

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203551Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 203,551
Supporting document/s: SDN 000
Applicant's letter date: March 14, 2012
CDER stamp date: March 14, 2012
Product: Docetaxel Injection Concentrate
Indication: Refer to the approved labeling for Reference Listed Drug (TAXOTERE®)
Applicant: Actavis, Inc.
Review Division: Division of Hematology Oncology Toxicology
(for Division of Oncology Products 1)
Reviewer: Wei Chen, Ph.D.
Supervisor/Team Leader: Todd Palmby, Ph.D.
Division Director: John Leighton, Ph.D., D.A.B.T. (acting)
(Robert Justice, M.D., M.S.)
Project Manager: Rajesh Venugopal

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203,551 are owned by Actavis, Inc. Any information or data necessary for approval of NDA 203,551 that Actavis, Inc. does not own constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203,551.

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	3
1.1	INTRODUCTION	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	4
1.3	RECOMMENDATIONS	5
2	DRUG INFORMATION	5
2.1	DRUG	5
2.2	RELEVANT INDS, NDAs, BLAs AND DMFs:.....	6
2.3	DRUG FORMULATION	6
2.4	COMMENTS ON NOVEL EXCIPIENTS:	6
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN:	6
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	6
2	STUDIES SUBMITTED.....	8
4	PHARMACOLOGY.....	9
4.1	PRIMARY PHARMACOLOGY	9
4.3	SAFETY PHARMACOLOGY.....	13
5	PHARMACOKINETICS/ADME/TOXICOKINETICS	13
6	GENERAL TOXICOLOGY.....	20
6.1	SINGLE-DOSE TOXICITY	20
6.2	REPEAT-DOSE TOXICITY	20
7	GENETIC TOXICOLOGY	35
8	CARCINOGENICITY.....	35
9	REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY	35
10	SPECIAL TOXICOLOGY STUDIES	35
12	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	35
	CONCLUSIONS	37

1 Executive Summary

1.1 Introduction

Docetaxel is an antineoplastic agent belonging to the taxoid family, and it acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel, administered via an intravenous (IV) infusion, was approved in the United States (US) for the treatment of various cancer types. Current approved dosage form of docetaxel (40 mg/mL, Taxotere®) is a two-vial formulation (Injection Concentrate and Diluent). Taxotere Injection Concentrate requires two dilutions prior to administration, which include an initial dilution from the Injection Concentrate, and a final dilution for infusion. The Applicant for the current NDA, Actavis, has developed a new formulation of Docetaxel, which is a 20 mg/mL solution for infusion (20 mg/1 mL; 80 mg/4 mL; 140 mg/7 mL). The following table (copied from the Applicant's submission) shows the compositions of the new formulation of Docetaxel 20 mg/mL and Taxotere®.

Components of the drug product	Docetaxel concentrate	
	Docetaxel 20 mg/ml (mg/ml)	Taxotere® (mg/ml)
Docetaxel anhydrous	20	40
Ethanol (b)(4)	400	-
Citric acid anhydrous	6	-
Polyvinylpyrrolidone (Kollidon 12 PF)	100	-
Polysorbate 80 (b)(4)	424	1040
Components of the drug solvent	Docetaxel concentrate	
	Docetaxel 20 mg/ml (mg/ml)	Taxotere® (mg/ml)
Ethanol (b)(4)	-	130 mg
Water q.s.ad.	-	1 ml

The Actavis formulation, Docetaxel 20 mg/mL, has a comparable composition to the reference listed drug (RLD), Taxotere®. The main differences consist in the addition of the (b)(4) citric acid and the (b)(4) Kollidon 12 PF® (Povidone k12). Nonclinical studies were conducted to compare efficacy, protein binding and toxicity between Docetaxel 20 mg/mL and Taxotere®. The study results from the conducted nonclinical studies together with some publically available information on nonclinical properties of docetaxel were submitted in support of this NDA for the same indications

as Taxotere®. The studies cited in this review consist primarily of original research conducted by the applicant.

1.2 Brief Discussion of Nonclinical Findings

A comparative toxicity study including toxicokinetic evaluation was conducted in rats with Docetaxel Injection Concentrate (20 mg/mL) and Taxotere®, consistent with the clinical route of administration. The toxicity of Kollidon 12 PF using the intravenous route of administration was also assessed in a separate toxicity study in rats. These two studies were conducted in compliance with Good Laboratory Practice regulations. Other nonclinical studies including pharmacology and *in vitro* protein binding studies have been conducted and the reports were submitted with this NDA.

Pharmacology

Comparison of the anti-cancer activities of Docetaxel Injection Concentrate (20 mg/mL) and Taxotere® were investigated in athymic (nu/nu) male mice with PC-3 human prostate xenografts and in athymic (nu/nu) female mice with MX-1 human mammary carcinoma xenografts. Treatment with Docetaxel Injection Concentrate (20 mg/mL) and Taxotere® at 20 mg/kg resulted in similar activity against both the MX-1 and PC-3 cells.

Pharmacokinetics

Absorption: Comparative toxicokinetics were analyzed as a part of the comparative rat study with Docetaxel Injection Concentrate (20 mg/mL) and Taxotere®. The study results demonstrated that there were no consistent differences in peak levels (C_{max}) or the systemic exposure (AUC) of docetaxel following dosing with either Docetaxel Injection Concentrate (20 mg/mL) or Taxotere®.

Distribution-plasma protein binding: The effects of the Docetaxel Injection Concentrate (20 mg/mL) and Taxotere® formulations on the degree of protein binding of docetaxel were studied *in vitro* with rat, dog and human plasma. The extent of binding of docetaxel to proteins in rat, dog, and human plasma was essentially comparable between the two formulations of docetaxel. Protein binding in plasma ranged between 94% and 98% across the three species.

General toxicology

Comparative rat study with Docetaxel 20 mg/ml and Taxotere®: Rats were given Docetaxel Injection Concentrate (20 mg/mL) or Taxotere® at 0, 2.5, 5.0 and 10 mg/kg (corresponding to 0, 15, 30 and 60 mg/m²) docetaxel active ingredient. There were no significant differences in the toxicological or toxicokinetic profiles following 2 intravenous infusions of either Docetaxel Injection Concentrate (20 mg/mL) or Taxotere® with a 3 week interval between dosing. The observed toxicities induced by either test article were consistent with the known toxicities of the active chemical entity, docetaxel.

Toxicology study with inactive ingredient: A general toxicology study with Kollidon 12 PF showed that intravenous administration of Kollidon 12 PF was well tolerated in rats at doses up to 837 mg/kg/day, 10 fold the human equivalent dose of povidone present in Docetaxel Injection Concentrate (20 mg/mL). Treatment-related changes were

observed at the injection sites (perivascular fibroplasia in males and females and tendon fibroplasia and tendonitis in males only) and in the kidneys (vacuolated tubular epithelium). The reversibility of the observed toxicities was not assessed in the study.

1.3 Recommendations

1.3.1 Approvability

Recommending approval. The nonclinical studies submitted to this NDA adequately support the safety of Docetaxel Injection Concentrate (20 mg/mL) administered by intravenous route for the indications approved for Taxotere®.

