

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-449/S-028

Medical Review(s)

Division Director's Memorandum

Date: May 18, 2004
NDA: 20-449/s-028
Sponsor: Aventis Pharmaceuticals, Inc
Proprietary Name: Taxotere® (docetaxel) for Injection Concentrate

Regulatory History

The original IND 35,555 was submitted on October 2, 1990.

On May 12, 1999, Rhone-Poulenc Rorer (RPR) had an EoP2 meeting with the Agency to receive guidance regarding the proposed clinical development plan for Taxotere in hormone refractory prostate cancer. RPR later merged with Hoeschst Marion Roussel and renamed themselves Aventis Pharmaceuticals, Inc.

After receiving a meeting request from Aventis, the Division had an internal pre-meeting on September 23, 2003 to discuss the format and content of the sNDA submission. Subsequently, the Division sent the preliminary responses to Aventis' questions which resulted in Aventis canceling the industry meeting as no further clarification was necessary.

On January 26, 2004, Aventis submitted the current sNDA.

The PDUFA goal date for this priority review is July 27, 2004.

Proposed Indication

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

Available Therapies

The only other approval for a chemotherapeutic regimen in this setting is mitoxantrone + prednisone, with efficacy based on palliation of pain.

Clinical Review (see review by Dr. Dagher)

The basis of approval is a large randomized study demonstrating a survival advantage, a first in this setting.

The components of the risk/benefit assessment forming the basis for this action are outlined below.

Safety and efficacy were demonstrated in TAX327, a randomized, multi-center global clinical trial designed to evaluate chemotherapy with Taxotere and prednisone in the treatment of men with metastatic, hormone-refractory prostate cancer. One thousand and six patients were randomized to one of three treatment arms as follows: (1) mitoxantrone + prednisone (control arm), (2) weekly Taxotere + prednisone, or (3) Taxotere once every three weeks + prednisone.

The primary efficacy endpoint was survival. The treatment arm of Taxotere every three weeks + prednisone demonstrated a survival advantage over mitoxantrone + prednisone control, providing a median survival advantage of approximately 2.5 months (18.9 vs. 16.5 months, $p = 0.0094$). The weekly Taxotere + prednisone arm did not demonstrate an advantage over control.

Most commonly occurring adverse events included anemia, neutropenia, infection, nausea, vomiting, anorexia, and fatigue. Adverse events occurring more frequently with Taxotere every 3 weeks + prednisone compared to mitoxantrone + prednisone included allergic reactions, fluid retention (mainly weight gain and peripheral edema), sensory neuropathy, alopecia, nail changes, diarrhea, and stomatitis.

Clinical Pharmacology & Biopharmaceutic Review (see Dr. Abraham's review)

The pharmacokinetics of docetaxel were assessed in a subset of patients in Study TAX 327 (total $n=40$ patients) on Day 1 (docetaxel alone treatment) and on Day 22 (docetaxel+prednisone treatment). Plasma concentration/time data were analyzed using a population pharmacokinetics (NONMEM) analysis to determine the effect of prednisone on docetaxel total body clearance. The results of the NONMEM analysis showed that prednisone does not affect docetaxel total body clearance when both drugs are administered in combination.

Chemistry, Manufacturing and Controls (CMC) Review (see Dr. Y. Hsieh's review)

The CMC team approved the applicant's request for categorical exclusion for an Environmental Assessment.

Nonclinical Review

There was no review of this application by the Pharmacology/Toxicology team.

Data Integrity Issues

Originally, the Division requested an inspection of two European sites. However, given the large number of patients enrolled, that it is an international trial, and the objective nature of the primary endpoint (survival), it was unlikely that the inspections would have altered the interpretation of the data. As such, the Division canceled the inspection request.

Tradename and Labeling Consultation

As this is an approved drug, the Division did not send a consult to the Division of Medication Errors and Tech Support (DMETS) for either the tradename or the labeling. However, a safety evaluator from the Division of Drug Risk and Evaluation (DDRE) did attend Division labeling meetings and no safety issues were identified.

Pediatric Considerations

This disease does not exist in children so the Division granted a full waiver to the applicant regarding conduct of pediatric studies.

Conclusions and Recommendations: Regular Approval

Survival benefit was demonstrated in a single trial. The Division has accepted survival as evidence of clinical benefit in similar disease settings.

Richard Pazdur, MD
Director, Division of Oncology Drug Products

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/s/

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Clinical Review Cover Sheet

Application #	20-449/S-028
Drug Name	Taxotere[®] (docetaxel)
Medical Reviewer and Team Leader	Ramzi Dagher, M.D.
Statistical Reviewer Statistical Team Leader	Ning Li, Ph.D. Raji Sridhara, Ph.D.
Documents reviewed	SE2-028 Hard Copy and Electronic Elements

CLINICAL REVIEW

Table of Contents

Executive Summary	1
I. Recommendations	1
A. Recommendation on Approvability.....	1
B. Recommendation on Phase 4 Studies and/or Risk Management Steps.....	2
II. Summary of Clinical Findings	2
A. Brief Overview of Clinical Program.....	2
B. Efficacy.....	3
C. Safety.....	3
D. Dosing.....	6
E. Special Populations.....	6
Clinical Review	9
I. Introduction and Background	9
A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups.....	9
B. State of Armamentarium for Indication(s).....	11
C. Important Milestones in Product Development.....	13
D. Other Relevant Information.....	13
E. Important Issues with Pharmacologically Related Agents.....	14
II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews	14
A. Clinical Pharmacology and Biopharmaceutics.....	
B. Statistics.....	
C. Chemistry.....	
D. Animal Pharmacology and Toxicology.....	

CLINICAL REVIEW

III.	Human Pharmacokinetics and Pharmacodynamics.....	15
A.	Pharmacokinetics	15
IV.	Description of Clinical Data and Sources	16
A.	Overall Data.....	16
B.	Tables Listing the Clinical Trials.....	16
C.	Postmarketing Experience	17
D.	Literature Review.....	17
V.	Clinical Review Methods.....	18
A.	How the Review was Conducted	18
B.	Overview of Materials Consulted in Review.....	18
C.	Overview of Methods Used to Evaluate Data Quality and Integrity	18
D.	Were Trials Conducted in Accordance with Accepted Ethical Standards.	19
E.	Evaluation of Financial Disclosure	19
VI.	Integrated Review of Efficacy.....	20
A.	Brief Statement of Conclusions	20
B.	General Approach to Review of the Efficacy of the Drug.....	20
C.	Detailed Review of Trials by Indication	20
D.	Efficacy Conclusions	55
VII.	Integrated Review of Safety	55
A.	Brief Statement of Conclusions	55
B.	Description of Patient Exposure	56
C.	Methods and Specific Findings of Safety Review	52
D.	Adequacy of Safety Testing.....	56

CLINICAL REVIEW

E.	Summary of Critical Safety Findings and Limitations of Data	60
VIII.	Dosing, Regimen, and Administration Issues.....	61
IX.	Use in Special Populations	61
A.	Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation.....	61
B.	Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy	61
C.	Evaluation of Pediatric Program.....	62
X.	Conclusions and Recommendations.....	62
A.	Conclusions.....	62
B.	Recommendations.....	63
	Appendix : Survival Curves.....	64

Appears This Way
On Original

Table of Tables

1. Cumulative Dose and Dose Intensity in TAX327.....	4
2. Clinical Trials Submitted to sNDA.....	17
3. Distribution of Participating Centers by Region.....	21
4. Protocol Milestones.....	22
5. Equivalent Glucocorticoid Doses.....	26
6. Dose Levels for dose Reduction.....	26
7. Dose Reduction Due to Neutropenia and Associated Complications.....	27
8. Dose Reduction and Delay Based on ANC on day 1 of infusion for Arm A and and Arm B.....	27
9. Recommended Treatments for Anaphylactic and Hypersensitivity Reactions... 	28
10. Clinical and Laboratory Assessments.....	33
11. Overall Tumor Response.....	38
12. Sponsor's List of Major Violations of Inclusion/Exclusion Criteria.....	42
13. Sponsor List of Major Deviations of Protocol Conduct.....	43
14. Baseline Patient Characteristics.....	44
15. Histologic Subtype and Staging.....	46
16. Baseline PSA in the ITT Population.....	47
17. Prior Anti-Cancer Therapy in the ITT Population.....	47
18. Sponsor Designation of Significance Level for Multiple Comparisons.....	48
19. Stratification Factors at Randomization.....	49
20. Sponsor's Assessment of Overall survival, ITT Population.....	49

CLINICAL REVIEW

21. Sponsor's Treatment Group Comparisons – SLR.....	50
22. Sponsor's Results for PSA Response Rate.....	51
23. Sponsor's Analysis of PSA Response Duration.....	52
24. Sponsor's Results for Pain Response Rate.....	53
25. Sponsor's Analysis of Pain Response Duration.....	54
26. Sponsor Assessment of Cumulative Dose and Dose Intensity of Study Chemotherapy for Docetaxel and Mitoxantrone.....	56
27. Clinically Important Treatment Emergent Adverse Events Regardless of Relationship to Study Drug.....	57
28. Reviewer's Assessment of Fluid Retention.....	59
29. Exposure on Trials and Worldwide Estimate for Recent Periods.....	60

Appears This Way
On Original

Clinical Review for NDA 20-449/S-028

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA recommends approval of docetaxel (taxotere) in combination with prednisone for the treatment of patients with metastatic hormone-refractory prostate cancer.

The assessment of benefit in this application is based on the clinical benefit endpoint of overall survival. In a phase 3 randomized open-label trial, there was statistical evidence for superiority of docetaxel + prednisone (every 3-week schedule of docetaxel) relative to the active control regimen of mitoxantrone + prednisone for the endpoint of survival. The efficacy results for this endpoint are summarized in section II of this document.

With regard to the risks associated with docetaxel therapy, the FDA's previous review of the safety databases submitted in prior NDA's that resulted in the approval of docetaxel for the treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy, for use in locally advanced or metastatic NSCLC after failure of platinum based therapy, and approval of docetaxel in combination with cisplatin in the first-line NSCLC setting, has identified a number of safety concerns. The review of the new database of patients with metastatic HRPC has allowed identification of the following issues, which are common to those noted in prior reviews. Furthermore, no new toxicities have been identified in this treatment setting :

The most commonly occurring TEAEs (25% or greater) on either arm (q3week docetaxel or mitoxantrone) included anemia, neutropenia, infection, sensory neuropathy, alopecia, nail changes, diarrhea, and fatigue. These occurred more frequently on the docetaxel arm than the mitoxantrone arm, and a 10% or greater difference between arms was noted for alopecia, infection, fluid retention, sensory neuropathy, nail changes, and diarrhea. All grade neutropenia was slightly more frequently observed in the mitoxantrone arm.

TEAE's that occurred in less than 25% of patients included thrombocytopenia, febrile neutropenia, epistaxis, fluid retention, motor neuropathy, rash, arthralgia, tearing, myalgia, stomatitis, taste disturbance, vomiting, anorexia, cough, dyspnea, and left ventricular dysfunction.

CLINICAL REVIEW

Executive Summary Section

Grade 3 / 4 neutropenia, anemia, infection, sensory neuropathy, motor neuropathy, nausea, diarrhea, anorexia, and dyspnea occurred more frequently on the docetaxel q3week arm than the mitoxantrone control.

Grade 3 / 4 thrombocytopenia, cardiac left ventricular dysfunction, and arthralgia occurred more frequently on the mitoxantrone + prednisone control than the docetaxel q3week arm.

It is the judgement of the FDA clinical and statistical review team that the potential benefits outweigh the risks associated with q3week docetaxel therapy in combination with prednisone in patients with metastatic HRPC.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The previously outlined phase IV commitments which are yet to be fulfilled will be reiterated.

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II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions.

The outcome for HRPC patients remains poor despite multimodality approaches utilizing surgery and chemotherapy with or without radiation. In this NDA, the first randomized study to show a survival benefit in men with metastatic HRPC has been submitted.

Aventis has submitted data for a docetaxel/prednisone combination regimen for treatment of metastatic HRPC from an open-label, randomized phase 3 study of docetaxel either weekly or every 3 weeks used in combination with prednisone. These experimental arms were compared

CLINICAL REVIEW

Executive Summary Section

with mitoxantrone + prednisone, a regimen previously approved based on findings of pain palliation. A total of 1006 patients were enrolled to the study. Exposure of cancer patients to docetaxel also includes approximately 2000 - 3000 patients yearly enrolled to clinical trials, and commercial use estimated at [] patients / year worldwide.

