJ
ZIP Code 08807	Telephone Number (908) 231-2972
FAX Number *(if available)* (908) 231-2626	E-Mail Address *(if available)* Ross.Oehler@sanofi-aventis.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Patent Information and Certification

Form FDA 3542a for United States Patent No. 5,698,582

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-449 (Supplemental - Head & Neck)

NAME OF APPLICANT / NDA HOLDER
sanofi-aventis U.S. LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
TAXOTERE®

ACTIVE INGREDIENT(S)	STRENGTH(S)
docetaxel	Single dose vials containing 20 mg (0.5 ml) or 80 mg (2.0 ml) EQ 40 mg Base/ml

DOSAGE FORM
Injection concentrate

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,698,582	12/16/1997	07/03/2012

d. Name of Patent Owner
Aventis Pharma S.A.

Address *(of Patent Owner)*
20 avenue Raymond Aron

City/State
Antony, F-92160 FRANCE

ZIP Code	FAX Number *(if available)*

Telephone Number	E-Mail Address *(if available)*
331-5571-6892	Gerald.Dahling@sanofi-aventis.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Carolyn D. Moon, Esq.

Address *(of agent or representative named in 1.e.)*
1041 Route 202/206

City/State
Bridgewater, NJ

ZIP Code	FAX Number *(if available)*
08807	(908) 231-2840

Telephone Number	E-Mail Address *(if available)*
(908) 231-2356	carolyn.moon@sanofi-aventis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
4.2 Claim Number (*as listed in the patent*) Not applicable	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6 Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	3/24/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Ross J. Oehler, Esq.	
Address 1041 Route 202/206	City/State Bridgewater, NJ
ZIP Code 08807	Telephone Number (908) 231-2972
FAX Number *(if available)* (908) 231-2626	E-Mail Address *(if available)* Ross.Oehler@sanofi-aventis.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm//fdahtm.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-449 (Supplemental - Head & Neck)

NAME OF APPLICANT / NDA HOLDER
sanofi-aventis U.S. LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
TAXOTERE®

ACTIVE INGREDIENT(S)	STRENGTH(S)
docetaxel	Single dose vials containing 20 mg (0.5 ml) or 80 mg (2.0 ml) EQ 40 mg Base/ml

DOSAGE FORM
Injection concentrate

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,750,561	05/12/1998	07/03/2012

d. Name of Patent Owner	Address *(of Patent Owner)*	
Aventis Pharma S.A.	20 avenue Raymond Aron	
	City/State Antony, F-92160 FRANCE	
	ZIP Code	FAX Number *(if available)*
	Telephone Number 331-5571-6892	E-Mail Address *(if available)* Gerald.Dahling@sanofi-aventis.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ Carolyn D. Moon, Esq.	1041 Route 202/206	
	City/State Bridgewater, NJ	
	ZIP Code 08807	FAX Number *(if available)* (908) 231-2840
	Telephone Number (908) 231-2356	E-Mail Address *(if available)* carolyn.moon@sanofi-aventis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
4.2 Claim Number (*as listed in the patent*) Not applicable	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

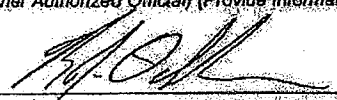
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	3/24/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Ross J. Oehler, Esq.	
Address 1041 Route 202/206	City/State Bridgewater, NJ
ZIP Code 08807	Telephone Number (908) 231-2972
FAX Number *(if available)* (908) 231-2626	E-Mail Address *(if available)* Ross.Oehler@sanofi-aventis.com

EXCLUSIVITY SUMMARY

NDA # 20-449 SUPPL # SE1-039 HFD # 150

Trade Name TAXOTERE Injection Concentrate

Generic Name docetaxel)

Applicant Name sanofi-aventis U.S. Inc.

Approval Date, If Known October 17, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-449 TAXOTERE® (docetaxel) Injection Concentrate, 20 mg and 80mg

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

TAX 323: A Randomized Phase III Multicenter Trial of Neoadjuvant Docetaxel (Taxotere) Plus Clisplatin Plus 5-fluorouracil (5-FU) versus Neoadjuvant Cisplatin Plus 5-fluorouracil in Patients With Locally Advanced inoperable Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

TAX 323: A Randomized Phase III Multicenter Trial of Neoadjuvant Docetaxel (Taxotere) Plus Cisplatin Plus 5-fluorouracil (5-FU) versus Neoadjuvant Cisplatin Plus 5-fluorouracil in Patients With Locally Advanced inoperable Squamous Cell Carcinoma of the Head and Neck (SCCHN)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
YES ☒ Explain: Investigation conducted by the sponsor not under the IND and outside the U.S.	! NO ☐ ! Explain:
Investigation #2	!
YES ☐ Explain:	! NO ☐ ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Frank H. Cross, Jr.
Title: CPMS
Date: October 17, 2006

Name of Office/Division Director signing form: Robert Justice, M.D
Title: Division Director, Division of Drug Oncology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Robert Justice
10/17/2006 05:20:32 PM
The answer to question 1.a) should include SE1.