1.3.2 Additional Nonclinical Recommendations

Additional nonclinical studies are not needed at this time.

1.3.3 Labeling

No changes in nonclinical section of the label are needed with the formulation change of Docetaxel Injection Concentrate (20 mg/mL); therefore, a separate labeling review is not deemed necessary.

2 Drug Information

2.1 Drug

CAS Registry Number: 114977-28-5

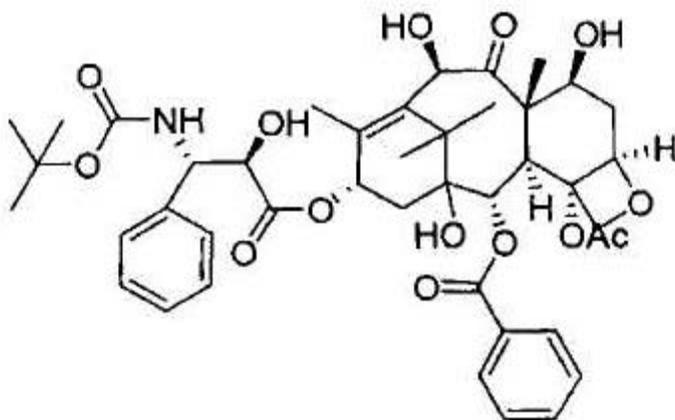
Generic Name: Docetaxel

Code Name: SPT1141

Chemical Name: - (2R, 3S)-N-Carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5beta, 20-epoxy- 1,2alpha,4,7beta, 10beta, 13alpha hexahydroxytax-11-en-9-one 4-acetate 2-benzoate

Molecular Formula/Molecular Weight: C₄₃H₅₃NO₁₄ / 807.88

Structure or Biochemical Description



Pharmacologic Class: microtubule inhibitor

Mechanism of action: 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.

2.2 Relevant INDs, NDAs, BLAs and DMFs:

NDA 020449 (Taxotere)

2.3 Drug Formulation: solution for infusion

Composition of vials

Docetaxel concentrate (20 mg/mL, 80 mg/4 mL, 140 mg/7 mL)	
Docetaxel anhydrous	20 mg/mL
Ethanol (b)(4)	400 mg/mL
Citric acid*	6 mg/mL
Polyvinylpyrrolidone (Kollidon 12 PF)*	100 mg/mL
Polysorbate 80 (b)(4)	424 mg/mL

Composition of solution for infusion

Docetaxel 0.74 mg/mL in infusion solution	
Docetaxel anhydrous	0.74 mg/mL
Ethanol (b)(4)	14.80 mg/mL
Citric acid*	0.22 mg/mL
Polyvinylpyrrolidone (Kollidon 12 PF)*	3.70 mg/mL
Polysorbate 80 (b)(4)	15.69 mg/mL

*RLD (Taxotere[®]) does not contain the (b)(4) citric acid and the (b)(4) Kollidon 12 PF[®] (Povidone).

2.4 Comments on Novel Excipients:

Kollidon 12 PF is included as an excipient in this formulation of docetaxel. Based on the Sponsor's response to the information request by FDA (December 5, 2012), Kollidon 12 PF has been used as an inactive ingredient in many FDA approved drugs at similar or higher levels via oral and intravenous administration.

2.5 Comments on Impurities/Degradants of Concern:

Pharm/Tox input was requested by the CMC review team regarding the potential genotoxic impurity RRT 1.12, and extractables from the container closure system. From a pharm/tox perspective, there is no safety concern on these impurities/extractables at the proposed exposure levels. See the CMC review by Dr. Xiaohong Chen for more detail information.

2.6 Proposed Clinical Population and Dosing Regimen

Docetaxel injection should be administered intravenously over 1 hour every 3 weeks.

- Breast Cancer (BC) locally advanced or metastatic: 60 mg/m² to 100 mg/m² single agent

- **BC adjuvant:** 75 mg/m² administered 1 hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks for 6 cycles
- **Non-Small Cell Lung Cancer (NSCLC):** after platinum therapy failure: 75 mg/m² single agent
- **NSCLC:** chemotherapy-naive: 75 mg/m² followed by cisplatin 75 mg/m²
- **Hormone Refractory Prostate Cancer (HRPC):** 75 mg/m² with 5 mg prednisone twice a day continuously
- **Gastric Adenocarcinoma (GC):** 75 mg/m² followed by cisplatin 75 mg/m² (both on day 1 only) followed by fluorouracil 750 mg/m² per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion
- **Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN):** 75 mg/m² followed by cisplatin 75 mg/m² IV (day 1), followed by fluorouracil 750 mg/m² per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion; for 4 cycles
- **SCCHN:** 75 mg/m² followed by cisplatin 100 mg/m² IV (day 1), followed by fluorouracil 1000 mg/m² per day as a 24-hr IV (days 1-4); for 3 cycles

2 Studies Submitted

Studies Reviewed

Toxicology studies

Repeat dose

	Title	Study no.	Folder/file name
1	Cyclical Intravenous (Infusion) Comparative Study in the Rat	DVC0002	M4.2.3.2
2	Repeat Dose Cyclical Intravenous Infusion Study in the Rat	DVC0016	M4.2.3.2

Studies summarized, but not reviewed

Pharmacology

	Title	Study no.	Folder/file name
1	Efficacy Evaluation of Docetaxel Actavis and Taxotere® Against MX-1 Human Mammary Carcinoma Xenografts	ACTA200801R4	M4.2.1.1
2	Efficacy Evaluation of Docetaxel Actavis and Taxotere® Against PC-3 Human Prostate Carcinoma Xenografts	ACTA200802R4	M4.2.1.1

ADME

	Title	Study no.	Folder/file name
1	Comparative Determination of the Effect of Formulation on the Plasma Protein Binding of Docetaxel Actavis and Taxotere® in Rat, Dog, and Human Plasma	DVC0007	M4.2.2.2

4 Pharmacology

4.1 Primary Pharmacology

In vivo xenograft models were used to determine the anti-tumor activity of the study drug (Docetaxel Injection Concentrate (20 mg/mL)) compared to the RLD (Taxotere®).

These studies were not GLP compliant. The studies were conducted by (b)(4). The following information was summarized by the Applicant. Plasma exposures for the tested drugs and treatment related toxicities (body weight, limited pathology evaluation) were also evaluated in these studies, but these results are not captured in this review.

Efficacy Evaluation of Docetaxel Actavis and Taxotere® Against MX-1 Human Mammary Carcinoma Xenografts

Summary: Administration of Docetaxel Injection Concentrate (20 mg/mL) at 20 mg/kg resulted in similar anti-tumor activity against MX-1 human mammary carcinoma as compared to the anti-tumor activity of Taxotere® administered at the same dose level and frequency.