B. Efficacy

The DODP is recommending approval of this sNDA based on the clinical benefit endpoint of overall survival, which was the primary endpoint of TAX327. Kaplan-Meier median estimates of overall survival were 18.92 months, 17.38 months, and 16.49 months for the docetaxel + prednisone q3 week, docetaxel + prednisone weekly, and mitoxantrone + prednisone arms respectively in this global trial that enrolled 1006 patients. There was statistical evidence for superiority in survival of q3week docetaxel + prednisone over mitoxantrone + prednisone ($p=0.0094$). No survival advantage was demonstrated for qweek docetaxel + prednisone over mitoxantrone + prednisone ($p=0.362$).

Secondary endpoints of tumor response rate and duration, pain response rate and duration, PSA response rate and duration, as well as PSA, pain, and tumor progression free survival. These analyses are considered exploratory due to the absence of a prespecified plan for dealing with multiplicity which should include a plan for prioritization. For many of these analyses, less than 50% of patients were eligible for evaluation. Finally, for time to event endpoints such as progression-free survival, heavy censoring makes it difficult to interpret the findings. Due to these considerations, medical and statistical reviewers recommend that no comparative efficacy claims are made.

C. Safety

1. Adequacy of safety testing

With respect to specific dosing, the following table summarizes cumulative dose and weekly dose intensity of each drug across the three treatment arms. Docetaxel dose intensity was slightly lower in the weekly docetaxel regimen, but these small differences are not likely to explain the differences found in efficacy outcomes between the two docetaxel regimens.

CLINICAL REVIEW

Executive Summary Section

Table 1 : Cumulative Dose and Dose Intensity

Treatment Group	TXT q3w N = 332	TXT qw N = 330	MTZ q3w N = 335
Cumulative Dose (mg/m²)			
Median	651.3	602.7	60.1
Min	38.3	30.8	11.6
Max	826.4	903.1	129.2
Actual Dose Intensity (mg/m²/week)			
Median	24.6	24.0	3.9
Min	12.8	15.4	2.6
Max	26.8	28.7	4.4
Relative Dose Intensity (% of planned)			
Median	0.98	0.96	0.99
Min	0.51	0.62	0.66
Max	1.07	1.15	1.10

The incidence of deaths within 30 days of last treatment infusion was equally distributed across the three arms: 3.3% for q3week docetaxel + prednisone, 3.3% for qweek docetaxel + prednisone, and 2.7% for mitoxantrone + prednisone. Most of these were attributed to malignant disease or 'other' causes. Of the deaths occurring within 30 days of last infusion, one on the q3week docetaxel arm and 2 on the mitoxantrone arm were attributed to drug toxicity.

The majority of deaths occurred more than 30 days after last infusion. These occurred more frequently on the mitoxantrone arm compared to q3week docetaxel (57% versus 46.1%).

CLINICAL REVIEW

Executive Summary Section

2. Serious side effects

Although more than 90% of patients enrolled on TAX327 had at least one TEAE reported, serious adverse events were less commonly reported in individual patients. Individual serious or life-threatening adverse events included infection, anemia, neutropenia, neuropathy, nausea, vomiting, diarrhea, and cardiac left ventricular dysfunction. These are discussed as a comparison between the q3week docetaxel (TXTq3w) arm and the mitoxantrone arm (MTZ). Although allergic reactions (all grade) did occur more commonly on the TXTq3w arm, grade 3 or 4 events were observed in less than 1% of patients.

Infection : Grade 3 or 4 infections occurred in 6% versus 4% of patients in the TXTq3w and MTZ arms respectively.

Anemia: Grade 3 / 4 anemia occurred in 5% versus 2% of patients in the TXTq3w and MTZ arms respectively.

Neutropenia : This was the most commonly observed grade 3 / 4 cytopenia, occurring in 32% of patients in the TXTq3w arm and 22% of patients in the MTZ arm.

Neuropathy : Although sensory and motor neuropathies of any grade occurred more frequently with TXTq3w compared to MTZ, grade 3 or 4 events were observed in less than 2% of patients on either arm.

Nausea: Grade 3 / 4 nausea occurred in less than 3% of patients in either arm.

Vomiting : Grade 3 / 4 vomiting occurred in less than 3% of patients in either arm.

Diarrhea : Grade 3 or 4 diarrhea occurred slightly more commonly with TXTq3w, but it occurred in less than 3% of patients on TXTq3w

Fluid Retention : Peripheral edema and weight gain were the major signs of fluid retention. However, severe or life-threatening fluid retention events were uncommon, occurring in approximately 2% of patients across the three treatment arms.

Cardiac left ventricular dysfunction : All grade events occurred much more frequently on the MTZ arm (22.1% versus 9.6%), consistent with known cardiotoxicity of mitoxantrone. Grade 3 or 4 events occurred in 1.2% of patients on MTZ and 0.3% on TXTq3w

Deaths : See section II.C.1 above.

3. Drug-drug interactions

CLINICAL REVIEW

Executive Summary Section

The pharmacokinetics of docetaxel were assessed in a subset of patients in Study TAX 327 (total n=40 patients) on Day 1 (docetaxel alone treatment) and on Day 22 (docetaxel+prednisone combination treatment). Plasma concentration/time data were analyzed using the previously developed population pharmacokinetic (NONMEM) model to determine the effect of prednisone on docetaxel total body clearance. The results of the population pharmacokinetic analysis showed that prednisone does not affect docetaxel total body clearance when both drugs are administered in combination.

4. Warnings

No other warnings are recommended in addition to those currently outlined in the package insert.

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D. Dosing

The recommended dose of docetaxel when administered in combination with prednisone for the treatment of metastatic HRPC is 75 mg/m² administered intravenously over 1 hour every 21 days plus prednisone 5 mg twice a day continuously.

E. Special Populations

1. Pediatrics

Although the sponsor has not conducted any clinical trials of docetaxel in the pediatric population, there are two phase I trials of docetaxel in children with refractory solid tumors reported in the medical literature. These were reviewed in the sNDA for docetaxel for the treatment of newly diagnosed advanced / metastatic NSCLC.

CLINICAL REVIEW

Executive Summary Section

2. Elderly

In TAX327, Of the 333 patients treated on the q3week docetaxel arm, 209 were 65 years old or older and 68 patients were 75 years of age or older. The following TEAE's occurred at rates $\geq 10\%$ higher in patients 65 or older compared to younger patients: anemia (70.7% versus 59.3%), infection (37% versus 24.2%) nail changes (33.7% versus 22.6%), anorexia (20.7% versus 9.7%) and weight loss (15.4% versus 4.8%) respectively.

3. Renal or Hepatic Impairment

Two phase I studies of docetaxel in patients with cancer and varying degrees of liver dysfunction are ongoing.

4. Gender

All patients enrolled were men with HRPC.

5. Ethnicity

The majority of patients enrolled onto TAX327 were caucasian, consisting of 93% of the population in each treatment group. Black, hispanic, asian or other groups consisted of 7% of the population in each treatment arm. No definitive conclusions can be drawn regarding safety or efficacy differences among these groups due to the small number of non-caucasian patients in the study population.

6. Pregnancy

Docetaxel 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/m² basis), administered during the period of organogenesis, have shown that docetaxel 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 docetaxel. If docetaxel 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 docetaxel.

CLINICAL REVIEW

Executive Summary Section

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CLINICAL REVIEW

Executive Summary Section

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: docetaxel

Proprietary Name: Taxotere®

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

Drug Class: Antineoplastic

Indication:

Current:

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

Non-Small Cell Lung Cancer:

TAXOTERE 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.

Proposed: *Addition of the prostate indication as follows*

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

Dosage and Administration

Current Label:

Breast Cancer: The recommended dose of TAXOTERE is 60-100 mg/m² administered intravenously over 1 hour every 3 weeks.

CLINICAL REVIEW

Executive Summary Section

Non-Small Cell Lung Cancer: For treatment after failure of prior platinum-based chemotherapy, TAXOTERE was evaluated as monotherapy, and the recommended dose is 75 mg/m² administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m² in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials (see **BOXED WARNING**, **WARNINGS** and **CLINICAL STUDIES** sections).

Premedication Regimen: All patients should be premedicated with oral corticosteroids 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).

Dosage Adjustments During Treatment

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

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

Patients who are dosed initially at 75 mg/m² and who experience either febrile neutropenia, neutrophils < 500 cells/mm³ for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during TAXOTERE treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m². Patients who develop ≥ grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Combination Therapy with TAXOTERE for Chemotherapy-Naïve NSCLC

For patients who are dose initially at TAXOTERE 75 mg/m² in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is < 25,000 cells/mm³, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the TAXOTERE dosage in subsequent cycles should be reduced to 65 mg/m². In patients who require a further dose reduction, a dose of 50 mg/m² is recommended. For cisplatin dose adjustments, see manufacturer's prescribing information.

CLINICAL REVIEW

Executive Summary Section

Proposed : Addition of the following

For prostate cancer, the recommended dose of TAXOTERE is 75 mg/m² every three weeks as a 1-hour infusion. Prednisone 5 mg orally twice daily is administered continuously.

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

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B. State of Armamentarium for Indication(s)

Prostate cancer is the most common malignancy in men in the United States. It is estimated that over 220,000 men were diagnosed with the disease in 2003 in the US, with over 28,000 deaths from the disease in that year alone. The risk of developing prostate cancer begins to increase at age 50 years in white men and at age 40 years in black men and those who have first-degree relatives with prostate cancer. (1)

The grading system adopted by Gleason from data accumulated by the Veterans Administration Cooperative Urologic Research Group appears to provide the best prognostic information in addition to clinical stage. (2) The most widely used staging system is the TNM system. In this system, T1 and T2 tumors designate localized disease, whereas T3 and T4 tumors have local extension. N1 designates positive regional nodes and M1 designates distant metastases. (3)

Adenocarcinomas of the prostate may spread locally through direct extension into periprostatic fat or via the ejaculatory ducts into seminal vesicles; lymphatically to regional lymph nodes; and hematogenously to bone. The most common sites of bony metastases are the lumbosacral spine and the axial skeleton. Rare sites of metastatic spread include the liver and lung. (1)

First line treatment of advanced disease that has not responded to local treatment or that cannot be treated with surgery or radiation begins with surgical or medical castration, which may involve bilateral orchiectomy, LHRH agonists, antiandrogen blockade, combined androgen blockade, and/or DES. Second-line hormonal therapy strategies may include addition/subtraction of an antiandrogen, aminoglutethimide and hydrocortisone, or ketoconazole.

CLINICAL REVIEW

Executive Summary Section

After development of anti-androgen insensitivity, metastatic prostate cancer is an essentially incurable disease, with median survival of 9-12 months. In this setting, a number of chemotherapy regimens have been utilized.

Mitoxantrone was approved in the United States for use in combination with corticosteroids as initial chemotherapy for hormone refractory prostate cancer based on findings from a randomized multicenter trial (CCI-NOV22) comparing mitoxantrone plus prednisone 5 mg twice a day to prednisone alone. A total of 161 patients were randomized to this study which had palliative response as a primary endpoint. The approved mitoxantrone dose is 12 to 14 mg per m²

Two other agents approved for the treatment of advanced prostate cancer are estramustine phosphate and zoledronate. None of the studies conducted with these drugs suggests any effect on survival:

<u>Drug</u>	<u>Approval Date</u>	<u>Class</u>	<u>Endpoint</u>
Estramustine Phosphate	1974	estrogen/ alkylator	endocrine effects
Zoledronate	2002	bisphosphonate	prolongation in Time to SRE

Docetaxel has been evaluated in single arm studies in HRPC, either as a single dose every 3 weeks or in a weekly dosing regimen. PSA declines and responses in those patients with bidimensionally measurable lesions were noted. (4, 5) Some of these studies were also suggestive of a reduced analgesic requirement or reduced bone pain. (6, 7, 8)

With respect to randomized studies, S9916, a phase 3 study coordinated by the Southwest Oncology Group (SWOG) compares the combination of 3-weekly docetaxel 60 mg/m² plus estramustine versus 3-weekly mitoxantrone 12 mg/m² plus prednisone. This study is designed to evaluate overall survival and progression free survival in patients with HRPC, and has enrolled 770 patients. Preliminary results of this study will be presented at ASCO in June, 2004. Although of interest for the treatment of HRPC, this study design does not isolate a docetaxel treatment effect.

The randomized study TAX327 submitted with this NDA supplement was designed to evaluate two schedules of docetaxel administration with prednisone to a control arm of mitoxantrone with prednisone with overall survival as a primary endpoint. The every three week docetaxel schedule is used in a number of settings such as breast cancer and NSCLC, and has been evaluated in single arm studies of docetaxel in HRPC as discussed above. The weekly schedule has also been evaluated in a non-randomized setting.

