CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203551Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	203551/000
Submission Date:	14 Mar., 2012
Brand Name:	Docetaxel Injection Concentrate™
Generic Name:	Docetaxel
Formulation:	One vial Docetaxel Injection Concentrate: Single use vials 140 mg/7 mL, 80 mg/4 mL and 20mg/mL
OCP Reviewer:	Jeanne Fourie Zirkelbach, PhD
OCP Team Leader:	Qi Liu, PhD
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Actavis Inc.
Submission Type; Code:	Original NDA
Dosing regimen:	IV over 1 hr every 3 weeks. Breast Cancer: 60-100 mg/m^2, Non-small cell lung cancer: 75 mg/m^2, Prostate cancer: 75 mg/m^2, Gastric adenocarcinoma: 75 mg/m^2, Head and Neck Cancer: 75 mg/m^2.
Indication:	Breast cancer, non-small cell lung cancer, hormone refractory prostate cancer and gastric adenocarcinoma, head and neck cancer.

Table of contents

1 Executive Summary 2
- 1.1 Phase IV commitments 2
- 1.2 Regulatory Background 2
- 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings 2
- 1.4 Recommendations 4

2 Detailed Labeling Recommendations 4

1 EXECUTIVE SUMMARY

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Actavis Incorporated submitted an original New Drug Application (NDA 203551/S-000/SDN1) for single vial formulation of docetaxel (Docetaxel Injection Concentrate® 20 mg/mL) for intravenous infusion.

Based on the comparison to the listed drug (Taxotere® Injection Concentrate; single vial formulation; Sanofi-Aventis), Actavis was granted a waiver for the bioequivalence study requirements in accordance with 21 CFR 320.22 (b)1 by the ONDQA.

The current submission includes proposed labeling based on the most recently approved label for the single vial formulation of Taxotere Injection Concentrate® (label revised 9/7/11). The purpose of the current review is to summarize the relevant Clinical Pharmacology labeling recommendations for this 505(b)(2) application.

1.1 PHASE IV COMMITMENTS

None.

1.2 REGULATORY BACKGROUND

- The listed drug that is the basis for this NDA submission is Taxotere Injection Concentrate®, available as single use vials 80 mg/4mL and 20 mg/mL, marketed by Sanofi-Aventis (NDA 020-449;, supplement 54, most recent revision 9/7/11).

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The Actavis product is proposed for use in all of the indications listed for the reference drug product (Taxotere Injection Concentrate®) as follows:

- Breast Cancer: Indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy. Docetaxel in combination with Doxorubicin and Cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.
- Non-Small Cell Lung Cancer: As a single agent Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. In combination with Cisplatin, Docetaxel 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.

- Hormone Refractory Prostate Cancer: In combination with Prednisone, Docetaxel is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.
- Gastric Adenocarcinoma: In combination with Cisplatin and. Fluorouracil for untreated, advanced gastric cancer, including the gastroesophageal junction.
- Squamous cell carcinoma of the head and neck cancer: With cisplatin and fluorouracil for induction treatment of locally advanced cancer.

The supplement describes a single vial formulation of docetaxel (Docetaxel Injection Concentrate; 20 mg/mL - 1 mL, 4 mL and 7 mL) for intravenous infusion. The drug product solution is further diluted either in 0.9% Sodium Chloride Infusion or 5% Glucose Infusion.

The following table, prepared by the reviewer, provides a side-by-side comparision (active and inactive ingredients) of the listed drug (Taxotere Injection Concentrate®) one vial formulation versus the applicant proposed single vial formulation. The proposed drug product contains docetaxel:polysorbate 80 in a ratio of 1:21.2, whereas the ratio for the reference product is 1: 27. The proposed drug product contains two inactive ingredients not found in the listed drug, these are a (b)(4) for docetaxel (Povidone (Kollidon 12PF)), and the (b)(4) citric acid.

Table 1: Comparison of active and inactive ingredients in the listed drug (Taxotere Injection Concentrate®) single vial formulation and the applicant's proposed Docetaxel Injection Concentrate single vial formulation.