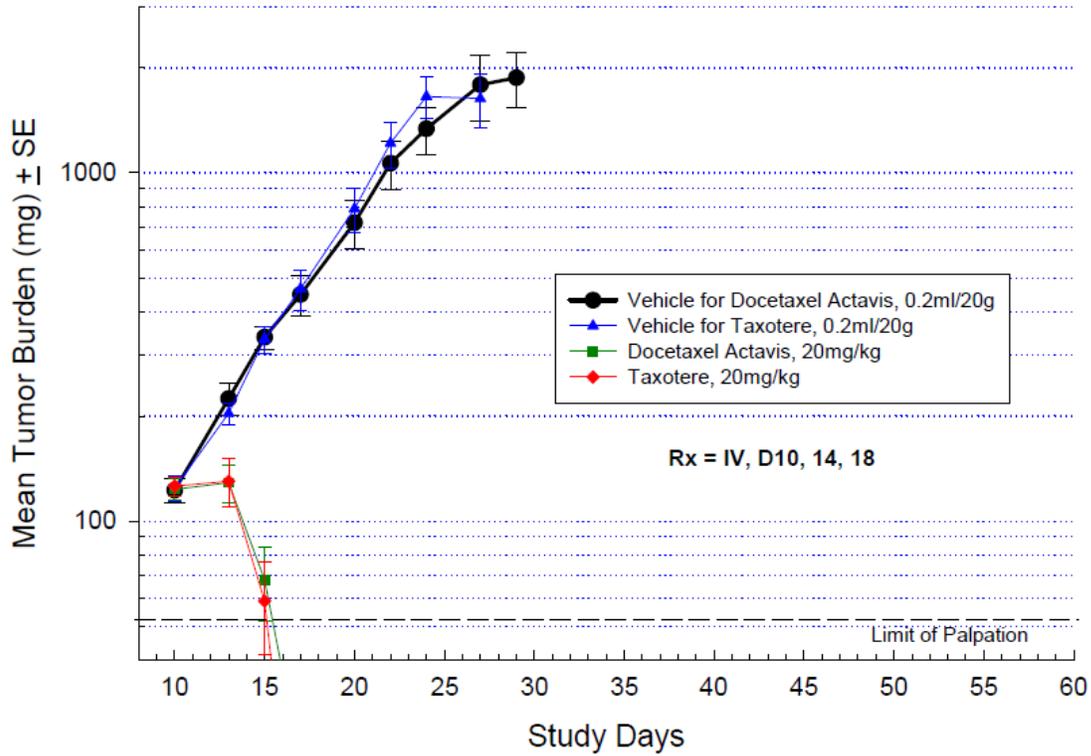
Method: Female athymic mice (nu/nu) were implanted subcutaneously on Day 0 with 30 to 60 mg MX-1 human mammary carcinoma tumor fragments. All animals were dosed with Docetaxel Injection Concentrate (20 mg/mL) or Taxotere® at 20 mg/kg on Day 10. Tumor measurements were recorded three times weekly. Tumor burden (mg) was estimated from caliper measurements by the formula for the volume of a prolate ellipsoid assuming unit density as: Tumor burden (mg) = $(L \times W^2)/2$, where L and W are the respective orthogonal tumor length and width measurements (mm).

Results:

- 1) A tumor growth delay of >38.3 days was observed with administration of Docetaxel Injection Concentrate (20 mg/mL) at 20 mg/kg. The treatment resulted in 100% complete regressions and the animals remained tumor-free at study termination (day 29). The tumor growth delay was statistically significant ($p < 0.00001782$).
- 2) A tumor growth delay of >38.3 days was observed with administration of Taxotere® at 20 mg/kg. The treatment resulted in 100% complete regressions and the animals remained tumor-free at study termination (day 29). The tumor growth delay was statistically significant ($p < 0.00001782$).

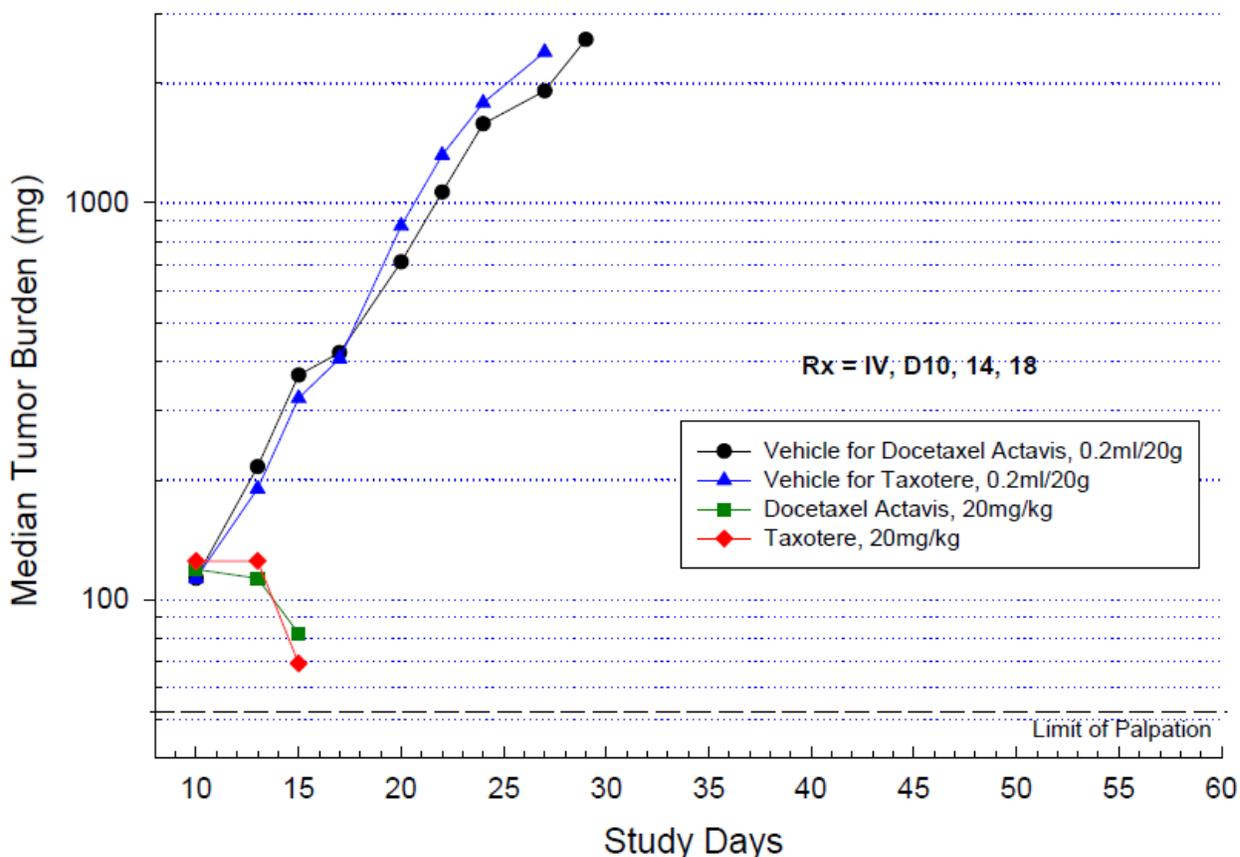
The follow figures are copied from the Applicant's submission:

ACTA200801R4, MIR1046
MX-1 Tumor Burden
Group Comparison with Std. Error



Note: tumor burdens under the limit of palpation do not appear on a log scale graph

ACTA200801R4, MIR1046
 MX-1 Tumor Burden
 Group Median Comparison



Note: tumor burdens under the limit of palpation do not appear on a log scale graph

Efficacy Evaluation of Docetaxel Actavis and Taxotere® Against PC-3 Human Prostate Carcinoma Xenografts

Summary: Administration of Docetaxel Injection Concentrate (20 mg/mL) at 20 mg/kg resulted in similar anti-tumor activity against PC-3 human prostate carcinoma cell tumors when compared to Taxotere® administered at the same dose level with the same treatment regimen.