CLINICAL REVIEW

Clinical Review Section

C. Important Milestones in Product Development

- 05/14/96 Approved for use in patients with locally advanced or metastatic breast cancer who have progressed or relapsed during anthracycline-based therapy (original NDA 20449).
- 6/30/99 TAX 308 (docetaxel versus best supportive care) submitted as part of S-012 for the first-line treatment of NSCLC. The supplemental application was withdrawn on 4/26/00.
- 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).
- 1/27/04 NDA supplement submitted for use of docetaxel q 3weeks in combination with prednisone in the treatment of metastatic hormone-refractory prostate cancer (S-028).
- March, 2004 Sponsor presentation to DODP

D. Other Relevant Information

CLINICAL REVIEW

Clinical Review Section

Docetaxel is approved in 103 countries around the world including the United States. In the United States, the indications currently include the treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy, locally advanced or metastatic NSCLC after failure of prior platinum-based therapy, and first -line therapy for advanced / metastatic NSCLC. Outside the United States, indications include first and second line breast cancer, NSCLC, squamous cell carcinoma of the head and neck, and ovarian cancer.

E. Important Issues with Pharmacologically Related Agents

No issues exist.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Clinical Pharmacology and Biopharmaceutics

Clinical pharmacology/biopharmaceutics reviewers agree with the sponsor's proposal to add the following statement to the CLINICAL PHARMACOLOGY / HUMAN PHARMACOKINETICS section of the package insert (This is a slight modification to the sponsor's proposal since only 40 of 42 patients had PK data submitted):

L

J²

B. Statistics

This was a joint medical / statistics review. (See executive summary and efficacy sections).

C. Chemistry

Chemistry reviewers have determined that this efficacy supplement qualifies

CLINICAL REVIEW

Clinical Review Section

for a categorical exclusion from the requirement to prepare an Environmental Assessment.

D. Animal Pharmacology and Toxicology

No animal data were submitted.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

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.

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m² in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70-115 mg/m² with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α , β , and γ phases of 4 min, 36 min, and 11.1 hr, respectively. 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/m² and 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of 10-90 mg/m² was similar to that of European/American populations dosed at 100 mg/m², suggesting no significant difference in the elimination of docetaxel in the two populations.

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

CLINICAL REVIEW

Clinical Review Section

A population pharmacokinetic analysis was carried out after docetaxel treatment of 535 patients dosed at 100 mg/m². Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel 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).

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.

In the randomized study TAX327, a subgroup of 42 patients had PK sampling. This study showed that docetaxel pharmacokinetics are not affected by dosing with prednisone. (Please see Biopharmaceutics review for more information).

IV. Description of Clinical Data and Sources

A. Overall Data

NDA 20449/S-028 contains the primary data from TAX327 as listed in section IV.B. below. This trial was conducted by the sponsor. A clinical pharmacology substudy consisted of PK sampling from 42 of the 1006 patients enrolled on TAX327.

B. Table Listing the Clinical Trial

Table 1 lists the clinical trial submitted by the sponsor and reviewed by medical, statistical, and clinical pharmacology reviewers. As a

CLINICAL REVIEW

Clinical Review Section

secondary objective, pharmacologic sampling was evaluated in a subgroup of patients (N = 42) treated on TAX327.

Table 2 : Clinical Trials Submitted to sNDA

Protocol	Design	Population, N	Endpoints
TAX327	Randomized 1:1:1 Multicenter	HRPC N = 1006	Efficacy, Safety, PK

C. Postmarketing Experience

As exposure to docetaxel was increasing over time and new safety information was becoming available, the safety related sections of the docetaxel company core safety information and the US Package Insert have been updated. As discussed in the safety review, several thousand patients are exposed to docetaxel on clinical trials each year, with estimated commercial use by [] patients yearly.

D. Literature Review

The sponsor conducted an extensive literature search. In addition, the reviewer has used these references to support information provided in the state of the armamentarium.

1. Pienta KJ, Sandler H, Javidan J et al. Chapter 17 : Prostate Cancer. In Cancer Management: A Multidisciplinary Approach. Editors Pazdur R, Coia L, Hoskins WJ, Wagman LD. 7th Edition. The Oncology Group. NY, NY.
2. Albertsen PC, Hanley JA, gleason DF et al. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 280:975-980, 1998.
3. Greene FI, Page DL, Fleming ID et al. (eds) AJCC Cancer Staging Manual, 6th edition. New York, Springer-Verlag, 2002.

[Related Articles, Links](#)

4. Picus J and Schultz M. Docetaxel as monotherapy in the treatment of hormone-refractory prostate cancer: preliminary results. Seminars in Oncology 26(5 Suppl):14-18, 1999.

CLINICAL REVIEW

Clinical Review Section

5. Friedland D, Cohen J, Miller R Jr et. al. A Phase II Trial of Docetaxel in hormone-refractory prostate cancer: correlation of anti-tumor effect to phosphorylation of Bcl-2. *Seminars in Oncology* 26 (Suppl 5):19-23, 1999.
6. Beer TM, Pierce WC, Lowe BA et. al. Phase II study of weekly Taxotere in symptomatic androgen-independent prostate cancer. *Annals of Oncology* 12:1273-1279, 2001
7. Petrioli R, Pozzessere D, Messinese S et. al. Weekly low-dose Taxotere in advanced hormone-refractory prostate cancer subjects previously exposed to chemotherapy. *Oncology* 64:300-305, 2003.
8. Berry W, Dakhil S, gregorich MA, et. al. Phase II trial of single-agent weekly Taxotere in hormone-refractory, symptomatic, metastatic carcinoma of the prostate. *Seminars in Oncology* 28 (Suppl 15):8-15, 2001.

V. Clinical Review Methods

A. How the Review was Conducted

The efficacy review is based primarily on data from TAX327, the open-label, three-arm randomized phase III trial of docetaxel weekly or q 3 weeks in combination with prednisone each compared to mitoxantrone plus prednisone in patients with metastatic hormone-refractory prostate cancer.

B. Overview of Materials Consulted in Review

The following materials were reviewed:

- The regulatory history of the application
- Electronic submission of the sNDA
- Relevant published literature
- Sponsor's presentation slides of 3/13/02
- Relevant submissions in response to medical officer's questions

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A number of methods were utilized in order to evaluate the quality and integrity of the data from TAX327 as outlined below :

CLINICAL REVIEW

Clinical Review Section

1. The reviewers have conducted independent efficacy and safety analyses based on the primary data submitted in SAS transport files after conversion to JUMP format. Any discrepancies between the reviewer's results and those of the sponsor are discussed in relevant sections of the review.
2. Copies of the case report forms (electronic or hard copy) were reviewed in select patients.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Consent was required prior to enrollment.

E. Evaluation of Financial Disclosure

Certification of financial disclosure was provided by Cheryl Anderson, Senior Director and Oncology Therapeutic Area Head, Aventis, North America. Documentation of financial disclosure was provided for most investigators, the majority of whom indicated no financial interest.

Three investigators indicated a financial interest in the outcome. Dr. [redacted] disclosed payment of [redacted] Dr. [redacted] disclosed [redacted] Dr. [redacted] subinvestigator [redacted] disclosed [redacted]

Twenty-six investigators did not have financial disclosure information available. However, none of these investigators enrolled any patients to the pivotal study. An additional five subinvestigators did not provide financial disclosure information despite multiple attempts. Three were from the US, one from Germany, and one from Italy.

Due to the large number of patients enrolled in over 100 centers worldwide, the randomization process employed, and the objective nature of the primary endpoint of survival, it is not likely that these disclosures cast any doubt on the outcome of the pivotal study TAX327.

VI. Integrated Review of Efficacy**A. Brief Statement of Conclusions**

The results of an international, open-label randomized phase 3 trial of combination chemotherapy in patients with metastatic hormone refractory prostate cancer (TAX327) were submitted. Patients were randomized to docetaxel weekly + prednisone, docetaxel q 3 weeks + prednisone, or an active control of mitoxantrone + prednisone.

The primary endpoint was overall survival. According to the sponsor's primary analysis, the docetaxel q 3 week schedule plus prednisone demonstrated a statistically significant survival advantage over mitoxantrone plus prednisone, with median survivals of 18.9 versus 16.5 months ($p = 0.0094$). The docetaxel q week plus prednisone arm did not demonstrate an overall survival advantage over the control arm ($p = 0.36$). The FDA's analysis agreed with these findings.

Secondary endpoints included pain response and duration, PSA response and duration, tumor response and duration, tumor progression-free survival, pain progression-free survival, and PSA progression-free survival. For pain response, PSA response, and tumor response durations there was no difference between the docetaxel q 3 week arm and control. Furthermore, there was no prespecified plan for adjustment for multiplicity / ordering of these secondary endpoints. In addition, less than 50% of the ITT population were eligible for response assessments. Finally, for time-to event endpoints such as response duration and progression free survival, more than 50% of patients were censored, mainly due to further therapy or inability to assess the patient. Due to these considerations, we do not recommend allowing for any comparative claims for these endpoints in the labeling.

B. General Approach to Review of the Efficacy of the Drug

The efficacy database consists mainly of an open-label, randomized phase 3 trial of weekly docetaxel plus prednisone versus docetaxel q 3 weeks plus prednisone versus mitoxantrone plus prednisone in patients with metastatic HRPC.

C. Detailed Review of Trials by Indication

The efficacy review is based primarily on one multicenter trial of docetaxel titled:

A Multicenter Phase 3 Randomized Trial Comparing Docetaxel Administered Either Weekly or Every Three Weeks in Combination with

CLINICAL REVIEW

Clinical Review Section

Prednisone versus Mitoxantrone in Combination with Prednisone for Metastatic Hormone Refractory Prostate Cancer.

1. Protocol Review

A total of 105 centers participated in the trial. The distribution of centers by region is outlined in Table 2.

Table 3 : Distribution of Participating Centers by Region

Region	Number of Centers
United States and Canada	24
South America	6
Europe	63
Australia and South Africa	10
Middle East	2

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CLINICAL REVIEW

Clinical Review Section

Table 4 : Protocol Milestones

Milestone	Date	Comments
Protocol open		
First patient enrolled	3/20/00	
Administrative change #1 (Austria)	4/10/00	Allow use of oral prednisolone instead of prednisone in case oral tablets of prednisone are not marketed in the country
Amendment #1	2/28/00	'center' has been deleted as a stratification factor, leaving only 'pain level' and 'karnofsky performance status' ; analgesic scoring system refined; pain assessment schedule revised to monthly; new storage conditions for docetaxel; wording of data analysis clarified
Amendment #2	11/03/00	Prior estramustine accepted regardless of route of administration ; timing of rising PSA at study entry refined ; no longer requiring a rising PSA for response analysis ; number of acceptable missing values for PPI and AS specified ; QoL parameters to be defined in a specific SAP ; originally planned TTP analysis (including pain, PSA, tumor progression) changed to separate analyses of event progression-free survival ; interim efficacy analysis cancelled ; description of statistical analyses modified to include more details (management of multiplicity etc.); analgesic scoring table updated ; pain and PSA responses more accurately defined

CLINICAL REVIEW

Clinical Review Section

Amendment #3	10/01/01	Sample size increased from 804 to 1002; analgesic scoring table updated ; definiton of SAE corrected to be consistent with ICH/FDA ; study period now referred to as observation period
Amendment #4	8/27/02	Change in statistical analysis strategy so that the closed testing procedure was replaced by the modified Bonferroni method ; analgesic scoring table updated
Last patient completed study	2/27/03	
sNDA submitted	1/26/04	

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Objectives:

Primary

To compare overall survival (OS) after mitoxantrone and prednisone (arm A), and docetaxel and prednisone (arm B:docetaxel q3 weeks combined with arm C:weekly docetaxel) in subjects with metastatic hormone-refractory prostate cancer.

Reviewer comment: A modified Bonferroni method for simultaneous evaluation of arm A versus B, arm A versus C, and arm A versus (arm B + arm C) was discussed with FDA and agreed to by the sponsor. This change in the proposed analysis plan was incorporated in amendment #4 dated 8/27/02.