Ingredients	Actavis Formulation	Actavis Formulation	Actavis Formulation	Actavis Formulation	Taxotere Injection Concentrate®
		Quantity (mg/vial)			
	Quantity per mL (in mg)	20 mg/mL	80 mg/4mL	140 mg/7mL	Quantity per mL (in mg)
Docetaxel	20.0	20.0	80.0	140.0	20.0
Anhydrous Citric [USP]	6.0	6.0	24.0	42.0	Not present
Povidone (Kollidon 12 PF)	100.0	100.0	400.0	700.0	Not present
Polysorbate 80 [USNF]	424.0	424.0	1696.0	2968.0	540.0
(b)(4) alcohol [USP]	To 0.95 g/1.0 mL	To 0.95 g/1.0 mL	To 0.95 g/1.0 mL	To 0.95 g/1.0 mL	395.0

Note: The density of the solution (applicant's product) is 0.950 g/mL (b)(4)

1.4 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 203551 (000). This submission is considered acceptable from a clinical pharmacology perspective.

Labeling Recommendations

Please refer to Section 2 - Detailed Labeling Recommendations.

Signatures:

Reviewer: Jeanne Fourie Zirkelbach, PhD Division of Clinical Pharmacology 5	Team Leader: Qi Liu, PhD Division of Clinical Pharmacology 5

Cc: DDOP: CSO - R Venugopal; MTL - V Maher; MO - P Kluetz,
DCP-5: Reviewers - J Fourie Zirkelbach,
DDD - B Booth
DD - A Rahman

2 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are shown in track change format below. The sponsor's proposed changes from the most recent Taxotere label are shown in <u>underlined</u> text. FDA proposed changes are shown in blue text or in yellow highlight.

Listed Drug Label	Proposed Label for the Actavis Docetaxel Injection Concentrate	Reviewer's Comments
DRUG INTERACTIONS---------- • Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism. (7)	**DRUG INTERACTIONS**---------- • Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism. (7)	No change.
FULL PRESCRIBING INFORMATION **2. DOSAGE AND ADMINISTRATION** **2.7 Dosage Adjustments During Treatment** Combination Therapy with Strong CYP3A4 inhibitors: Avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir,	**FULL PRESCRIBING INFORMATION** **2. DOSAGE AND ADMINISTRATION** **2.7 Dosage Adjustments During Treatment** Combination Therapy with Strong CYP3A4 inhibitors: Avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir,	The reviewer deleted a period (see yellow highlight) in this section.

telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require co-administration of a strong CYP3A4 inhibitor. *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.	telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require co-administration of a strong CYP3A4 inhibitor. *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.	
5.2 Hepatic Impairment Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with TAXOTERE *[see Boxed Warning, Use in Specific Populations (8.6), Clinical studies (14)]*.	**5.2 Hepatic Impairment** **5.2 Hepatic Impairment** Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with Docetaxel Injection Concentrate *[see Boxed Warning, Use in Specific Populations (8.6), Clinical studies (14)]*.	The applicant changed TAXOTERE to docetaxel injection concentrate. The reviewer further capitalized the full product name "Docetaxel Injection Concentrate".
7. DRUG INTERACTIONS Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. *In vivo* studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of TAXOTERE and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients	**7. DRUG INTERACTIONS** Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. *In vivo* studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of Docetaxel Injection Concentrate and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel Injection Concentrate, close monitoring for toxicity and a Docetaxel Injection	The applicant changed TAXOTERE to Docetaxel injection concentrate. The reviewer further capatalized the full product name to "Docetaxel Injection Concentrate".

receiving treatment with TAXOTERE, close monitoring for toxicity and a TAXOTERE dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.	Concentrate dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.	
8.4 Pediatric Use Pharmacokinetics: Pharmacokinetic parameters for docetaxel were determined in 2 pediatric solid tumor trials. Following docetaxel administration at 55 mg/m^2 to 235 mg/m^2 in a 1-hour intravenous infusion every 3 weeks in 25 patients aged 1 to 20 years (median 11 years), docetaxel clearance was 17.3±10.9 L/h/m^2. Docetaxel was administered in combination with cisplatin and 5-fluorouracil (TCF), at dose levels of 75 mg/m^2 in a 1-hour intravenous infusion day 1 in 28 patients aged 10 to 21 years (median 16 years, 17 patients were older than 16). Docetaxel clearance was 17.9±8.75 L/h/m^2, corresponding to an AUC of 4.20±2.57 µg.h/mL. In summary, the body surface area adjusted clearance of docetaxel monotherapy and TCF combination in children were comparable to those in adults *[see Clinical Pharmacology (12.3)]*.	Deleted Section.	Pediatric Use Section PK data were appropriately deleted by the applicant in this 505(b)(2) applications.
	8.6 Hepatic Impairment Patients with bilirubin >ULN should not receive Docetaxel	Throughout Section 8.6, TAXOTERE is changed by the Applicant to Docetaxel injecton concentrate. The FDA reviewer has capatalized the full product