Method: Male athymic mice (nu/nu) were implanted subcutaneously on Day 0 with 5×10^6 human PC-3 cells in 50% Matrigel® per animal. All animals were dosed with Docetaxel Injection Concentrate (20 mg/mL) or Taxotere® at 20 mg/kg on Day 6. Tumor measurements were recorded three times weekly. Tumor burden (mg) was estimated from caliper measurements by the formula for the volume of a prolate

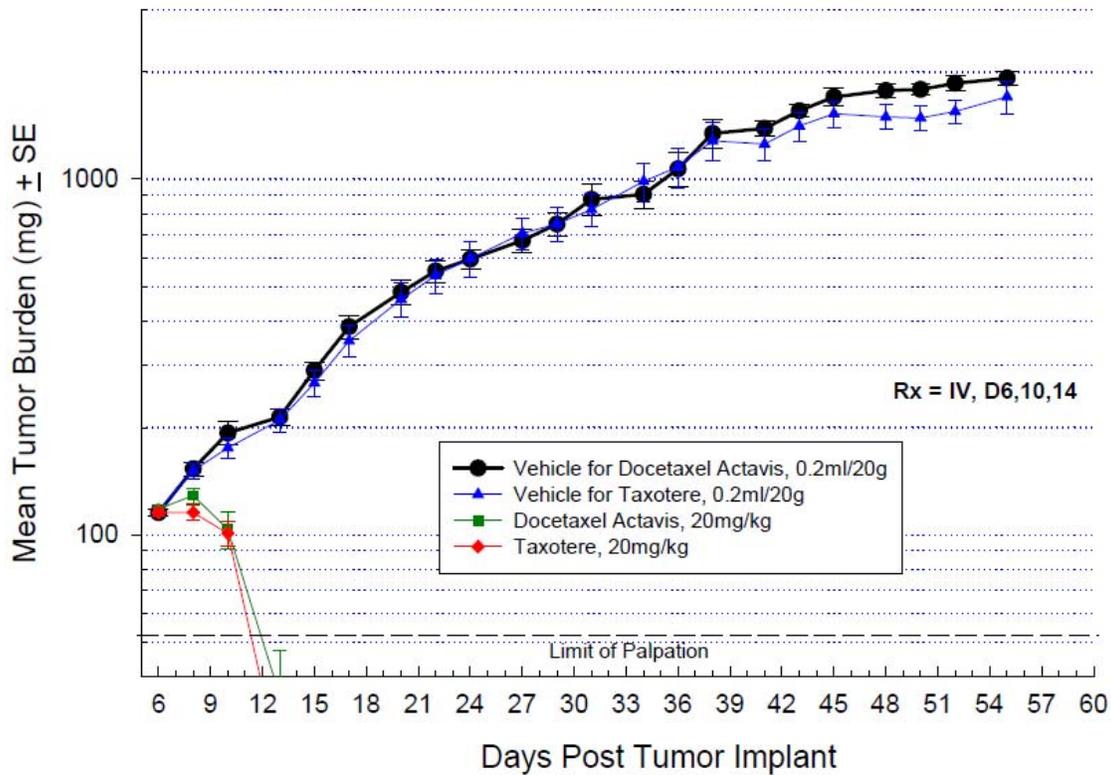
ellipsoid assuming unit density as: Tumor burden (mg) = (L x W²)/2, where L and W are the respective orthogonal tumor length and width measurements (mm).

Results:

A tumor growth delay of >25.8 days was observed with the treatment of Docetaxel Injection Concentrate (20 mg/mL) and Taxotere® at 20 mg/kg. The treatment produced 100% complete regressions (CR's), with all animals remaining tumor-free at study termination (Day 55).

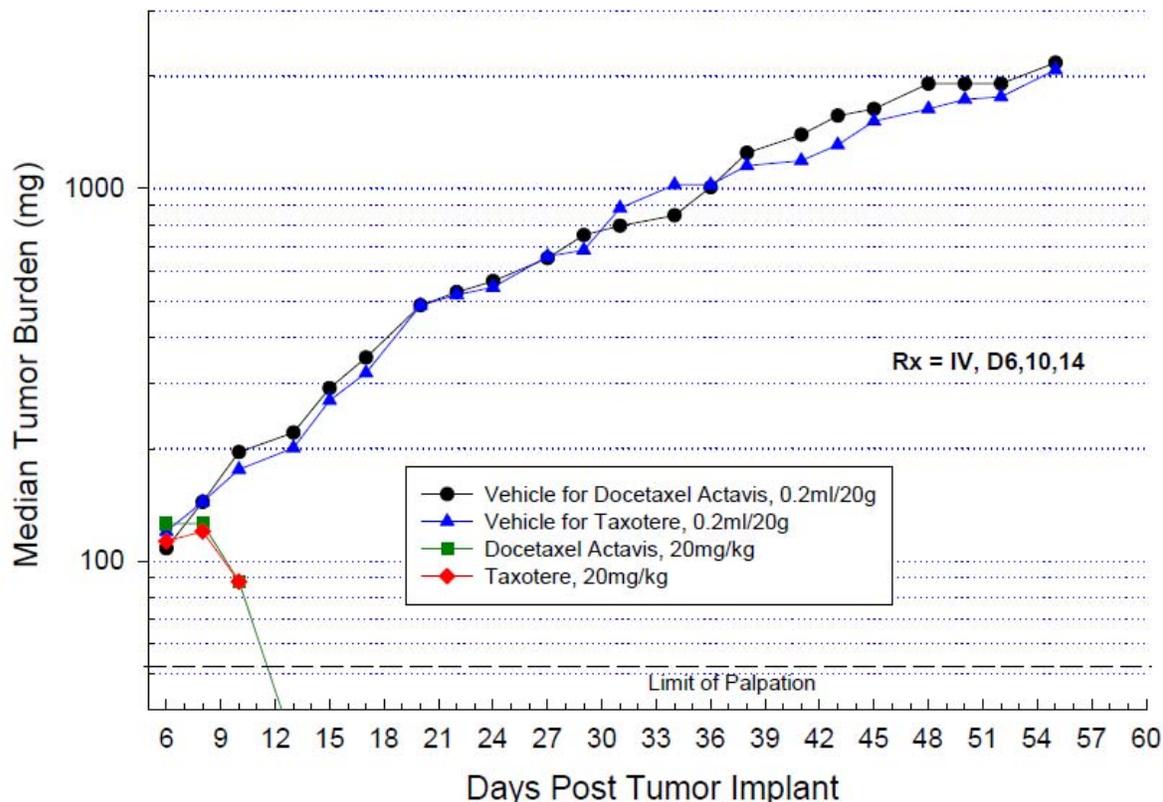
The follow figures are copied from the Applicant's submission.