Secondary

CLINICAL REVIEW

Clinical Review Section

1. Pain progression-free survival
2. PSA progression-free survival
3. Tumor progression-free survival
4. Disease progression-free survival
5. Pain improvement (incidence and duration)
6. PSA response (incidence and duration)
7. Quality of life
8. Response rate in subjects with measurable disease
9. Safety
10. Pharmacokinetics of taxotere in combination with prednisone

Reviewer comment : The original protocol included TTP as a secondary endpoint. Since this was a composite endpoint including rising PSA, pain, tumor, and disease progression, the FDA suggested that such a composite endpoint would be difficult to assess. The sponsor subsequently changed this to separate analyses of event progression free survival (progression due to rising PSA, pain, etc. separately)

Selection Criteria

Inclusion Criteria

1. Signed informed consent
2. Histologically or cytologically proven adenocarcinoma
3. Metastatic disease that was unresponsive or refractory to hormone therapy
4. Subjects had to have received prior hormonal therapy as follows:
 - Castration by orchiectomy and/or LHRH agonists with or without
 - Antiandrogens
 - Antiandrogen withdrawal
 - Monotherapy with estramustine
 - Other hormonal agents (e.g. ketoconazole)
5. Documented progression detected by PSA increase, physical examination and/or imaging:
6. Stable analgesia for a minimum of 7 consecutive days prior to randomization. A pain diary was required for this 7-day period. Stable analgesia was defined by both
7. Prior treatment with corticosteroids was allowed.
8. Prior radiation therapy (<25% of bone marrow) was allowed. At least a 4 week period from last radiation treatment was required with recovery from side effects.
9. At least 4 weeks had to have elapsed from any prior surgery.
10. Life expectancy \geq 3 months
11. KPS \geq 60
12. Normal cardiac function (LVEF above LLN based on MUGA or ECHO)

CLINICAL REVIEW

Clinical Review Section

13. Laboratory requirements

Hemoglobin \geq 10.0 gm/dL, erythropoietin allowed but not RBC transfusion

Neutrophil count \geq 1.5×10^9 cells/L

Platelet count \geq 100×10^9 /L

Creatinine \leq 1.5 X ULN (\leq NCI grade 1)

Total bilirubin \leq ULN

AST/SGOT \leq 1.5 times ULN

ALT/SGPT \leq 2.0 times ULN

14. accessible for treatment and followup

Exclusion Criteria

1. Previous cytotoxic chemotherapy, except monotherapy with estramustine.
2. Prior isotope therapy.
3. Prior radiotherapy to $>25\%$ of bone marrow.
4. Prior malignancy except the following: adequately treated basal cell or squamous cell skin cancer, or any other cancer from which the subject has been disease-free for \geq 5 years.
5. Known brain or leptomeningeal involvement.
6. Symptomatic peripheral neuropathy grade \geq 2 according to the NCI CTC.
7. Other serious illness/condition:
 - Congestive heart failure, previous history of myocardial infarction or angina within 1 year from study entry, uncontrolled hypertension / arrhythmia.
 - Active uncontrolled infection.
 - Peptic ulcer, unstable diabetes mellitus or other contraindications for corticosteroid use.
 - Autoimmune disease.
8. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational agent within 30 days prior to study screening.
9. Treatment with any other anti-cancer therapy (except LHRH agonists) including any prescribed compounds and/or OTC products for the treatment of prostate cancer had to be stopped prior to randomization.
10. Treatment with systemic corticosteroids used for reasons other than specified by the protocol must be stopped prior to randomization.
11. Treatment with bisphosphonates had to be stopped prior to randomization.

Treatment Plan

Patients were randomized to one of three treatment arms : A, B, or C

CLINICAL REVIEW

Clinical Review Section

Arm A (MTZq3w): Mitoxantrone 12 mg/m² intravenously (day 1) as a 30 minute infusion every 21 days, plus prednisone 5 mg orally twice daily for 10 cycles. Prednisone could be continued after completion of 10 cycles.

Arm B (TXT q3w): Docetaxel 75 mg/m² intravenously (day1) as a 1-hour infusion every 21 days, plus prednisone 5 mg orally twice daily for 10 cycles. Prednisone could be continued after completion of 10 cycles. Prophylactic dexamethasone 8 mg was to be administered orally at 12 hours, 3 hours and 1 hour before docetaxel.

Arm C (TXT qw): Docetaxel 30 mg/m² intravenously as a 30 minute infusion on days 1,8,15,22,29 every 6 weeks, plus prednisone 5 mg orally twice daily, for 5 cycles. Prednisone could be continued after completion of 5 cycles. Dexamethasone 8 mg was to be administered orally 1 hour before docetaxel infusion.

In patients receiving docetaxel, substitution of another steroid for prophylactic dexamethasone was permitted as follows;

Table 5: Equivalent Glucocorticoid Doses

Dexamethasone	Methyl-prednisolone or Triamcinolone	Prednisolone and Prednisone	Hydrocortisone	Cortisone
0.75 mg	4 mg	5 mg	20 mg	25 mg

Derived from clinical study report, table 5, page 101

Toxicity and Dose Modifications

If possible, toxicities were to be managed symptomatically. The appropriate treatment was to be used to ameliorate signs and symptoms including antiemetics for nausea and vomiting, antidiarrheals for diarrhea, and antipyretics and/or antihistamines for drug fever.

If a subject experienced several toxicities with different recommendations for dose modifications, the most conservative dose adjustment was to be adopted. No more than two dose reductions were to be implemented for each subject.

Doses were to be adjusted according to the following recommendations, with no dose re-escalation :

Table 6 : Dose Levels for Dose Reduction

CLINICAL REVIEW

Clinical Review Section

Dose level	TXT q3w	TXT qw	MTZ q3w
0	75 mg/m ²	30 mg/m ²	12 mg/m ²
-1	60 mg/m ²	25 mg/m ²	10 mg/m ²
-2	45 mg/m ²	20 mg/m ²	8 mg/m ²

Derived from section 3.3.2 of the study report, page 37

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Pertinent guidelines for specific organ toxicities are outlined below:

Myelosuppression

Neutropenia

Table 7 : Dose Reduction Due to Neutropenia and Associated Complications

Adverse Event	Action to be Taken
Grade 4 neutropenia for ≥ 7 days Grade 3-4 neutropenia with oral temperature ≥ 38.5 C Infection (documented with grade 3-4 neutropenia)	If the subject developed one of these adverse events, the next infusion was to be given with a one-level dose reduction

¹in accordance with NCI-CTC, version 2

Derived from study report section 3.3.2.2 page 38

Table 8 : Dose Reduction and Delay Based on Absolute Neutrophil Count on Day of Infusion for Arm A and Arm B

ANC on Day of Infusion	Action to be Taken
$\geq 1.5 \times 10^9/L$	Treat on Schedule
$< 1.5 \times 10^9/L$	Treatment delay no more than 2 weeks. Blood counts were to be performed until the ANC was $\geq 1.5 \times 10^9/L$, at which time treatment would be resumed with a one-level dose reduction. If not recovered (ANC $< 1.5 \times 10^9/L$) after 2 weeks, remove from study treatment

Derived from study report section 3.3.2.2, page 38

The required actions in response to ANC for patients in the weekly docetaxel arm were different from those for patients receiving every 3 week MTZ or TXT. With

CLINICAL REVIEW

Clinical Review Section

weekly TXT, an ANC $\geq 1.0 \times 10^9/L$ was required on the day prior to each infusion, with an ANC $\geq 1.5 \times 10^9/L$ required on day 1 of each cycle. If ANC was $< 1.0 \times 10^9/L$ on days prior to scheduled infusion, treatment was to be delayed for a maximum of 2 weeks and retreatment subsequently with one level dose reduction. If recovery to $1.0 \times 10^9/L$ had not occurred by 2 weeks, the patient was to be removed from treatment.

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On Original

Thrombocytopenia

For grade 3 or worse thrombocytopenia, treatment was to be delayed for a maximum of 2 weeks until recovery to at least $100 \times 10^9/L$ and the subject was to be treated with one dose level reduction.

Anaphylactic and Hypersensitivity Reactions

If a reaction occurred, the specific treatment medically indicated was to be instituted. In addition, the measures listed in Table 9 were recommended.

Table 9 : Recommended Treatments for Anaphylactic and Hypersensitivity Reactions

<p>Mild symptoms: Localized cutaneous reaction such as pruritis, flushing, rash</p>	<p>Decrease the rate of infusion until recovery of symptoms, investigator stay at bedside. Then, complete docetaxel infusion at the initial planned rate. Prophylactic premedication with subsequent cycles.</p>
<p>Moderate symptoms: Generalized pruritis, more severe flushing, rash, dyspnea, hypotension with systolic blood pressure (BP) > 80 mm Hg</p>	<p>Stop docetaxel infusion. Give IV histamine and IV corticosteroid. Resume docetaxel infusion after recovery of symptoms. At subsequent cycles, antihistamines and steroids were to be given IV 1 hour before infusion, in addition to dexamethasone.</p>
<p>Severe symptoms:</p>	<p>Stop docetaxel infusion.</p>

CLINICAL REVIEW

Clinical Review Section

Bronchospasm, generalized urticaria, systolic BP \leq 80 mm Hg, angioedema	Give IV antihistamine and steroids. If medically indicated, epinephrine or bronchodilators and/or IV plasma expanders. Whenever possible resume docetaxel infusion within 24 hours after interruption. The premedication regimen was only recommended when study drug was reinfused more than 3 hours after interruption. At subsequent cycles, give at 24, 18, 13, 7 and 1 hour before study drug infusion. If a severe reaction recurred, go off protocol therapy.
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Derived from Clinical Study Report section 3.3.2.3

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On Original

Nausea / Vomiting

All patients were to receive prophylactic anti-emetics beginning with cycle 1. Metoclopramide was recommended. More aggressive therapy was to be given for grade 3 or worse n/v in a preceding cycle.

Diarrhea

Following the first episode of diarrhea, loperamide was recommended with a maximal daily dose of 16 mg. If grade 3 or worse diarrhea occurred despite loperamide, study drug was to be reduced one dose level. If grade 3 or worse diarrhea continued to occur, the patient was to discontinue therapy.

Stomatitis

In case of stomatitis \leq grade 2, study drug was to be withheld until resolution to \leq grade 1. In the TXT qw arm, the dose of docetaxel was to be reduced by one dose level for all subsequent infusions.

If grade 3 stomatitis occurred, study drug was to be withheld until resolution to grade \leq 1. Treatment could then be resumed, but with a reduction by one dose level. If grade 4 stomatitis occurred, the patient was to be taken off study.

Peripheral neuropathy

A one-level dose reduction was to be implemented upon re-treatment for grade 2 toxicity, whereas for grade 3 toxicity, the subject was to be discontinued from protocol therapy.

Skin toxicity

For grade 3 skin toxicity, treatment was to be delayed for a maximum of 2 weeks until resolution to \leq grade 1. Subsequent treatments were to be reduced by one dose level. If recovery to grade 1 or less did not occur within 2 weeks, the patient was to be removed from therapy.

Liver toxicity

If ALT or AST increases to $> 1.5 \times$ ULN or bilirubin increases to $> \text{ULN}$, study drug treatment was to be delayed for up to 2 weeks until AST or ALT returns to $\leq 1.5 \times$ ULN and bilirubin to $\leq \text{ULN}$. Retreatment was to be reduced by one dose level.

Docetaxel-induced fluid retention

If fluid retention occurred during docetaxel treatment, signs and symptoms were to be graded as recommended in Appendix 5 of the protocol.

Furosemide 20 mg PO daily was the recommended treatment, with increase to 40 mg if needed. Addition of metozalone PO with potassium +/- magnesium supplements was considered useful.

Withdrawal for fluid retention of grade 3 or worse severity was recommended.

Hyperlacrimation

No dose reduction was planned. Recommended treatments included artificial tears and steroid ophthalmic solutions.

Mitoxantrone-induced cardiac toxicity

The total cumulative dose of mitoxantrone was restricted to $\leq 120 \text{ mg/m}^2$. All patients randomized to MTZq3w were to be followed by echocardiography or angioscintigraphy according to the following schedule:

- Baseline LVEF at rest before registration
- LVEF repeated after cycle 5, 8 and 10 and/or the end of study if treatment was discontinued earlier.
- LVEF was to be repeated every month after treatment complete in patients with LVEF decrease observed on study.

Appears This Way
On Original

CLINICAL REVIEW

Clinical Review Section

If symptoms suggestive of congestive heart failure are confirmed with LVEF, the patient was to be removed from treatment. A patient would also be removed from treatment if there was an absolute decrease in LVEF $\geq 10\%$ associated with a decline to a level $< 50\%$.

Other

Other Toxicities Not Defined Above : For Grade ≤ 2 , manage symptomatically and retreat without dose reduction. For Grade ≥ 3 other than anemia, withhold drug for a maximum of 2 weeks until resolution to Grade ≤ 1 or baseline, then reinstitute if appropriate with one dose level reduction.

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Withdrawal Procedures

Patients were to receive 10 cycles of treatment in the MTZq3w and TXtq3w arms and 5 cycles in the TXTqw arm unless the following events occurred earlier:

1. Development of a life-threatening and/or irreversible toxicity not manageable by symptomatic care, dose reduction, or delay.
2. Administration of any other antitumor chemotherapy, radiotherapy, or experimental drug during the trial.
3. Withdrawal of consent
4. Progression of disease as follows
 - a. rising PSA

In PSA responders and subjects not evaluable for PSA response, progression was defined as a $\geq 50\%$ increase over the nadir and an increase in the absolute value PSA level by at least 5 ng/mL, confirmed by a second value at least 1 week later.

CLINICAL REVIEW

Clinical Review Section

In PSA non-responders, progression was defined by a $\geq 25\%$ increase over nadir (provided that the rise is a minimum of 5 ng/mL) and confirmed by a second value at least 1 week later.