	Injection Concentrate. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive Docetaxel Injection Concentrate *[see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.	name to "Docetaxel Injection Concentrate".
12.3 Human Pharmacokinetics Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m^2. Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. *In vitro* studies showed that docetaxel is about 94% protein bound, mainly to α$_1$-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the	**12.3 Human Pharmacokinetics** **Absorption:** The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m^2. **Distribution:** The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. *In vitro* studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel. **Metabolism:** *In vitro* drug interaction studies revealed that	

protein binding of docetaxel. Metabolism: *In vitro* drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4 *[see Drug Interactions (7)]*. Elimination: A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug. Effect of Age: A population pharmacokinetic analysis was carried out after TAXOTERE treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age. Effect of Gender: The population pharmacokinetics analysis	docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4 *[see Drug Interactions (7)]*. **Elimination:** A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug. **Effect of Age:** A population pharmacokinetic analysis was carried out after docetaxel ~~injection concentrate~~ treatment of 535 patients dosed at 100 mg/m^2. 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. **Effect of Gender:** The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel. **Hepatic Impairment:** The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with	The FDA reviewer has changed "docetaxel injection concentrate" to "docetaxel" in the place where the product was evaluated in the clinical trial by the innovator.

described above also indicated that gender did not influence the pharmacokinetics of docetaxel. Hepatic Impairment: The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with TAXOTERE. Patients with severe hepatic impairment have not been studied. *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]* Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/m^2 to 90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations. Effect of Ketoconazole: The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were	alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with Docetaxel Injection Concentrate. Patients with severe hepatic impairment have not been studied. *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*. **Effect of Race:** Mean total body clearance for Japanese patients dosed at the range of 10 mg/m^2 to 90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations. **Effect of Ketoconazole:** The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were randomized to receive either docetaxel (100 mg/m² intravenous) alone or docetaxel (10 mg/m² intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was ~~co-administration~~ co-administered with ketoconazole *[see Dosage and Administration (2.7)*	The FDA reviewer has capatalized the full product name, "Docetaxel Injection Concentrate". The reviewer deleted a period (see yellow highlight) in this section and added a period after the reference (see yellow highlight) The reviwer changed "co-administration" to 'co-administered' as this sentence was not gramatically correct in the label for the innovator product. The reviewer changed "Drug-Drug Interactions" to "Drug Interactions", as this is the correct Section title reference.

randomized to receive either docetaxel (100 mg/m² intravenous) alone or docetaxel (10 mg/m² intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was co-administration with ketoconazole *[see Dosage and Administration (2.7) and Drug-Drug Interactions (7)]*. • Effect of Combination Therapies: Dexamethasone: Docetaxel total body clearance was not modified by pretreatment with dexamethasone. • Cisplatin: Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone. • Cisplatin and Fluorouracil: The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug. • Prednisone: A population	*and Drug-~~Drug~~ Interactions (7)]*. **Effect of Combination Therapies:** • **Dexamethasone:** Docetaxel total body clearance was not modified by pretreatment with dexamethasone. • **Cisplatin:** Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone. • **Cisplatin and Fluorouracil:** The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug. • **Prednisone:** A population pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone. • **Cyclophosphamide and Doxorubicin:** A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m²), doxorubicin (50	

pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone. • Cyclophosphamide and Doxorubicin: A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.	mg/m²), and cyclophosphamide (500 mg/m²) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.	