ACTA200802R4 (MIR1047)
 PC-3 Tumor Burden
 Group Comparison with Std. Error



Note: Tumor burdens of zero do not appear on a log scale graph

ACTA200802R4 (MIR1047)
 PC-3 Tumor Burden
 Group Median Comparison



Note: Tumor burden of zero do not appear on a log scale graph

4.2 Secondary Pharmacology

No study submitted

4.3 Safety Pharmacology

No study submitted

5 Pharmacokinetics/ADME/Toxicokinetics

Study title: Cyclical Intravenous (Infusion) Comparative Study in the Rat

Key Study Findings:

There were no consistent differences for peak levels or systemic exposures of docetaxel following dosing with either Docetaxel Injection Concentrate (20 mg/mL) or Taxotere at 2.5 mg/kg, 5 mg/kg, and 10 mg/kg.

Study no.: DVC0002**Volume #, and page #:** electronic submission, Module 4**Conducting laboratory and location** (b)(4)**Date of study initiation:** October 2, 2008**GLP compliance:** yes**QA report:** yes (x) no ()**Drug, lot #, and % purity:** **Docetaxel** Injection Concentrate **Taxotere®**
(20 mg/mL)

Batch#: DD08001A

Batch#: D8A570

Purity: 99.8%[&]

Purity: not provided*

* marketed drug, manufactured by Sanofi Aventis. A certificate of analysis was not supplied.

Methods

Species/strain: Rat/Crl:CD(SD)

#/sex/group: 3/sex for controls, 9/sex/group for treat groups

Schedule: Once on Day 1, and once Day 22

Doses in administered units: 2.5, 5, 10.0 mg/kg, at the dose volume of 13.5 mL/kg/hour

Route: 1 hour IV infusion

Blood samples collection: 5 minutes and 4 hours post-end of infusion for control groups

5, 15 and 45 minutes and 2, 4 and 8 hours post-end of infusion for treatment groups

Results: The table below is excerpted from the Applicant's submission.

Summary of Docetaxel Toxicokinetics in Male and Female Rats Given Intravenous infusion of Docetaxel at 2.5, 5, 10 on Day 1 and Day 22

Test article	Docetaxel Injection Concentrate (20 mg/mL)						Taxotere®					
	2.5		5		10		2.5		5		10	
Dose level (mg/kg)	2.5		5		10		2.5		5		10	
Gender	M	F	M	F	M	F	M	F	M	F	M	F
Study day	Day 1											
C _{max} (ng/mL)	53	53	173	141	540	737	67	47	155	191	1130	477
Dose normalized C _{max}	21	21	35	28	54	74	27	19	31	38	113	48
AUC ₀₋₈ (µg.min/mL)	5.7	4.6	11.5	9.9	33.8	32	5.6	5.4	11.1	12.2	38.5	31
Dose normalized AUC ₀₋₈	2.3	1.8	2.3	2.0	3.4	3.2	2.2	2.2	2.2	2.4	3.9	3.1

Study day	Day 22											
C _{max} (ng/mL)	69	67	206	123	689	416	74	56	182	119	470	385
Dose normalized C _{max}	28	27	41	24.6	68.9	41.6	30	22	36	24	47	39
AUC ₀₋₈ (µg.min/mL)	7.7	4.1	16.2	9.3	44.8	26.2	5.8	5.0	16	12.4	40.8	27.3
Dose normalized AUC ₀₋₈	3	2	3	2	4.5	2.6	2	2	3	2	4.1	2.7

Summary:

- C_{max} and AUC increased in an approximately dose proportional manner at doses ≤ 5 mg/kg; C_{max} and AUC increased greater than the dose level increase at doses > 5 mg/kg;
- There was no suggestion of accumulation with repeated dosing;
- There was no apparently gender difference on study day 1, although the plasma exposures were slightly higher in male rats on study day 22 ;
- the apparent T_{max} generally occurred at 5 minutes post-dose (data not listed in the above table);
- There were no consistent differences for peak levels or systemic exposures of docetaxel following dosing with either Docetaxel Injection Concentrate (20 mg/mL) or Taxotere.

Study Title: Comparative Determination of the Effect of Formulation on the Plasma Protein Binding of Docetaxel Actavis and Taxotere in Rat, Dog, and Human Plasma

Key Study Findings:

- Protein binding in the rat ranged from 94.55 % to 95.36 % across all formulations
- Protein binding in the dog ranged from 97.22 % to 97.41 % across all formulations
- Protein binding in human ranged from 97.37 % to 97.78 % across all formulations.

Study no: DVC0007

Volume #, and page #: electronic submission, Module 4

Conducting laboratory and location: (b)(4)

Date of study initiation: December 2, 2008

GLP compliance: no*

*No QA report was provided, though the sponsor claimed that it was a GLP study.

QA report: yes () no (x)

Drug, lot #, radiolabel, and % purity:

Docetaxel Actavis 40 mg/mL

Batch No.: CN07002

Purity: 99.75 %

Taxotere 40 mg/mL

Batch No.: D8C209

Purity: not provided

- Formulation/vehicle:** (1) Docetaxel Actavis 20 mg/mL
(2) Docetaxel Actavis 20 mg/ 0.5 mL (40mg/mL)
(3) Taxotere 20 mg (40 mg/mL)
(4) Docetaxel API 10 mg/mL in polysorbate 80:ethanol [1:1 (v/v)]
(5) Docetaxel API 10 mg/mL in 80% (v/v) ethanol

Methods: The *in vitro* protein bindings of docetaxel with different formulations were determined using plasma from rats, dogs, and humans. Incubation samples were prepared at 1, 2.5 and 5 µg/mL in rat, dog and human plasma from each of five formulations of docetaxel. The docetaxel concentrations in the buffer chamber and the sample (plasma) chamber were determined by LC-MS/MS. The degree of plasma protein binding was calculated using the following equations:

% protein binding = 100 - % free fraction

% free fraction =
$$\frac{\text{Conc. of analyte in buffer chamber}}{\text{Conc. of analyte in sample (plasma) chamber}}$$

Results: The following tables were copied from the Applicant's submission.