- b. radiologic progression (see below)
- c. progression in non-measurable lesion according to WHO criteria
- d. appearance of a new lesion including on bone scan
- e. pain progression (see below)

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Prior and Concomitant Treatments

Full supportive care including antibiotics, antiemetics, etc. should be provided as appropriate. Reasons for treatment, dosage, and dates of treatment should be documented.

Allowed: G-CSF (for febrile neutropenia and/or infection), antiemetics (except systemic corticosteroids), and anti-allergic measures.

Not allowed: other investigational drugs and anticancer treatments while on study. Systemic corticosteroids, concomitant bisphosphonates.

In case of febrile neutropenia or infection, dose reduction is indicated at subsequent cycles instead of prophylactic G-CSF

CLINICAL REVIEW

Clinical Review Section

Safety Considerations

Clinical and laboratory assessments at screening, during the chemotherapy treatment phase, and during the followup period are outlined in Table 10.

Table 10 : Clinical and Laboratory Assessments

Investigations	Timing Prior to Randomization	Timing on-study	Timing end of study and followup
Informed consent	Pre registration		
History / Physical Exam and clinical tumor assessment	Within 14 days	Every 3 weeks (day 1 before infusion)	End of study Clinical tumor assessments; every 2 months
Hematology*	Within 14 days	On day 1 before infusion. Every 2 days in case of febrile neutropenia or infection up to fever < 38 C and neutrophils $\geq 1 \times 10^9/L$	End of study
Biochemistry ⁺	Within 14 days	Every 3 weeks (day 1 before infusion)	End of study
PSA**	Within 14 days	Every 3 weeks (day 1 before infusion)	End of study Every month until PD or further antitumor therapy
Adverse Events	Within 14 days	Day 1 before infusion	End of study Every month until PD or further antitumor therapy
Radiology# Tumor Assessment##	Within 21 days	After weeks 6,12,21,30 and to confirm response	End of study Every two months until PD or further antitumor therapy
Bone scan	Within 21 days	After weeks 12,21,30 and to confirm a response	End of study Every two months until PD or further antitumor therapy

CLINICAL REVIEW

Clinical Review Section

ECG	Within 14 days	As indicated	End of study, then as indicated
LVEF [%]	Within 14 days	Post cycles 5,8,10 (arm A) and as indicated	End of study, then as indicated
QOL ^{%%}	Within 3 days	Every 3 weeks (day 1 before infusion)	End of study Every month up to initiation of further anticancer therapy
Pain assessments:PPI + analgesic score	Within 3 days averaged over 7 days	Every 3 weeks (day 1 before infusion) averaged over 7 days	End of study Every month up to initiation of further anticancer therapy
Other investigations	Within 14 days	As indicated	As indicated

*WBC, neutrophils, platelets, hemoglobin

**rising PSA at baseline (same laboratory from baseline to end)

+alkaline phosphatase, LDH, bilirubin, AST, ALT, creatinine, Na, K, Ca, protein, albumin, testosterone at baseline, alpha-1 glycoprotein in patients with PK

same technique at baseline and followup

##baseline chest X-ray and CT,abdominal/pelvic CT, bone scan, others as needed

%in arm A only:on-study LVEF required following cycles 5,8,10 or earlier if indicated. Follow-up only if decreased on study

%%self-administered Fact-P questionnaire, McGill Pain scale and Pain Medication log.QoL questionnaire should be administered before patient is informed of treatment assignment protocol defined stable analgesia should be observed within 3 days prior to randomization

(Derived from section 5.2 of the study protocol)

Efficacy Assessment Methods

Pain and Analgesics

Pain was to be evaluated at baseline, every 3 weeks, at end of study and then every month until further anti-cancer therapy with the Present Pain Intensity scale (PPI) from the McGill-Melzack questionnaire. The patient was asked to complete the PPI every day for the one week period prior to each evaluation.

Analgesic consumption was to be evaluated with the Pain Medication Log prior to registration, every 3 weeks, at end of study and then every month until further anti-cancer therapy. Analgesic use for the one week period prior to each evaluation was to be recorded. Analgesic score was calculated as the mean daily score, averaged over the prior week, using the following scale:

CLINICAL REVIEW

Clinical Review Section

Standard narcotic dose = 2 points

e.g. morphine 10 mg (5 mg if given parenterally)
hydromorphone 2 mg (1 mg if given parenterally)
codeine 30 mg
oxycodone 2.5 mg

standard non-narcotic dose = 1 point

e.g. aspirin 325 mg
acetaminophen 325 mg
naproxen 250 mg

Pain response was defined as a 2-point or greater reduction in analgesic score, or a reduction of at least 50% in analgesic use (from baseline) with no increase in pain. Criterion must be maintained for 2 consecutive evaluations 3 weeks apart. Duration of response was defined from first to last assessment at which criteria were satisfied. Pain response applied only to patients with PPI ≥ 2 on McGill-Melzack scale and/or analgesics score ≥ 10 points.

Pain progression was defined as an increase of ≥ 1 point in the PPI scale from its nadir noted on 2 consecutive visits 3 weeks apart or $\geq 25\%$ increase in daily analgesic score compared with baseline and noted 2 consecutive 3 week apart visits or requirement for local palliative radiotherapy.

PSA Response / Progression

PSA response applies only to patients with rising PSA at baseline and PSA ≥ 20 ng/ml and requires a PSA decline of $\geq 50\%$ confirmed three weeks later. Duration of response will be measured from first to last assessment at which the above criteria are satisfied.

PSA progression in non-responders will be defined as 25% increase over nadir and confirmed by a second value (rise at least 5 ng/ml). PSA progression in non-responders will be defined as a 50% increase over nadir and confirmed by a second value (rise at least 5 ng/ml).

Tumor Lesion Assessment

All tumor lesions present at baseline were to be followed with the same examinations on weeks 6 (except bone scan), 12, 21 and 30 or earlier if clinically indicated) during chemotherapy, at end of study and every two months during the follow-up until progression or further anti-cancer therapy. For physically assessable lesions, exam was to be repeated every 3 weeks. Confirmation of CR or PR was to be performed at least 28 days after the first declaration of response and required assessment of measurable and non-measurable disease.

CLINICAL REVIEW

Clinical Review Section

Appears This Way
On Original

Measurable Lesions

Bidimensionally Measurable:

This was defined as a tumor deposit with clearly defined margins. Examples of such lesions evaluated by clinical exam or imaging include:

- A skin nodule or palpable lymph node assessed by physical exam ≥ 20 mm x 10 mm.
- A clearly defined lung lesion surrounded by aerated lung ≥ 20 mm x 10 mm.
- A liver lesion, soft tissue, lymph node and masses investigated by CT, MRI or ultrasound (≥ 20 mm x 10 mm)

Unidimensional Measurable Disease

This was defined as a tumor deposit with only one identifiable margin, such as abdominal tumor masses, or lung lesions not completely surrounded by aerated lung. The minimum size requirement was one diameter ≥ 20 mm on CT, ultrasound, MRI, chest X-ray, or physical exam.

Response Criteria

Complete Response (CR)

Complete disappearance of all known disease, determined by 2 observations no less than 4 weeks apart (an intermediate visit with appropriate investigations may be planned 4 weeks ahead from the day when the CR has been assessed).

Partial Response (PR)

A 50% or greater decrease in the sum of the products of the largest perpendicular diameters of all bidimensionally measurable lesions. For unidimensionally measurable disease, decrease by at least 50% in the sum of the largest diameters of all lesions. Should be determined by 2 observations no less than 4 weeks apart. No progression and no new lesions.

Stable Disease (SD)

CLINICAL REVIEW

Clinical Review Section

Does not qualify for a complete response (CR), partial response (PR), or progressive disease (PD). No lesion should have progressed and no new lesions should appear. Assignment can be made only after at least 6 weeks after start of treatment.

Progressive Disease (PD)

An increase of $\geq 25\%$ in the size of at least one bidimensionally or unidimensionally measurable lesion (in comparison with nadir) or appearance of a new lesion. When progression is observed before 6 weeks after entry, this will be considered early progression.

Development of Brain Metastasis

This will be considered a sign of progression, even if the disease is responding outside the brain. However, an investigator may choose to continue study drug.

Non-Measurable Lesions

Definition

Lesions with the largest diameter below the protocol-defined cut-off threshold for measurability. Either blastic or lytic bone lesions. Other lesions such as effusions, previously irradiated lesions not in progression, and carcinomatous lymphangitis (skin and lung).

Response Criteria

Complete Response

Complete disappearance of all known disease for at least four weeks including normalized bone scan.

Progressive Disease

For bone lesions, PD will be assessed based on the appearance of new lesions on bone scan (i.e. new hot spots). An intensity increase of existing hot spots on bone scan does not constitute evidence of progression, neither does pathological fracture or collapse of bone.

For other lesions, PD will be based on the appearance of any new lesions not previously identified or on the estimated increase of 25% or more in existing lesions. The occurrence of effusions is considered progressive disease if substantiated by positive cytology.

Overall Tumor Response

Will be determined according to Table 11 below:

Table 11 : Overall tumor response

Response in measurable lesions (bi or uni dimensional)	Response in non measurable lesions	Overall response
PD or new lesion	Any	PD
Any	PD or new lesion	PD
SD	Any except PD	SD
PR	Any except PD	PR
CR	Any except PD	PR
CR	CR	CR

Derived from section 7.1.3.3 of the study protocol page 50.

Time to disease progression is defined as the time from the date of randomization to the date of documentation of disease progression.

Survival is defined as the time interval from the date of randomization to the date of death.

Quality of Life

The domains covered by the FACT-P (version 4) will be used. It will be assessed in countries where the questionnaire is available in the local language. Questionnaires will be self-administered. Baseline assessment should be obtained from all patients, within 3 days prior to randomization or at randomization, but before the patient is informed of the treatment assignment. Assessments should be obtained every 3 weeks, before chemotherapy and at end of chemotherapy while on study treatment. Assessments will be obtained monthly during followup.

Statistical Methods

Sample Size Determination

CLINICAL REVIEW

Clinical Review Section

The primary objective was to detect a statistically significant difference in OS for the combined docetaxel containing arms relative to the control arm using mitoxantrone. The median survival for patients receiving mitoxantrone/prednisone was expected to be about 12 months. A total of 535 events were required to detect with 0.90 power a 33% increase in median OS using a two-sided logrank test. Assuming a median follow-up of 24 months, and assuming a maximum of 2% of patients lost to follow-up, 804 patients were to be randomized (268 per treatment arm).

Definition of Populations

All randomized patients were to be included in the intent to treat (ITT) analysis. PSA response was to be analyzed in patients who experienced a protocol-defined PSA increase before study entry along with PSA ≥ 20 ng/ml at baseline. Pain response was to be analyzed in patients with PPI ≥ 2 and/or AS ≥ 10 at baseline. Safety analyses were to be conducted in all treated patients.

Efficacy Endpoints

Primary endpoint and analysis of overall survival

Defined as the time from randomization to death from any cause. Patients alive at last contact or at the cut-off date of the analysis were to be censored at their date of last contact for the OS analysis. The primary analysis was defined as comparison of overall survival using an ITT analysis between the two combined docetaxel groups versus the control based upon the adjusted logrank test. The final analysis of survival data was to be performed provided at least 535 deaths had been observed. This was estimated to occur one year after recruitment of the last patient.

Reviewer comment

Secondary endpoints and analyses

TTP

A comparison of TTP between the two combined docetaxel groups versus the mitoxantrone group was to be done in the ITT population based on the adjusted logrank test at 0.05 level. The first TTP analysis was to be performed as soon as 258 events had been observed. The final analysis of TTP was to be undertaken at the end of the study (i.e. when the final OS was to be performed).

Pain response and PSA response

CLINICAL REVIEW

Clinical Review Section

Pain response and PSA response were to be compared between the combined docetaxel containing groups and the mitoxantrone group using the chi-square test in the corresponding evaluable patients. For PSA response, the hypothesis was that a response rate of 35% will be observed in the control arm and 50% for the docetaxel arms. Assuming that 80% of patients would be evaluable, the power of the final analysis would be 94%. For pain response, the hypothesis was that a 35% (control arm) versus 50% (docetaxel) response rate would be observed. The power of the final analysis was estimated at 79% assuming that 50% of patients would be evaluable for pain response.

Duration of response

Duration of response was to be analyzed using the kaplan-meier method. The comparison of response duration will be based on the adjusted logrank test. Response rate in patients with measurable disease would be compared between docetaxel containing group and mitoxantrone group using the chi-square test.

Exploratory analyses

For each of the above endpoints where there is significance for the primary analysis (comparison of combined docetaxel groups versus mitoxantrone), separate comparisons of docetaxel treatment groups to control and of the two docetaxel groups will be made at the 0.05 level.