Statements of Claimed Exclusivity and Associated Certification

This letter serves as an official request for a period of extended marketing exclusivity under 21 CFR Part 314.50(j) and 21 CFR Part 108(b)(5), for Taxotere (docetaxel). As a new supplemental application, containing a report of a new clinical investigation {XRP6976F-323/EORTC 24971 (EFC6042) (TAX 323) that was conducted and sponsored by the applicant under IND 35,555, and that is essential to the approval of this supplemental application, docetaxel is entitled to three (3) years of exclusivity.

To the best of the applicant's knowledge, the clinical investigation (TAX 323) included in this application meets the definition of "new clinical investigation" set forth in 21 CFR Part 314.108(a). In a literature search conducted by the applicant, no published or otherwise publicly available study reports were found for clinical investigations that are relevant to the conditions for which the applicant is seeking approval, *i.e.*, demonstration *via* Phase III pivotal study of significantly increased overall survival resulting from use of docetaxel in combination with cisplatin and 5-fluorouracil in the induction treatment of patients with locally advanced unresectable squamous cell cancer of the head and neck. The applicant was the sponsor named in Form FDA 1571 for IND 35,555, under which study TAX 323 was conducted.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 20-449 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** 039

Stamp Date: April 14, 2006 **Action Date:**

HFD -150 **Trade and generic names/dosage form:**

Applicant: Sanofi-Aventis **Therapeutic Class:** 1

Indication(s) previously approved: Breast , NSCLC, Prostate, gastric

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

Is there a full waiver for this indication (check one)?

- ☐ **X Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **X Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**

- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Ann Staten, RD
Regulatory Project Manager

cc: NDA 20-449/S-039
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Ann Staten
6/6/2006 03:02:11 PM

Pediatric Waiver Request

Sanofi-aventis U.S. LLC believes Taxotere qualifies for a waiver of the pediatric study requirement, and is requesting a waiver of this requirement since there is a very low incidence of head and neck cancer in the pediatric population. The low incidence of head and neck cancer in the pediatric population is supported by the SEER Program data contained in the 2005 Cancer Statistics Report (Jemal, A, et al., Cancer Statistics, 2005. CA Cancer J Clin 2005; 55(1): 10-30). Reference available on request.

Debarment Certification

February 10, 2006

Sanofi-aventis U.S. LLC hereby certifies that it has not used and will not use in any capacity the services of any person debarred pursuant to section 306(a) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 335(a) and (b)] in connection with this application.

Eric Phillips, ScD
Associate Director, Oncology Products
Drug Regulatory Affairs
sanofi-aventis U.S. Inc
On behalf of sanofi-aventis U.S. LLC

ACTION PACKAGE CHECKLIST

Application Information			
A # DA # 20-449	BLA STN# NDA Supplement # S-039	If NDA, Efficacy Supplement Type SE1	
Proprietary Name: Taxotere Established Name: docetaxel Dosage Form: Injection Concentrate, 20 mg and 80 mg		Applicant: Sanofi-aventis U.S. Inc.	
RPM: Cross/Staten		Division: DDOP	Phone # (301) 796-0876

NDAs: NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: - **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	October 17, 2006
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Burst

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☒ Yes If yes, NDA # 20-449 and date exclusivity expires: March 22, 2007; May 19, 2007; August 18, 2007
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	

(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day

period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	April 14, 2006
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	April 14, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	

❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: N/A ☐ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☐ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	October 6, 2006 (MO); October 6, 2006 (TL, October 13, 2006 (DD))
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	October 6, 2006 (MO)
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☐ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	October 16,2006
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	October 16, 2006
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	July 18, 2006
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None September 18, 2006
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☒ None

Comment [I1]:

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Staten, Ann M
From: Staten, Ann M
Sent: Thursday, June 22, 2006 1:15 PM
To: 'Eric.Phillips@sanofi-aventis.com'
Subject: Taxotere info. request

Hi Eric,

Here is another request for Taxotere.

> Please submit a sensitivity analysis of TTP censoring patients on the first day of radiation treatment or disease progression, whichever comes first. TTP for this analysis should be the from randomization date to the date of last tumor assessment.

Please confirm receipt.

Thanks,
Ann

Ann Staten, RD
CDR, United States Public Health Service
Food and Drug Administration
Division of Drug Oncology Products
ph: 301.796.1468
fax: 301.796.9867
new email: ann.staten@fda.hhs.gov

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 20-449 Supplement # S-039 SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Taxotere
Generic Name: docetaxel
Strengths: 20mg and 80 mg concentrate

Applicant: Aventis

Date of Application: 4-14-06
Date of Receipt: 4-17-06
Date clock started after UN:
Date of Filing Meeting: 5-23-06
Filing Date: 6-16-06
Action Goal Date (optional): User Fee Goal Date: 10-17-06

Indication(s) requested: TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

Type of Original NDA: (b)(1) _____ (b)(2) _____
OR
Type of Supplement: (b)(1) ____X____ (b)(2) _____

NOTE:

(3) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(4) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

__X__ NDA is a (b)(1) application OR ___ NDA is a (b)(2) application

Therapeutic Classification: S _____ P ____X_____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) _____
Other (orphan, OTC, etc.) _____

Form 3397 (User Fee Cover Sheet) submitted: X YES NO

User Fee Status: Paid ____X_____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b).*

Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application?