Docetaxel Protein Binding in Rat Plasma

Rat			
Formulation	Concentration (ug/mL)	Free fraction (%)	Bound fraction (%)
1. Docetaxel Actavis 20mg/mL	1	3.97	96.03
	2.5	5.06	94.94
	5	4.91	95.09
	Mean	4.64	95.36
	SD	0.591	0.591
	CV (%)	12.73	0.62
2. Docetaxel Actavis 40mg/mL	1	4.86	95.14
	2.5	5.09	94.91
	5	5.27	94.73
	Mean	5.07	94.93
	SD	0.206	0.206
	CV (%)	4.06	0.22
3. Taxotere 40mg/mL	1	5.06	94.94
	2.5	4.41	95.59
	5	4.66	95.34
	Mean	4.71	95.29
	SD	0.328	0.328
	CV (%)	6.96	0.34
4. Docetaxel API 10mg/mL	1	5.43	94.57
	2.5	5.72	94.28
	5	5.20	94.80
	Mean	5.45	94.55
	SD	0.258	0.258
	CV (%)	4.73	0.27
5. Docetaxel API 10mg/mL	1	5.28	94.72
	2.5	4.91	95.09
	5	4.52	95.48
	Mean	4.90	95.10
	SD	0.382	0.382
	CV (%)	7.78	0.40

Formulation 4 – polysorbate 80 : ethanol [1 : 1 (v/v)]

Formulation 5 – 80 % (v/v) ethanol

Docetaxel Protein Binding in Dog Plasma

Dog			
Formulation	Concentration (ug/mL)	Free fraction (%)	Bound fraction (%)
1. Docetaxel Actavis 20mg/mL	1	2.71	97.29
	2.5	2.71	97.29
	5	2.76	97.24
	Mean	2.73	97.27
	SD	0.0265	0.0265
	CV (%)	0.97	0.03
2. Docetaxel Actavis 40mg/mL	1	2.61	97.39
	2.5	2.44	97.56
	5	2.73	97.27
	Mean	2.59	97.41
	SD	0.144	0.144
	CV (%)	5.54	0.15
3. Taxotere 40mg/mL	1	2.40	97.60
	2.5	2.74	97.26
	5	2.71	97.29
	Mean	2.62	97.38
	SD	0.187	0.187
	CV (%)	7.13	0.19
4. Docetaxel API 10mg/mL	1	2.84	97.16
	2.5	2.67	97.33
	5	2.84	97.16
	Mean	2.78	97.22
	SD	0.102	0.102
	CV (%)	3.66	0.10
5. Docetaxel API 10mg/mL	1	2.74	97.26
	2.5	2.88	97.12
	5	2.66	97.34
	Mean	2.76	97.24
	SD	0.109	0.109
	CV (%)	3.93	0.11

Formulation 4 – polysorbate 80 : ethanol [1 : 1 (v/v)]

Formulation 5 – 80 % (v/v) ethanol

Docetaxel Protein Binding in Human Plasma

Human			
Formulation	Concentration (ug/mL)	Free fraction (%)	Bound fraction (%)
1. Docetaxel Actavis 20mg/mL	1	1.85	98.15
	2.5	2.42	97.58
	5	2.37	97.63
	Mean	2.22	97.78
	SD	0.314	0.314
	CV (%)	14.16	0.32
2. Docetaxel Actavis 40mg/mL	1	2.16	97.84
	2.5	2.38	97.62
	5	2.60	97.40
	Mean	2.38	97.62
	SD	0.218	0.218
	CV (%)	9.17	0.22
3. Taxotere 40mg/mL	1	2.09	97.91
	2.5	2.25	97.75
	5	2.98	97.02
	Mean	2.44	97.56
	SD	0.473	0.473
	CV (%)	19.36	0.48
4. Docetaxel API 10mg/mL	1	2.08	97.92
	2.5	2.37	97.63
	5	2.65	97.35
	Mean	2.37	97.63
	SD	0.284	0.284
	CV (%)	12.02	0.29
5. Docetaxel API 10mg/mL	1	2.52	97.48
	2.5	2.39	97.61
	5	2.99	97.01
	Mean	2.63	97.37
	SD	0.316	0.316
	CV (%)	11.99	0.32

Formulation 4 – polysorbate 80 : ethanol [1 : 1 (v/v)]

Formulation 5 – 80 % (v/v) ethanol

6 General Toxicology

6.1 Single-Dose Toxicity

No study submitted

Repeat-Dose Toxicity

Study Title: Cyclical Intravenous (Infusion) Comparative Study in the Rat

Study no.: DVC0002

Study report location: electronic submission, Module 4

Conducting laboratory and location: (b)(4)

Date of study initiation: October 2, 2008

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity:

Docetaxel Injection Concentrate (20 mg/mL)	Taxotere®
Batch#: DD08001A	Batch#: D8A570
Purity: 99.8% ^{&}	Purity: not provided [*]

[&] Kollidon 12 PF is an excipient contained in this formulation

^{*} marketed drug, manufactured by Sanofi Aventis, a certificate of analysis was not supplied

Key study findings:

- Both formulations of docetaxel were well tolerated in rats at doses up to 10 mg/kg;
- The toxicity profiles were similar between the two docetaxel formulations;
- The following treatment-related toxicities were observed during the study, which were not completely resolved at the end of recovery period.
 - Lower body weight gain and reduced food consumption in the male and female rats;
 - Reduced counts for red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, and LUC;
 - Pathologic changes in the reproductive system (testes, epididymides and seminal vesicles) in male rats, and in the thymus in male and female rats.

Methods

Doses: 2.5, 5, 10.0 mg/kg
 Frequency of dosing: Once on Day 1, and once Day 22
 Route of administration: 1 hour IV infusion
 Dose volume: 13.5 mL/kg/hour
 Formulation/ Vehicle: Docetaxel Injection Concentrate (20 mg/mL): 0.9% saline
 Taxotere®: 0.9 % saline
 Species/Strain: Rat/Crl:CD(SD)
 Number/Sex/Group: 10/sex/group (LD, MD)
 15/sex/group (control and HD, including 5/sex/group for recovery)
 Age: approximately 5 to 6 weeks
 Weight: Males: 199 g to 286 g
 Females: 139 g to 199 g
 Satellite groups: Used for TK study, 3/sex for controls, 9/sex/group for treat groups
 Unique study design: none
 Deviation from study protocol: none

Observations and times:

Clinical signs: twice daily for mortality and morbidity.

Clinical observations were made on each day of dosing immediately after dosing, and at approximately 5, 15, 45 minutes, and 1 hour after dosing.

Body weights: at the start of treatment and weekly thereafter

Food consumption: weekly

Ophthalmoscopy: only for control and HD - once pretreatment; and once during week 5 or 6

EKG: not performed

Hematology: week 3 for all animals, week 6 for main study, week 9/10 for recovery

Clinical chemistry: week 3 for all animals, week 6 for main study, week 9/10 for recovery

Urinalysis: week 6 for main study, week 9/10 for recovery

Gross pathology: all animals found dead or at scheduled necropsy on Day 43, or day 64 (recovery)

Organs weigh: all animals found dead or at scheduled necropsy on Day 43, or day 64 (recovery)

Histopathology: all animals found dead or at scheduled necropsy on Day 43, or day 64 (recovery)

Adequate Battery: yes (x), no ()

Peer review: yes (x), no ()

Toxicokinetics: 5 minutes and 4 hours after the end of infusion for control groups; 5, 15 and 45 minutes and 2, 4 and 8 hours after the end of infusion for treatment groups

Results:

Mortality: 3 unscheduled deaths in main study. The Applicant claimed that none of them were considered as treatment related deaths. This reviewer agrees with the Applicant's conclusion. See the details below.