Interim analyses

An interim safety analysis was to be conducted after entry of the first 120 randomized patients (40 in each arm) in order to ensure the safety and tolerability of the selected dosing regimens.

An interim safety/efficacy analysis was to be conducted when 258 events (disease progression or death) had been observed.

At the time of the interim analysis, and assuming an exponential distribution of events, 54% of patients are estimated to have been recruited and 22% of deaths are estimated to have been observed. The interim OS analysis was to be conducted at the 0.001 level. This allows the final analysis to be conducted at just under the 0.05 level.

The interim analysis of TTP was to be conducted at 0.05 significance level. Multiplicity was to be managed for the TTP endpoint by requiring both the interim and final to have $p \leq 0.05$

Quality of Life Analyses

Clinical Review Section

The FACT-P scale comprises 5 subscales as follows:

Physical well-being : 7 items

Social/Family “ : 7 items

Emotional “ : 6 items

Functional “ : 7 items

Additional concerns (prostate cancer specific) “ : 12 items

Quality of life evaluation was to be performed on the overall population of randomized patients for whom at least one QOL questionnaire has been considered evaluable for analysis. The rules for evaluability are outlined on page 61 of the study protocol section 9.4. QOL response for a patient will be considered as a 10-point improvement in the FACT-P score for 2 consecutive visits as compared to baseline.

2. Trial Results

Study Conduct

Informed Consent

Prior to trial participation, the patient was to be informed of the nature of the study in the form of a ‘patient information sheet’ prepared in the local language (appendix 6 of the study protocol) and approved by the EC or IRB. The formal consent of any patient was required before undertaking any study-specific procedures.

Treatment Assignment and Randomization

Protocol Violations

The sponsor reported major eligibility protocol violations in 120 patients (11.9%). The most commonly occurring are summarized in table 11 below. In addition to those outlined in table 12, other violations of eligibility such as prior chemotherapy (except estramustine) or progression not documented at study entry occurred in 1 or two patients only.

CLINICAL REVIEW

Clinical Review Section

Table 12 : Sponsor's List of Major Violations of Inclusion/Exclusion Criteria

Protocol Violation	TXT q3w N (%)	TXT qw N (%)	MTZ q3w N (%)
Not castrated	6 (1.8)	5 (1.5)	6 (1.8)
MI or angina within 1 year	6 (1.8)	3 (0.9)	5 (1.5)
Baseline hemoglobin < 10 g/dl	5 (1.5)	7 (2.1)	3 (0.9)
Prior XRT > 25% of BM	5 (1.5)	2 (0.6)	5 (1.5)
Bilirubin > ULN	4 (1.2)	2 (0.6)	4 (1.2)
Peripheral neuropathy ≥ grade 2	4 (1.2)	0	1 (0.3)
Baseline KPS > 21 days prior to randomization	3 (0.9)	3 (0.9)	5 (1.5)
Baseline SGPT > 1.5 x ULN	3 (0.9)	2 (0.6)	4 (1.2)
Testosterone ≥ 100 ng/dl	3 (0.9)	2 (0.6)	1 (0.3)
CHF before randomization	3 (0.9)	1 (0.3)	0
Date of progression at study entry before anti-androgen stop date	2 (0.6)	2 (0.6)	3 (0.9)
Uncontrolled hypertension or arrhythmia at randomization	2 (0.6)	2 (0.6)	0
Contraindication for steroids at baseline	2 (0.6)	0	0
Baseline SGOT > 1.5 x ULN	1 (0.3)	2 (0.6)	3 (0.9)
Randomized too soon after antiandrogen	1 (0.3)	1 (0.3)	2 (0.6)
Prior malignancy	0	3 (0.9)	1 (0.3)

Derived from table 17, section 6.2 of the clinical study report

CLINICAL REVIEW

Clinical Review Section

Reviewer Comment: In general, the medical reviewer's analysis of the submitted dataset 'udevia.xpt' agrees with that of the sponsor. However, no patients are noted to have tumor type other than adenocarcinoma. The reviewer observed that the definition of variables for the 'udevia.xpt' dataset describes a convention for histology that if pathology is missing, the patient was designated as having adenocarcinoma. A query asking about how many patients received such a designation and their patient ID's was forwarded to the sponsor on 3/24/04.

The sponsor also reported that major deviations during the study occurred in 72 patients. Three patients received incorrect therapy; 2 who were randomized to receive TXT q3w actually received TXTqw and one patient randomized to receive TXT qw actually received TXTq3w. One subject (#03309), randomized to MTZq3w, received mitomycin C in the first cycle and subsequently continued to receive MTZ q3w. The sponsor's list of major deviations during the study are outlined in Table 13.

Table 13 : Sponsor List of Major Deviations of Protocol Conduct

Deviation	TXT q3w N (%)	TXT qw N (%)	MTZ q3w N (%)
No study chemotherapy	2 (0.6)	5 (1.5)	2 (0.6)
No study prednisone	2 (0.6)	5 (1.5)	2 (0.6)
Received medication different to randomization	2 (0.6)	1 (0.3)	0
Chemotherapy delayed > 14 days	1 (0.3)	4 (1.2)	4 (1.2)
Abnormal dose of chemotherapy	2 (0.6)	5 (1.5)	4 (1.2)
Too low	2 (0.6)	1 (0.3)	2 (0.6)
Too high	0	4 (1.2)	2 (0.6)
Abnormal dose of prednisone (Too low)	12 (3.6)	10 (3.0)	9 (2.7)
Ongoing LHRH was discontinued	3 (0.9)	3 (0.9)	3 (0.9)

CLINICAL REVIEW

Clinical Review Section

Concurrent experimental drug	0	0	0
All	22 (6.6)	28 (8.4)	22 (6.5)

Derived from table 18, clinical study report section 6.2, page 146

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Demographics and Baseline Characteristics

Baseline Demographics

Age, race, Karnofsky performance status and pain level at baseline are listed by distribution across the three study arms in Table 14. These appear to be evenly distributed across treatment groups.

Table 14 : Baseline Patient Characteristics

Characteristic	TXT q3w N = 335 (%)	TXT qw N = 334 (%)	MTZ q3w N = 337 (%)
Age (years)			
Median	68.0	69.0	68.0
Range	42-92	36-92	43-86
Race			
Black	8 (2.4)	8 (2.4%)	10 (3%)
Caucasian	312 (93.1%)	312 (93.4%)	312 (92.6%)
Hispanic	8 (2.4%)	7 (2.1%)	9 (2.7%)
Oriental	3 (0.9%)	2 (0.6%)	3 (0.9%)
Other	4 (1.2%)	5 (1.5%)	3 (0.9%)
Karnofsky PS (%)			
≥ 80	293 (87.5)	292 (87.4)	290 (86.1)
≤ 70	42 (12.5)	41 (12.3)	47 (13.9)
Missing	0	1 (0.3)	0
Present Pain Intensity (PPI)			
Median and range	1.0; 0-5	1.0; 0-4	1.0 ; 0-3
< 2	228 (68.1)	222 (66.5)	248 (73.6)
≥ 2	106 (36.1)	109 (32.6)	87 (25.8)
Missing	1 (0.3)	3 (0.9)	2 (0.6)

CLINICAL REVIEW

Clinical Review Section

Analgesic Score (AS)			
Median and range	4.0 ; 0-387	3.8 ; 0-363	3.1 ; 0-449
< 10	221 (66.0)	226 (67.7)	215 (63.8)
≥ 10	113 (33.7)	106 (31.7)	120 (35.6)
Missing	1 (0.3)	2 (0.6)	2 (0.6)

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CLINICAL REVIEW

Clinical Review Section

Primary Disease Characteristics of the Patient Population

Histologic subtype, staging, and Gleason score by treatment group are provided in Table 15. These appear to be evenly distributed across treatment arms.

Table 15 : Histologic Subtype and Staging

Disease Characteristic	TXT q3w N (%)	TXT qw N (%)	MTZ q3w N (%)
Histologic Subtype			
Adenocarcinoma	335 (100.0)	333 (99.7)	337 (100.0)
Missing	0	1 (0.3)	0
Staging at Diagnosis			
I	0	1 (0.3)	1 (0.3)
II	54 (16.1)	49 (14.7)	56 (16.6)
III	60 (17.9)	48 (14.4)	51 (15.1)
IV	192 (57.3)	193 (57.8)	183 (54.3)
Missing	29 (8.7)	43 (12.9)	46 (13.6)
Gleason Score			
2-4	19 (5.7)	13 (3.9)	23 (6.8)
5-7	123 (36.7)	121 (36.2)	119 (35.3)
8-10	105 (31.3)	102 (30.5)	93 (27.6)
Missing	88 (26.3)	98 (29.3)	102 (30.3)

Derived from Table 33, section 6.6 of the clinical study report

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On Original

CLINICAL REVIEW

Clinical Review Section

Table 16 : Baseline PSA in the ITT Population

	TXT q3w N = 335 (%)	TXT qw N = 333 (%)	MTZ q3w N = 336 (%)
Mean	536.64	403.70	408.83
Median	114.00	107.63	122.60
Range	0.15 - 40740	0 - 16709	0.30 - 8022
Missing	0	1	1
< 20	44 (13.1)	52 (15.6)	37 (11)
≥ 20	291 (86.9)	281 (84.1)	299 (88.7)

Derived from table 35, page 96 of the clinical study report

Table 17 : Prior Anti-Cancer Therapy in the ITT Population

Prior therapy	Yes or No	TXT q3w N (%)	TXT qw N (%)	MTZ q3w N (%)
Surgery	Yes	161 (48.1)	174 (52.1)	162 (48.1)
	No	174 (51.9)	160 (47.9)	175 (51.9)
Radiotherapy	Yes	175 (52.2)	147 (44.0)	173 (51.3)
	No	160 (47.8)	187 (56.0)	164 (48.7)
Hormonal therapy	Yes	335 (100)	334 (100)	337 (100)
	No	0	0	0
Estramustine	Yes	64 (19.1)	60 (18.0)	69 (20.5)
	No	271 (80.9)	274 (82.0)	268 (79.5)

Derived from Table 36, page 97 of the clinical study report

Surgery for hormonal control is included in hormonal therapy

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CLINICAL REVIEW

Clinical Review Section

Efficacy Results

Primary Endpoint : Survival

The primary efficacy endpoint was survival, defined as time from randomization to the date of death from any cause. According to the sponsor, the primary analysis was performed on the intent-to-treat population (ITT). The ITT population consisted of all randomized patients.

The study cutoff date for the primary analysis was 3/24/03, the date on which the sponsor received notification of the 535th death. By that date, a total of 557 subjects were dead. All subjects known to be alive at the cutoff date were censored either on the date of last assessment or on the date of cutoff if the last contact had taken place at a later time.

Three simultaneous comparisons of OS were performed using a modified Bonferroni adjustment to control for multiplicity; TXT q3w versus control MTZ q3w, TXT qw versus control MTZ q3w, or the two pooled docetaxel treatment groups versus the control. The nominal significance levels for each comparison are as follows in Table 18.

Table 18 : Sponsor Designation of Significance Level for Multiple Comparisons

Comparison vs Mitoxantrone	Significance Level
Combined TXT groups	0.04
TXT q3w	0.0175
TXT qw	0.0175

The primary analysis was to be considered positive if at least one of the three adjusted logrank test comparisons was less than the prespecified nominal significance level for that comparison.

It was prospectively specified that the stratified logrank test, stratified on baseline pain and Karnofsky performance status, would be the primary means of determining if TXT q3w and/or TXT qw increased OS compared with MTZ q3w.

CLINICAL REVIEW

Clinical Review Section

Randomization stratification factors are listed in Table 19.

Table 19 : Stratification Factors at Randomization

Factor	Categories
Baseline Pain	Median PPI > or = 2 or mean AS > or = 10 versus median PPI < 2 and mean AS < 10
Baseline KPS	< or = 70 versus > or = 80

Overall survival was significantly superior in the TXT q3w group compared with the MTZ qw group. OS was also significantly superior for the combined TXT groups compared with the MTZ q3w group. OS for the once weekly docetaxel arm was not statistically significant from that of the MTZ q3w group. Results are summarized in Tables 20 and 21.