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/s/

JEANNE FOURIE ZIRKELBACH
11/26/2012

QI LIU
11/28/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203551	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	March 14, 2012		
Division:	Division of Oncology Products 1	**Team Leader:** Angelica Dorantes, PhD	
Applicant:	Actavis Inc.	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	TBD	**Date Assigned:**	March 19, 2012
Established Name:	Docetaxel	**Date of Review:**	November 24, 2012
Indication:	Breast Cancer; Non-Small Cell Lung Cancer; Prostate Cancer; Gastric Adenocarcinoma; Head and Neck Cancer	**Type of Submission:** Original New Drug Application – 505(b)(2)	
Formulation/ strengths	Concentrated Solution for Infusion /20 mg/mL		
Route of Administration	IV infusion		
Type of Review:	Biowaiver Request		

SUBMISSION:

The proposed drug product is a sterile solution for IV injection containing docetaxel as the active ingredient. Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. This application is an electronic NDA, filed as a 505(b)(2) application, with Taxotere (NDA 20449) as the reference listed drug (RLD). The proposed docetaxel injection (containing 20 mg docetaxel /mL) is a single use vial formulation (1, 4, or 7 mL) that is ready for immediate dilution and administration (unlike the 2-vial reference listed drug (RLD) that requires a pre-mix step before dilution). The difference between the proposed product and the RLD product, is in the identity and amounts of the inactive excipients as well as the active pharmaceutical ingredient, which is docetaxel anhydrous, instead of docetaxel trihydrate used in Taxotere. Note that Taxotere is also available as a 1-vial formulation, which was approved under supplement S-054 to NDA 20449 on 8/2/2010. Since the 1-vial RLD was approved after the development of the proposed drug product was completed, the Applicant used the 2-vial Taxotere product as the reference product. In addition, the osmolarity and pH of the proposed docetaxel solution is different than that of the (2-vial) Taxotere solution.

BIOPHARMACEUTICS INFORMATION:

In this submission, the Applicant is requesting a waiver of the requirement to submit *in vivo* bioequivalence data as allowed under 21 CFR 320.22(b)(1)(i). The applicant claims that the bioequivalence of the proposed drug product and the RLD is self-evident. In addition, the Applicant claims that the proposed drug product has undergone extensive physico-chemical characterization in order to support the comparability with the (2-vial) reference product,

Reference ID: 3220846

Taxotere®.

ASSESSMENT OF BIOWAIVER REQUEST:

The compositions for the formulations of the proposed drug products are as follows:

Components	Product: Docetaxel 20 mg/mL		
	20 mg/1mL	80 mg/4mL	140 mg/7mL
Docetaxel, anhydroyus	20.0 mg	80.0 mg	140.0 mg
Citric acid anhydrous	6.0 mg	24.0 mg	42.0 mg
Ethanol (b)(4)	400.0 mg	1600.0 mg	2800.0 mg
Povidone (Kollidon 12PF)	100.0 mg	400.0 mg	700.0 mg
Polysorbate 80 (b)(4)	424.0 mg	1696.0 mg	2968.0 mg
(b)(4)	+	+	+
Colourless glass vial, (b)(4)	5 mL	8 mL	11 mL
Rubber closure	(b)(4)		
Metallic cap with (b)(4) disk	+	+	+

Note that the active pharmaceutical ingredient in the proposed drug product is docetaxel (anhydrous), instead of docetaxel (trihydrate) used in Taxotere. Both the proposed Docetaxel Injection 20 mg/mL and Taxotere are diluted to a 0.74 mg/mL docetaxel (as anhydrous) admixture infusion solution, prior to use.

Comparison of the (2-vial) RLD and proposed drug product admixtures (diluted infusion solutions):

Components	Docetaxel 20 mg/mL (mg/mL)	Taxotere® 40mg/mL (mg/mL)
Docetaxel anhydrous	0.74	0.74
Ethanol (b)(4)	14.80	7.22
Citric acid	0.22	-
Polyvinylpyrrolidone (Kollidon 12 PF)	3.70	-
Polysorbate 80 (b)(4)	15.69	19.24

Both the proposed Docetaxel Injection and Taxotere are micelle-containing solutions, and the aqueous solubility of the active ingredient in both the proposed Docetaxel Injection and Taxotere is largely maintained by (b)(4) in a micelle system, when diluted as an admixture solution prior to intravenous use. A series of comparative studies have been performed to demonstrate that the physical characteristics of the micelles and the solubility behaviors of the active ingredient in the solutions for intravenous use are comparable. The NDA contained data showing that upon dilution in normal saline and 5% dextrose to the same docetaxel concentration, the proposed drug product and (2-vial) Taxotere® form micelles that are monodisperse and comparable in size.