10 mg/kg Taxotere®: 1 male was euthanized on Day 20, as the animal developed a wet lesion at the base of the tail, which would have caused dosing procedures to be painful for the animal.

10.0 mg/kg Docetaxel Injection Concentrate (20 mg/mL):

1 male was euthanized on Day 39, due to worsening clinical condition, manifested as excessive body weight loss, hunched posture and piloerection. At necropsy, it was noted that this animal had a shortened lower jaw, which may have resulted in difficulty feeding.

1 male died on day 62 (recovery) while restrained for blood sampling for the purpose of clinical pathology investigations.

Clinical signs: unremarkable

Body weights: The following figures were copied from the Applicant's submission. The data were verified by this reviewer.

Figure 1 - Body weights (g) - group mean values - males - main study

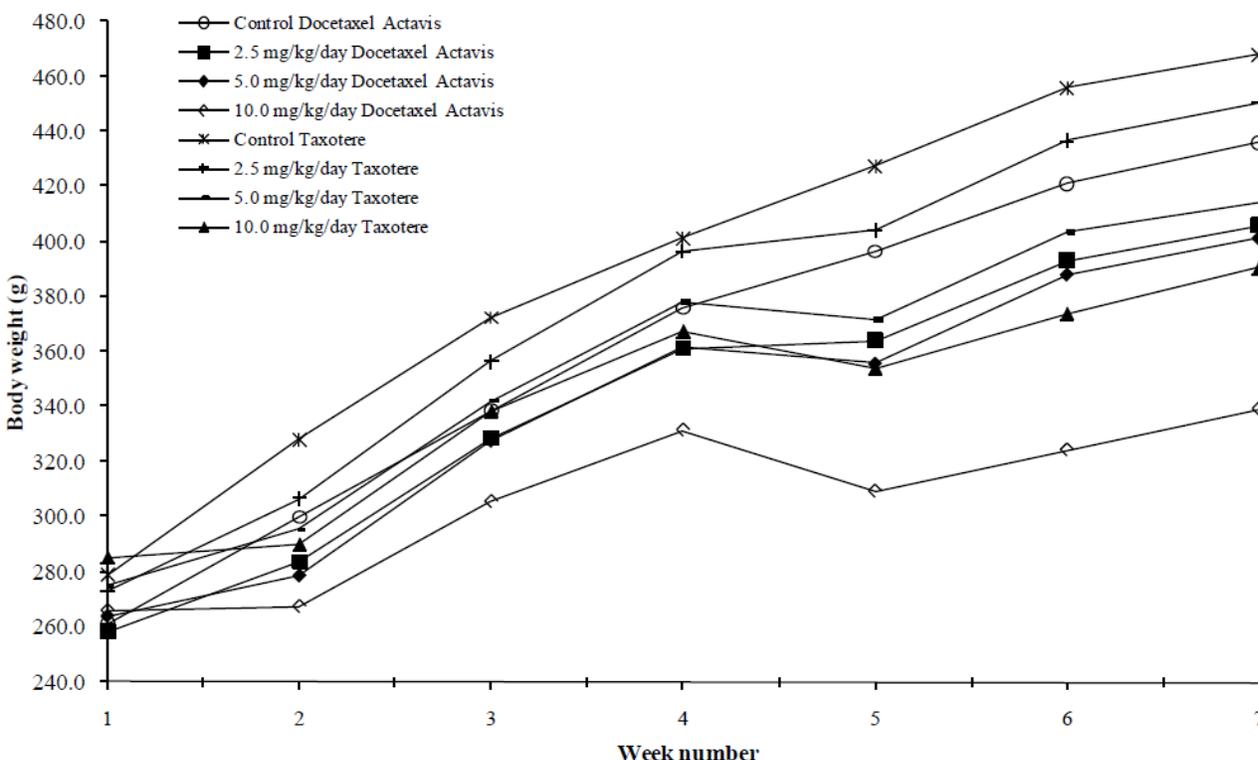
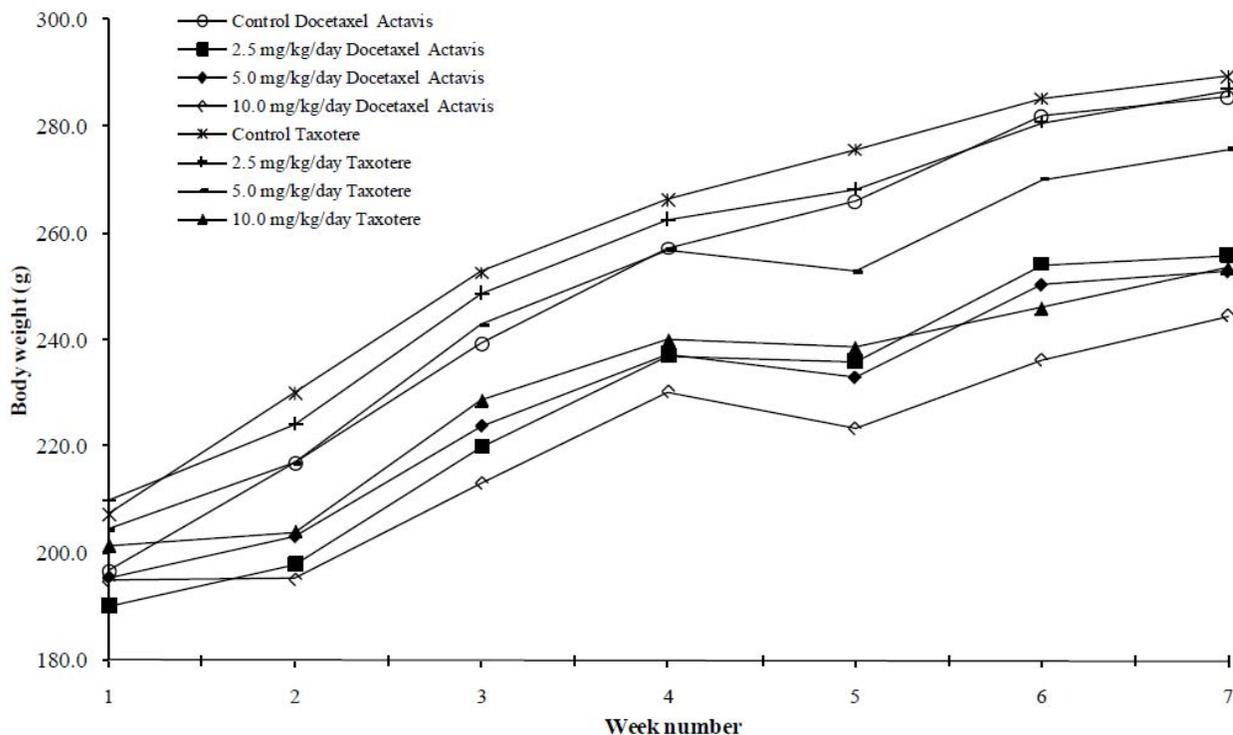


Figure 2 - Body weights (g) - group mean values - females - main study



Summary: A dose related decrease in body weight gain was observed in both male and female rats treated with Docetaxel Injection Concentrate (20 mg/mL) or Taxotere® at 2.5, 5, 10 mg/kg/day. Animals allocated to the recovery period (Weeks 7 to 10) continued to display lower group mean body weight gain when compared with Controls (not shown in the above figures). At the end of the recovery period mean body weight gains at 2.5, 5 and 10 mg/kg of Docetaxel Injection Concentrate (20 mg/mL) were 15%, 21% and 58% lower, respectively, than the control group; mean body weight gains at 2.5, 5 and 10 mg/kg of Taxotere® were 6%, 26% and 43% lower, respectively, than the control group.