Table 20 : Sponsor's Assessment of Overall Survival , ITT Population

	Combined TXT Groups N (%)	TXT q3w N (%)	TXT qw N (%)	MTZ q3w N (%)
Subjects in ITT population	669 (100)	335 (100)	334 (100)	337 (100)
Deaths	356 (53.2)	166 (49.6)	190 (56.9)	201 (59.6)
Censored	313 (46.8)	169 (50.4)	144 (43.1)	136 (40.4)
Reason for censoring				
*Dead after cutoff	6 (0.9)	4 (1.2)	2 (0.6)	4 (1.2)
*Death not observed	307 (45.9)	165 (49.3)	142 (42.5)	132 (39.2)
Kaplan-Meir median survival	18.27 months	18.92 months	17.38 months	16.49 months
95% C.I.	17.02-19.25	17.02-21.22	15.7-19.02	14.42-18.56
KM survival probability (%)				
12 months	70.9	73.3	68.6	64.8
24 months	33.5	37.2	29.9	28.5

Derived from Table 43, page 105 of the clinical study report

CLINICAL REVIEW

Clinical Review Section

Table 21 : Sponsor's Treatment Group Comparisons - Stratified Logrank

	Combined TXT groups vs MTZ q3w	TXT q3w vs MTZ q3w	TXT qw vs MTZ q3w
P value	0.0398	0.0094	0.3624
Nominal significance level	0.0400	0.0175	0.0175
Statistically significant	YES	YES	NO
HR for OS	0.834	0.761	0.912
95% C.I.	0.701 – 0.992	0.619 – 0.936	0.747 – 1.113

Derived from Table 43, page 105 of the clinical study report

Reviewer's Comments

FDA Analysis :The reviewers considered the stratified logrank test as the primary analysis for the comparison of each docetaxel-containing arm to mitoxantrone control and for the comparison of the two docetaxel arms grouped to mitoxantrone control. The FDA's analysis is in agreement with the sponsor's findings. However, some questions regarding the censoring approach had to be clarified during the review process as follows :

The medical reviewer randomly examined 50 case report forms for patients enrolled at 28 different sites. A comparison of case report forms and the dataset UPAT.XPT was done with regard to date of randomization, date of death, or last contact date known to be alive. There were 3 patients who were censored for survival at the cutoff date of 3/24/03 although their last known date alive occurred prior to the cutoff date for the survival analysis. The sponsor was queried regarding these patients, whether there was contact information other than that listed in the CRF, and whether this censoring approach had been used in any other patients. The three patients are as follows: site AR00014 patients 301 and 306, site AR21958 patient 02404.

On 4/15/04, the sponsor replied that the CRF contains a follow-up status form which documents date of last followup at each visit.. The information from this section of the CRF was included in the dataset PATST.XPT. In addition, patients who did not have a death report form were recontacted to determine their survival status as of the cut-off date of 3/24/03. This information was recorded on a special CRF Patient Survival Status Form (PSSF) with the variable D_LCONT as the last known alive date. Data from the PSSF was provided in a separate file, PSSF.XPT. To establish the actual date for censoring if the subject was alive, data from the PSSF were used for the derived dataset UPAT.XPT.

CLINICAL REVIEW

Clinical Review Section

The sponsor also explained that of 1006 subjects randomized, 557 died and 449 subjects were censored in the survival analysis. 442 out of 449 subjects were known to be alive on or after March 24, 2003 and were censored on that date. The remaining 7 subjects were censored on the last date known to be alive prior to March 24, 2003, as recorded on the PSSF of the CRF.

Survival Curves generated by the FDA statistical reviewer are included in the Appendix (page 64).

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PSA Response Rate and Response Duration

PSA response rate was evaluated only for subjects with baseline PSA ≥ 20 ng/ml. The sponsor states that two subjects with unknown PSA at baseline were included in the ITT population for PSA response, one in the TXT qw group and one in the MTZ q3w group. A PSA response was defined as a decrease from baseline of at least 50% confirmed by a repeat measure ≥ 18 days later. The sponsor's PSA response rate results are outlined in Table 22.

Table 22: Sponsor's Results for PSA Response Rate

	TXT q3w	TXT qw	MTZ q3w
Number evaluable for response	291	282	300
Number of responders	132	135	95
PSA response rate and 95% confidence interval	45.4 39.5 – 51.3	47.9 41.9 – 53.9	31.7 26.4 – 37.3
P value for comparison to MTZ q3w	P < 0.0001	P = 0.0005	NA

Derived from table 56, page 188 of the clinical study report.

CLINICAL REVIEW

Clinical Review Section

Analysis using Cochran-Mantel-Haenszel test stratified on baseline pain and KPS

Reviewer Comments: As discussed above, the original protocol specified two requirements for patients to be evaluable for assessment of PSA response; baseline PSA of at least 20 ng/ml and rising PSA at enrollment. With amendment #2, the requirement for a rising PSA at baseline was removed. Furthermore, since multiple analyses were conducted based on several secondary endpoints without prespecified ordering or adjustment, the p-values reported by the sponsor for the two comparisons to the control arm are not interpretable.

Duration of PSA response was also analyzed by the sponsor with findings summarized in Table 23. There was no statistically significant difference in PSA response duration between either docetaxel treatment group and the control arm.

Table 23: Sponsor's Analysis of PSA Response Duration

	TXT q3w N (%)	TXT qw N (%)	MTZ q3w N (%)
Number with PSA response	132	135	95
Observed end of PSA response	50 (37.9)	45 (33.3)	40 (42.1)
Number censored for Further therapy	70 (53.0)	76 (56.3)	37 (38.9)
No end of response	12 (9.1)	14 (10.4)	18 (18.9)
KM median PSA response duration and 95% CI	7.72 7.06 – 8.64	8.25 6.34 – 11.53	7.79 5.36 – 10.55
p-value for comparison to MTZ	0.9561	0.2626	NA

Derived from table 57 of the clinical study report, page 125

Reviewer Comments: As discussed above, the number of analyses conducted for evaluation of secondary endpoints without ordering or adjustment for multiplicity makes it difficult to interpret the results. The large proportion of patients censored for evaluation of PSA response duration makes it even more difficult to evaluate these findings.

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Pain Response Rate and Response Duration

Pain response was defined as decrease from baseline of at least 2 in the median PPI score with no concomitant increase in mean AS, or as a decrease from baseline of at least 50% in the median AS with no concomitant increase in mean PPI score. According to the sponsor, 464 subjects were included in the population evaluable for pain response (baseline median PPI of ≥ 2 or a baseline AS of ≥ 10). Six subjects with unknown median PPI or unknown mean AS at baseline were included in the population for pain response and counted as non-responders.

Table 24: Sponsor's Results for Pain Response Rate

	TXT q3w N (%)	TXT qw N (%)	MTZ q3w N (%)
Number evaluable for response	153	154	157
Number of responders	53 (34.6)	48 (31.2)	34 (21.7)
Pain response rate and 95% confidence interval	34.6 27.1 – 42.7	31.2 24-39.1	21.7 15.5-28.9
P value for comparison to MTZ q3w	P= 0.0107	P = 0.0798	NA

Reviewers Comments: As previously discussed, these analyses were not adjusted for multiplicity or given an analysis sequence with ordering. It is also noted that even without adjustment, there is no statistically significant difference between the weekly schedule and control.

CLINICAL REVIEW

Clinical Review Section

Table 25: Sponsor's Analysis of Pain Response Duration

	TXT q3w N (%)	TXT qw N (%)	MTZ q3w N (%)
Number with Pain response	53	48	34
Observed end of Pain response	25 (47.2)	28 (58.3)	9(26.5)
Number censored for Further therapy	26 (49.1)	18 (37.5)	21 (61.8)
No end of response	2 (3.8)	2 (4.2)	4 (11.8)
KM median Pain response duration and 95% CI	3.55 2.43-8.08	5.55 2.79-6.80	4.83 4.37-NR
p-value for comparison to MTZ	0.2741	0.6356	NA

Derived from the clinical study report, tables 82 and 84

Reviewer's Comments: As discussed for PSA response duration, approximately half of the patients eligible were censored due to further therapy or no end.(mostly due to further therapy). This makes it difficult to interpret these findings.

Secondary endpoints also included tumor response and duration, tumor progression free survival, pain progression free survival, and PSA progression-free survival. As summarized above, only a portion of the ITT population was eligible for these assessments. As discussed above, there was no adjustment for these multiple secondary analyses. Finally, for time to event endpoints such as progression free survival, more than half of the patients were censored due to further therapy or inability to assess the event.The sponsor's own analyses of pain and PSA progression-free survival did not demonstrate an advantage for docetaxel q3week over mitoxantrone prednisone.

D. Efficacy Conclusions

The results of an international, open-label randomized phase 3 trial of combination chemotherapy in patients with hormone refractory prostate cancer were submitted. Patients were randomized to docetaxel every 3 weeks + prednisone, docetaxel weekly + prednisone, or an active control of mitoxantrone + prednisone.

The primary endpoint was overall survival. According to the sponsor's primary analysis, the docetaxel q 3 week schedule plus prednisone demonstrated a statistically significant survival advantage over mitoxantrone plus prednisone, with median survivals of 18.9 versus 16.5 months ($p = 0.0094$). The docetaxel q week plus prednisone arm did not demonstrate an overall survival advantage over the control arm ($p = 0.36$). The FDA's analysis agreed with these findings.

The finding of an overall survival advantage for the docetaxel q3week + prednisone arm over control in this large, multicenter, global, randomized trial provides, in the opinion of the medical and statistical reviewers, substantial evidence of effectiveness.

VII. Integrated Review of Safety**A. Brief Statement of Conclusions**

In summary, the safety profile of q3 week docetaxel + prednisone is generally comparable to mitoxantrone + prednisone, although several adverse events occurred more frequently with docetaxel. Alopecia, fluid retention (especially peripheral edema and weight gain), sensory neuropathy, allergic reactions, and nail changes occurred more frequently in the q3 week docetaxel + prednisone arm compared to the mitoxantrone + prednisone arm. Anemia, infection, nausea, diarrhea, anorexia, and dyspnea occurred more frequently and with more severity in the q 3 week docetaxel + prednisone arm compared to the mitoxantrone + prednisone arm. Although all grade neutropenia occurred approximately evenly in both arms, grade 3 / 4 neutropenia was more frequent in the docetaxel arm. In contrast, cardiac left ventricular dysfunction

CLINICAL REVIEW

Clinical Review Section

and thrombocytopenia occurred less commonly in the q 3 week docetaxel + prednisone arm compared to the mitoxantrone + prednisone arm.

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B. Description of Patient Exposure

The safety population consisted of 997 patients, including 332 subjects in the TXTq3w arm, 330 in the TXT qw arm, and 335 in the MTZ q3w arm.

The sponsor's analysis of cumulative dose, actual dose intensity, and relative dose intensity by treatment group is presented in Table 26. Relative dose intensity was calculated by dividing actual dose intensity by planned dose intensity.

Table 26 : Sponsor Assessment of Cumulative Dose and Dose Intensity of Study Chemotherapy for Docetaxel and Mitoxantrone

Treatment Group	TXT q3w N = 332	TXT qw N = 330	MTZ q3w N = 335
Cumulative Dose (mg/m²)			
Median	651.3	602.7	60.1
Min	38.3	30.8	11.6
Max	826.4	903.1	129.2
Actual Dose Intensity (mg/m²/week)			
Median	24.6	24.0	3.9
Min	12.8	15.4	2.6
Max	26.8	28.7	4.4
Relative Dose Intensity (% of planned)			
Median	0.98	0.96	0.99
Min	0.51	0.62	0.66
Max	1.07	1.15	1.10

CLINICAL REVIEW

Clinical Review Section

Reviewer Comment : The FDA medical reviewer's analysis agrees with that of the sponsor. It is unlikely that the small difference in relative docetaxel dose intensity between the two experimental arms contributed to the difference in survival outcomes compared to mitoxantrone control.

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C. Methods and Specific Findings of Safety Review

Adverse events were recorded using NCI or Meddra preferred terms. Overall, 906 of 997 patients who received study drug (90%) experienced at least one treatment emergent adverse event (TEAE) regardless of relationship to study treatment.

Table 27 provides the sponsor's analysis of the clinically relevant TEAE (Regardless of relationship to study drug) for all grade and grade 3 / 4 events comparing docetaxel q3week + prednisone to mitoxantrone plus prednisone.

Table 27 : Clinically Important Treatment Emergent Adverse Events Regardless of Relationship to Study Drug

Adverse Event	TAXOTERE 75 mg/m ² every 3 weeks + prednisone 5 mg twice daily n=332 %		Mitoxantrone 12 mg/m ² every 3 weeks + prednisone 5 mg twice daily n=335 %	
	Any	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
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

CLINICAL REVIEW

Clinical Review Section

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

Reviewer's Comments: The most commonly occurring TEAEs (25% or greater) on either arm included anemia, neutropenia, infection, fluid retention, sensory neuropathy, alopecia, nail changes, diarrhea, and fatigue. These occurred more frequently on the docetaxel arm than the mitoxantrone arm, and a 10% or greater difference between arms was noted for alopecia, infection, fluid retention, sensory neuropathy, nail changes, and diarrhea. Neutropenia was more frequently observed in the mitoxantrone arm.

TEAE's that occurred in less than 25% of patients included thrombocytopenia, febrile neutropenia, epistaxis, fluid retention, motor neuropathy, rash, arthralgia, tearing, myalgia, stomatitis, taste disturbance, vomiting, anorexia, cough, dyspnea, and left ventricular dysfunction.