  YES NO

  If yes, explain: NDA 20-449 Taxotere (docetaxel)

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

  YES NO

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
  If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO

  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A YES NO

- Is it an electronic CTD? N/A YES NO

If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, 3 years NO
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: IND 35,555

- End-of-Phase 2 Meeting(s)? Date(s) 7-16-97; 5-25-99; 1-8-01; 4-5-01 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 8-30-00; 1-25-06 NO
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? NA YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES
  NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 5-23-06

BACKGROUND:

ATTENDEES: Ann Farrell, MD; Amna Ibrahim, MD; Qin Ryan, MD; Hun Ke, PhD; Raji Sridhara, PhD

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Qin Ryan, MD
Secondary Medical:	Amna Ibrahim, MD Acting Team Leader
Statistical:	Kun He, PhD
Pharmacology:	N/A
Statistical Pharmacology:	N/A
Chemistry:	Chengyi Liang, PhD
Environmental Assessment (if needed):	Chengyi Liang, PhD
Biopharmaceutical:	N/A
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Lauren Iaconno-Conners
Regulatory Project Management:	Ann Staten
Other Consults:	SEALD; DDMAC; ODAC consultant

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE ___X___ REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known __ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY NA __X____ FILE _____ REFUSE TO FILE _____

STATISTICS FILE ___X____ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE ___N/A___ REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA ___X____ FILE _____ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE __X____ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

___X____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Document no filing issues conveyed to applicant by Day 74 (done).
2. SEALD consult (done)
3. DSI consult (done)
4. ODAC consultant –pending COI clearance

_____
Ann Staten, RD
Regulatory Project Manager, DDOP

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(3) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(4) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(5) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(6) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES NO

   *If "**No**," skip to question 3.*

3. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

4. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES NO

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

   YES NO

   If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

6. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(c) Is the approved drug product cited as the listed drug? YES NO

7. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

8. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

9. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO

10. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

11. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

12. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

13. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES NO

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND # _____ NO

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES NO

3. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

   YES NO

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

/s/

Ann Staten
6/20/2006 11:46:36 AM
CSO

Staten, Ann M
From: Staten, Ann M
Sent: Thursday, June 08, 2006 8:37 AM
To: 'Eric.Phillips@sanofi-aventis.com'
Subject: Taxotere s-039 Gastric

Dear Eric,

We have the following information request:

1. Please provide TAX 322 study report and an analysis of the reason the results for TAX322 were negative, where as those for TAX 323 and TAX 324 are positive.

2. Please provide updates for any OS updates after those for the cut off date of Sep 21, 2003 for study TAX 323.

Thanks,
Ann

Ann Staten, RD
CDR, United States Public Health Service
Food and Drug Administration
Division of Drug Oncology Products
ph: 301.796.1468
fax: 301.796.9867
new email: ann.staten@fda.hhs.gov

Staten, Ann M

From: Staten, Ann M
Sent: Thursday, June 08, 2006 1:41 PM
To: 'Eric.Phillips@sanofi-aventis.com'
Subject: information request

Dear Eric,

One more request:

Please submit the original protocol and all amendment of study TAX324.

Thanks,
Ann

Ann Staten, RD
CDR, United States Public Health Service
Food and Drug Administration
Division of Drug Oncology Products
ph: 301.796.1468
fax: 301.796.9867
new email: ann.staten@fda.hhs.gov

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: Ted Phillips, MD	**From:** Ann Staten
Fax: 415-353-8679	**Fax:** (301) 796-9845
Phone: 415-353-8900	**Phone:** (301) 796-1468
Pages, including cover sheet: 1	**Date: 6-1-05**

Re: Request to serve as a consultant to the FDA

Dr. Phillips,

I'm a project manager in the Division of Drug Oncology Products at the FDA. Members of the Division would like to consult with you regarding an NDA under FDA review for SCCHN. Your participation would involve a brief telephone conference with members of the FDA review team sometime in the next few months.

Please contact me as soon as possible at (301) 796-1468, or via e-mail at ann.staten@fda.hhs.gov, and let me know if you are interested in helping us on this project. If you decide to serve as our outside expert, our Advisors & Consultants Staff will contact you regarding conflict of interest (COI) screening. Once COI screening is completed, I will contact you to inform you of your clearance status and schedule the teleconference.

Regards,

Ann Staten
Project Manager