According to CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following criteria:

Reference ID: 3220846

It is a parenteral solution intended solely for administration by injection, and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application. The proposed drug product is a parenteral solution for administration by injection, and the proposed drug product has the same concentration of active ingredient (docetaxel), and has the same dosage form, route of administration and indication as the RLD. However, the inactive ingredients of the proposed product and the reference product are different.

The osmolarity values of the (diluted) proposed and (2-vial) RLD 0.74 mg/mL docetaxel infusion solutions were measured by the Applicant and reported as follows:

Sample	Osmol/L
Docetaxel 20 mg/1 mL (batch DD08001A) in NaCl 0.9%	0.633
Docetaxel 80mg/4mL (batch DE08001A) in NaCl 0.9%	0.658
Docetaxel 140 mg/7 mL (batch DF08001A) in NaCl 0.9%	0.662
Docetaxel 80mg/4 mL batch DE 09001A in NaCl 0.9%	0.597
Docetaxel 20 mg/1 mL (batch DD08001A) in Glucose 5%	0.671
Docetaxel 80mg/4mL (batch DE08001A) in Glucose 5%	0.688
Docetaxel 140 mg/7 mL (batch DF08001A) in Glucose 5%	0.687
Docetaxel 80mg/4 mL batch DE 09001 in Glucose 5%	0.609
Taxotere 80 mg (Batch D6C285) in NaCl 0.9%	0.325
Taxotere 80 mg (Batch D6C285) in Glucose 5%	0.327
NaCl 0.9% (Braun)	0.297
Glucose 5% (Braun)	0.305

Note: Taxotere in the above table was a 2-vial presentation.

The difference in osmolarity between the proposed and RLD products was a concern to the clinical reviewer; therefore, in an IR sent on 11/2/12, the Applicant was asked to provide an analysis of the osmolarity and components of the 1-vial U.S. Taxotere formulation. On 11/12/12, the Applicant responded to the IR and provided the following information:

Osmolarity of the drug products prior to addition to the infusion solution

Components of drug product	US Taxotere 1-vial 20 mg/mL concentrate			Docetaxel Actavis 20 mg/mL concentrate		
	g/L	Molecular mass	mOsm/L	g/L	Molecular mass	mOsm/L
Docetaxel	20	807.9	24.8	20	807.9	24.8
Citric acid anhydrous*	-	-	-	6	192.123	31.2
Ethanol (b)(4)	395	46.07	8573.9	400	46.07	8682.4
Polyvinylpyrrolidone (Kollidon 12 PF)	-	-	-	100	2000-3000	50.0
Polysorbate 80	540	1310	412.2	424	1310	323.7
Osmolarity			**9010.9**			**9112.1**

**not listed as component in US Product Information*

***The US Taxotere osmolarity value was calculated not measured.*

Reference ID: 3220846

Osmolarity of the drug products after addition to the infusion solution 0.74 mg/mL in glucose 5%:

Components of drug product	US Taxotere 1-vial 0.74 mg/mL in infusion solutions		Docetaxel Actavis 20 mg/mL 0.74 mg/mL in infusion solutions	
	g/L	mOsm/L	g/L	mOsm/L
Docetaxel	0.74	0.9	0.74	0.91
Ethanol (b)(4)	14.62	317.3	14.80	321.25
Citric acid anhydrous*	-	-	0.222	1.16
Polysorbate 80	19.98	15.3	15.69	11.98
Polyvinylpyrrolidone (Kollidon 12 PF)	-	-	3.70	1.9
Glucose 5%	50.0/180.16	277.5	50.0	277.53
Osmolarity		**611.0**		**614.7**

**not listed as component in US Product Information*

*****The US Taxotere osmolarity value was calculated not measured.***

Osmolarity of the drug products after addition to the infusion solution 0.74 mg/mL in NaCl 0.9%:

Components of the drug product	US Taxotere 1-vial 0.74 mg/mL in infusion solutions		Docetaxel Actavis 20 mg/mL 0.74 mg/mL in infusion solutions	
	g/L	mOsm/L	g/L	mOsm/L
Docetaxel anhydrous	0.74	0.9	0.74	0.91
Ethanol (b)(4)	14.62	317.3	14.80	321.25
Citric acid anhydrous*	-	-	0.222	1.16
Polysorbate 80	19.98	15.3	15.69	11.98
Polyvinylpyrrolidone (Kollidon 12 PF)	-	-	3.70	1.90
Sodium chloride 0.9%	9.0/58.44	308	9.0	308.0
Osmolarity		**641.5**		**645.2**

**not listed as component in US Product Information*

*****The US Taxotere osmolarity value was calculated not measured.***

The Applicant stated that the osmolarity values are driven by the amount of ethanol and the infusion solution content (glucose 5% or NaCl 0.9%).