Grade 3 / 4 neutropenia, anemia, infection, sensory neuropathy, motor neuropathy, nausea, diarrhea, anorexia, and dyspnea occurred more frequently on the docetaxel q3week arm than the mitoxantrone control.

CLINICAL REVIEW

Clinical Review Section

Grade 3 / 4 thrombocytopenia, cardiac left ventricular dysfunction, and arthralgia occurred more frequently on the mitoxantrone + prednisone control than the docetaxel q3week arm.

The medical reviewer agrees with most of these analyses. However, for fluid retention, the reviewer is proposing inclusion of the major elements of fluid retention in the labeling. In this case, peripheral edema and weight gain were the most notable elements of fluid retention seen. The reviewer's analysis of fluid retention elements is as follows in Table 28..

Table 28 : Reviewer's Assessment of Fluid Retention

Signs of Fluid Retention	Q3week docetaxel + prednisone N = 332 %		Mitoxantrone + prednisone N = 335 %	
	Any	G 3 / 4	Any	G 3 / 4
Weight Gain	11.4	0.3	3.0	0
Peripheral Edema	19.6	0.6	1.5	0
All	24.4	0.6	4.5	0.3

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Deaths

At the time of the cutoff date for survival analysis (March 24, 2003), 552 of the 997 treated patients had died (55.4%). Of those, 31 died within 30 days of their last study-treatment infusion. By treatment group, a similar number died within 30 days of last treatment: 3.3% for q3week docetaxel, 3.3% for qw docetaxel, and 2.7% for mitoxantrone. Of these most were attributed to malignant disease or other causes. The toxic death rate is presented as 0.3% (1 patient) for q3week docetaxel and 0.6% (2 patients) for mitoxantrone.

The vast majority of deaths occurred more than 30 days after the last infusion of study drug. These occurred more frequently in the mitoxantrone arm (57%) compared to the docetaxel weekly arm (46.1%). Only one death that occurred after 30 days from last infusion was attributed to drug-related toxicity and this was a death on the mitoxantrone arm.

CLINICAL REVIEW

Clinical Review Section

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D. Adequacy of Safety Testing

In addition to 662 HRPC patients who received docetaxel as a component of their participation in TAX327, the safety database also includes thousands of patients in the post-marketing phase worldwide who have received docetaxel alone or in a combination setting for the treatment of advanced NSCLC as well as those receiving docetaxel as a component of therapy for breast cancer or other malignancies.

Exposure on clinical trials and estimated worldwide use based on marketing/sales estimates are provided below for 3 recent time periods:

Table 29 : Exposure on Trials and Worldwide Estimate for Recent Periods

Period	Exposure on Trials	Estimated Worldwide from Marketing/Sales
4/1/01 to 9/31/01	2147	—
10/01/02 to 4/30/02	2341	—
5/01/02 to 9/30/02	3060	—

E. Summary of Critical Safety Findings and Limitations of Data

In summary, the safety profile of q3 week docetaxel + prednisone is generally comparable to mitoxantrone + prednisone, although several adverse events occurred more frequently with docetaxel.. Alopecia, fluid retention (especially peripheral edema and weight gain), sensory neuropathy, allergic reactions, and nail changes occurred more frequently in the q3 week docetaxel + prednisone arm compared to the mitoxantrone + prednisone arm. Anemia, infection, nausea, diarrhea, anorexia, and dyspnea occurred more frequently and with more severity in the q 3 week docetaxel + prednisone arm compared to the mitoxantrone + prednisone arm. Although all grade neutropenia occurred approximately evenly in both arms, grade 3 / 4 neutropenia was more frequent in the docetaxel arm. In contrast, cardiac left ventricular dysfunction and thrombocytopenia occurred less

CLINICAL REVIEW

Clinical Review Section

commonly in the q 3 week docetaxel + prednisone arm compared to the mitoxantrone + prednisone arm.

The medical reviewer agrees with many of the sponsor's conclusions. However, the medical reviewer disagrees with the sponsor's approach to list fluid retention as a general category without detailing the major contributing elements of fluid retention. In this case, these are peripheral edema and weight gain.

VIII. Dosing, Regimen, and Administration Issues

The recommended dose and schedule is as follows:

Docetaxel 75 mg/m² every three weeks as a 1 hour infusion. Prednisone 5 mg orally twice daily is administered continuously.

For prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours, and 1 hour before the docetaxel infusion. This approach is supported by the clinical data presented.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

A gender analysis is not relevant since all patients on study were men.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

1. Age

The sponsor conducted a subgroup analysis of adverse events using the following categories: patients under 65 years of age and patients 65 years of age or older. The number of patients older than 75 years was also noted. Of the 333 patients treated on the q3week docetaxel arm, 209 were 65 years old or older and 68 patients were 75 years of age or older. The following TEAE occurred at rates $\geq 10\%$ higher in patients 65 or older compared to younger patients: anemia (70.7% versus 59.3%), infection (37% versus 24.2%) nail changes (33.7% versus 22.6%), anorexia (20.7% versus 9.7%) and weight loss (15.4% versus 4.8%) respectively.

CLINICAL REVIEW

Clinical Review Section

Reviewer's Comments: The sponsor is proposing the addition of this information, which is appropriate. However, the reviewers do not agree with the proposal to include wording [] since this analysis is considered exploratory.

2. Race/Ethnicity

The majority of patients enrolled onto the trial were caucasian, consisting of 93% of the population in each treatment group. Black, hispanic, asian or other groups consisted of 7 % of the population in each treatment arm. No definitive conclusions can be drawn regarding safety or efficacy differences among these groups due to the small number of non-caucasian patients in the study population.

C. Evaluation of Pediatric Program

Although the sponsor has not conducted any clinical trials of docetaxel in the pediatric population, there are two phase 1 trials of docetaxel in children with refractory solid tumors reported in the medical literature. These were previously described in the sNDA for docetaxel treatment of first-line NSCLC. This are not relevant to the current sNDA, as prostate cancer does not occur in the pediatric population.

X. Conclusions and Recommendations

A. Conclusions

The results of an international, open-label randomized phase 3 trial of combination chemotherapy in patients with hormone refractory prostate cancer were submitted. Patients were randomized to docetaxel every 3 weeks + prednisone, docetaxel weekly + prednisone, or an active control of mitoxantrone + prednisone.

The primary endpoint was overall survival. According to the sponsor's primary analysis, the docetaxel q 3 week schedule plus prednisone demonstrated a statistically significant survival advantage over mitoxantrone plus prednisone, with median survivals of 18.9 versus 16.5 months ($p = 0.0094$). The docetaxel q week plus prednisone arm did not demonstrate an

CLINICAL REVIEW

Clinical Review Section

overall survival advantage over the control arm ($p = 0.36$) The FDA's analysis agreed with these findings.

The safety profile of docetaxel q3week plus prednisone is acceptable in this population with metastatic disease with no available therapy that currently provides a survival benefit.

The finding of an overall survival advantage for the docetaxel q3week + prednisone arm over control in this large, multicenter, global, randomized trial and the safety profile outlined provides, in the opinion of the medical and statistical reviewers, substantial evidence of effectiveness with an acceptable safety profile.

B. Recommendations

The Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA recommends approval of docetaxel (taxotere) in combination with prednisone for the treatment of patients with metastatic hormone-refractory prostate cancer.

The recommended dose of docetaxel when used in combination with prednisone for the treatment of patients with metastatic hormone-refractory prostate cancer is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks plus prednisone given as 5 mg twice a day on a continuous basis.

The previously outlined phase IV commitments which are yet to be fulfilled will be reiterated.

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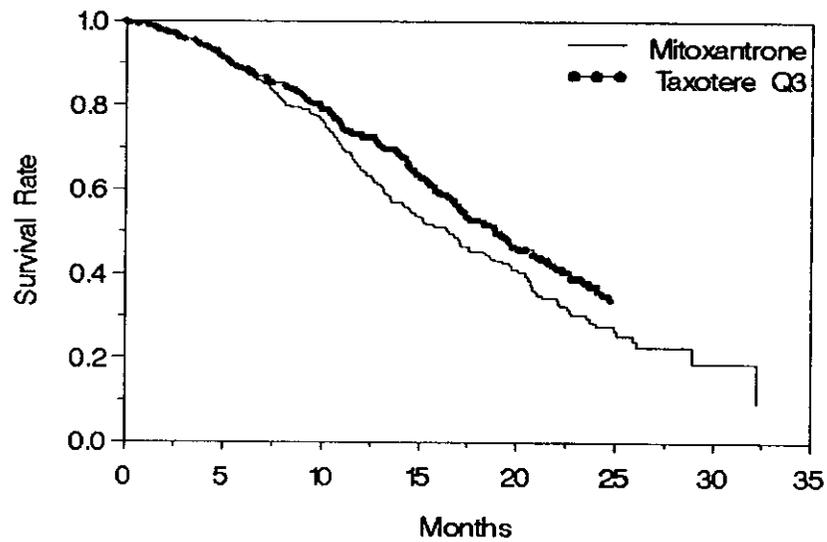
CLINICAL REVIEW

Clinical Review Section

Appendix

Survival Curves for Comparison of Individual Docetaxel Regimens to Mitoxantrone Regimen and Combined Docetaxel Regimens Compared to Mitoxantrone

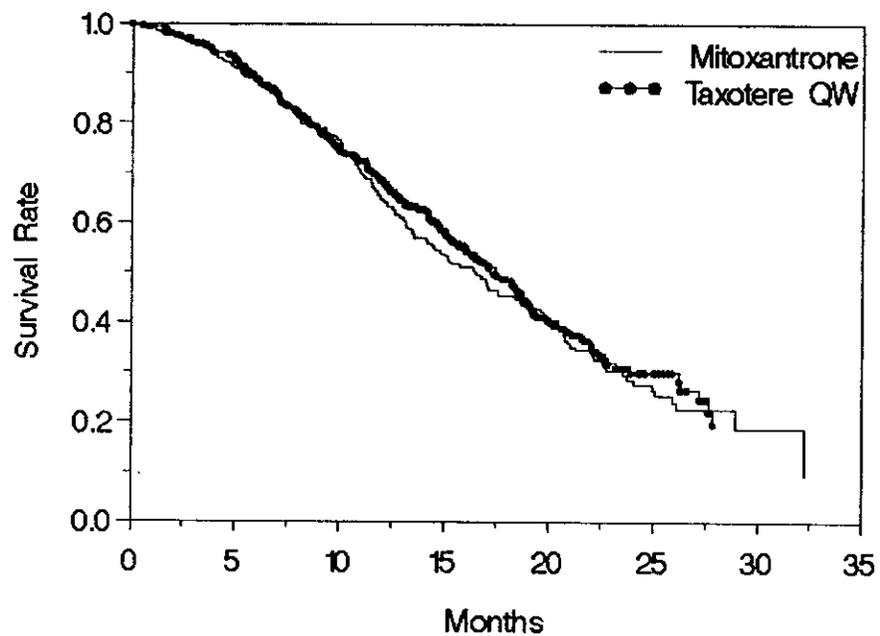
K-M Survival Curves for Study TAX327



CLINICAL REVIEW

Clinical Review Section

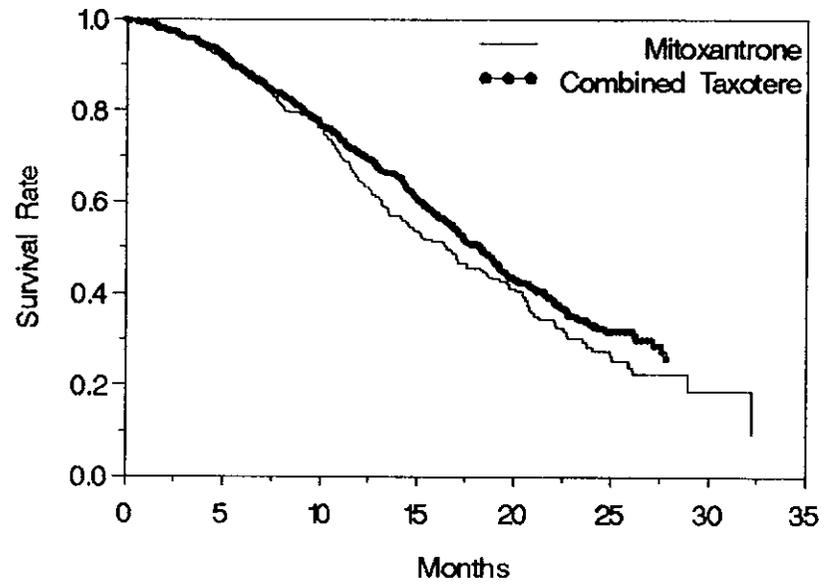
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CLINICAL REVIEW

Clinical Review Section

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