The pH of the proposed and RLD undiluted drug products are:

Drug product		Results					
		Docetaxel 20 mg/1mL	Docetaxel 80 mg/4 mL	Docetaxel 140 mg/7 mL	Taxotere 20mg/0.5mL	Taxotere 80mg/2mL	Taxotere 80mg/2mL
Test	Acceptance Criteria	Batch: DD 08001	Batch: DE 08001	Batch: DF 08001	Batch D8D077	Batch: D8C415	Batch: D8C836
pH	(b)(4)	3.0	3.0	3.1	3.5	3.53	3.62

The pH values of the diluted proposed and diluted RLD (0.74 mg/mL) solutions are not provided.

Reference ID: 3220846

The difference in pH is not expected to affect the bioavailability of docetaxel in the proposed drug product.

REVIEWER'S COMMENTS:

Even though the 1-vial proposed drug product in the infusion solution has double the osmolarity than that of the 2-vial Taxotere RLD, the osmolarity is comparable to the 1-vial Taxotere RLD. Therefore, we consider that the information provided by the Applicant adequately addresses our concerns and it is expected that the difference in osmolarity will not affect the bioavailability and safety of the proposed docetaxel product.

Although, the CFR requires that the active and inactive ingredients for the test product are the same as the reference product, the difference in the inactive ingredients (pH, ethanol and propylene glycol) are not expected to impact the amount of drug delivered to the site of action, since this is an injectable dosage form administered as an IV infusion. Therefore, we consider that the in vivo BA/BE of the proposed Docetaxel Injection is self-evident, and the Applicant's request for a biowaiver for their proposed Docetaxel product is acceptable and the biowaiver is granted.

RECOMMENDATION:

A waiver of the in vivo bioequivalence study requirement is granted. From the Biopharmaceutics perspective, NDA 203551 for Docetaxel Solution for Injection (20 mg/mL) is recommended for APPROVAL.

Signature	**Signature**
Elsbeth Chikhale, Ph.D.	Angelica Dorantes, Ph.D.
Biopharmaceutics Reviewer	Biopharmaceutics Team Leader
Office of New Drug Quality Assessment	Office of New Drug Quality Assessment

cc. DARRTS/NDA 203551, R. Lostritto

Reference ID: 3220846

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/s/

ELSBETH G CHIKHALE
11/24/2012

ANGELICA DORANTES
11/24/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	203-551
Submission Date	3/14/12
Product name, generic name of the active	Docetaxel Injection Concentrate
Dosage form and strength	Injection – 20 mg/mL
Applicant	Actavis Inc.
Clinical Division	Division of Oncology Product
Type of Submission	Original NDA – 505(b)(2)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Supervisory Lead	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		x	NA
2.	Is the dissolution test part of the DP specifications?		x	NA
3.	Does the application contain the dissolution method development report?		x	NA
4.	Is there a validation package for the analytical method and dissolution methodology?		x	NA
5.	Does the application include a biowaiver request?	x		The Original NDA did not include a biowaiver request. However, The Applicant submitted a request for a BE waiver in Amendment Serial-003 dated 4/26/2012
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	
8.	Is information on mixing the product with foods or liquids included?		x	Reference is made to the reference product
9.	Is there any in *vivo* BA or BE information in the submission?		x	

Reference ID: 3127498

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
10.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
11.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	Biopharmaceutics does not have any comments to be included in the 74-day letter

{See appended electronic signature page}

Elsbeth Chikhale, Ph.D. — 5/7/12
Biopharmaceutics Reviewer — Date
Office of New Drug Quality Assessment

{See appended electronic signature page}

Angelica Dorantes, Ph.D. — 5/7/12
Biopharmaceutics Supervisory Lead (acting) — Date
Office of New Drug Quality Assessment

Reference ID: 3127498

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/s/

ELSBETH G CHIKHALE
05/07/2012

ANGELICA DORANTES
05/09/2012