Food consumption: Group mean food consumption was lower in week 1 to 2 ($\downarrow \leq 37\%$), and in week 4 to 5 ($\downarrow \leq 46\%$) in all groups treated with either test article, when compared with relevant Control values. The observed reduced food consumption occurred in a dose dependant fashion, and was comparable between test articles.

Ophthalmoscopy: unremarkable

Hematology:

Male

Docetaxel Injection Concentrate (20 mg/mL)

Percentage deviation from control (%)							
Study week	3 (main)			6 (main)			9/10 (recovery)
Dose (mg/kg)	2.5	5	10	2.5	5	10	10
RBC				-6	-8	-6	
WBC	-24	-11	-26	-10	-8	-28	-31
Neut	-51	-26	-37	-23	-11	-23	-37
Lymph	-18	-9	-24	-8	-8	-29	-29
Mono						-17	-41
Luc			4		-9	-27	-50
Retics	12	45	8	26	67	30	11

Taxotere®

Percentage deviation from control (%)							
Study week	3 (main)			6 (main)			9/10 (recovery)
Dose (mg/kg)	2.5	5	10	2.5	5	10	10
RBC				-3	-4	-5	
WBC	-12	-10	-21	-4	-5	-30	-13
Neut	-37	-41	-16	-33	-47	-35	-65
Lymph	-5		-22			-29	-18
Mono					-24	-46	-13
Luc						-29	-25
Retics		15	45	28	41	62	

Female

Docetaxel Injection Concentrate (20 mg/mL)

Percentage deviation from control (%)							
Study week	3 (main)			6 (main)			9/10 (recovery)
Dose (mg/kg)	2.5	5	10	2.5	5	10	10
RBC					-5	-4	
WBC	-10	-17	-11	-9	-21	-33	-19
Neut	-35	-13	-8	-29	-31	-45	
Lymph	-6	-18	-12	-6	-20	-31	-19
Mono					-38	-37	-47
Luc				-10	-30	-40	-33
Retics	6	39	71	14	55	69	-22

Taxotere®

Study week	Percentage deviation from control (%)						
	3 (main)			6 (main)			9/10 (recovery)
Dose (mg/kg)	2.5	5	10	2.5	5	10	10
RBC					-5	-6	
WBC	-11	-23	-21	-12	-34	-39	-30
Neut	-12	-22	-22	13	-29	-31	-53
Lymph	-12	-24	-22	-15	-35	-40	-27
Mono				-24	-29	-48	-34
Luc					-50	-62	-44
Retics		29	68	16	22	50	-15

Blank: no related findings

Summary: The counts for white blood cells, neutrophils, lymphocytes, monocytes, and leukocytes were dose-dependently decreased for all treated groups compared to the control groups. The observed changes did not recover by the end of the recovery period. The counts for red blood cells were slightly lower at Week 6, and the counts for reticulocytes were higher at both Week 3 and Week 6. The changes in red blood cells and reticulocytes resolved at the end of recovery period. Docetaxel Injection Concentrate (20 mg/mL) and Taxotere® had similar effects on hematologic parameters.

Clinical chemistry: unremarkable

Urinalysis: unremarkable

Gross pathology:

Male

Test article	Number of animals affected							
	Docetaxel Injection Concentrate (20 mg/mL)				Taxotere®			
Group	1	2	3	4	5	6	7	8
Dose (mg/kg/day)	control	2.5	5	10	control	2.5	5	10
Main								
Number/Group	10	10	10	9	10	10	10	9
Tested								
Abnormal consistency				1				
Recovery								
Number/Group	5	0	0	4	5	0	0	5
Epididymides								
Abnormal size, general		-	-	2		-	-	2
Testes								
Abnormal consistency		-	-			-	-	3
Abnormal size		-	-	2		-	-	3
Incisor teeth								
Malocclusion								
Upper incision		-	-	1		-	-	
Lower incision		-	-	1		-	-	

Female

Test article	Number of animals affected							
	docetaxel actavis				taxotere [®]			
Group	1	2	3	4	5	6	7	8
Dose (mg/kg/day)	control	2.5	5	10	control	2.5	5	10
main								
Number/Group	10	10	10	10	10	10	10	10
unremarkable								
Recovery								
Number/Group	5	0	0	5	5	0	0	5
Incisor teeth Malocclusion Upper incision		-	-			-	-	1

“-“: not applicable

Blank: no related findings

Summary: Abnormal size and consistency were observed in the testes and epididymides in male rats at 10 mg/kg. These changes were still present at the end of recovery period.

Organ weights:

Main study

Test article	Percentage deviation from control (n=10)			
	Docetaxel Injection Concentrate (20 mg/mL)		Taxotere [®]	
Gender	Male	Female	Male	Female
Dose Group (mg/kg)	10	10	10	10
No. Animal/group	9	10	9	10
Absolute Organ Weight				
Thymus	-42	-21	-21	8
Organ weight/body weight				
Thymus	-20	-8	-5	25

Recovery study

Test article	Percentage deviation from control (n=10)			
	Docetaxel Injection Concentrate (20 mg/mL)		Taxotere [®]	
Gender	Male	Female	Male	Female
Dose Group (mg/kg)	10	10	10	10
No. Animal/group	5	4	5	5
Absolute Organ Weight				
Thymus	-25	-34	-8	-22
Organ weight/body weight				
Thymus	-8	-21	12	-9

Summary: Decreases in organ weights were observed in the thymus in both male and female rats at 10 mg/kg of Docetaxel 20 mg/mL or Taxotere[®], and the observed organ weight changes did not resolve at the end of recovery period.

Histopathology:

Male

Test article	Number of animals affected							
	Docetaxel Injection Concentrate (20 mg/mL)				Taxotere [®]			
	1	2	3	4	5	6	7	8
Group	1	2	3	4	5	6	7	8
Dose (mg/kg/day)	control	2.5	5	10	control	2.5	5	10
Main								
Number/Group	10	10	10	9	10	10	10	9
Testes								
Partial loss of germinal epithelium								
-minimal							9	7
-slight				3				
-moderate				1				
Apoptosis								1
-minimal								
Epididymides								
Epithelial degeneration/dysplasia								
-minimal				2				3
-slight				4				2
-moderate				3				
Occasional apoptotic cells in Epithelium								
-minimal		6	7			5	6	4
Seminal Vesicles								
Epithelial vacuolation								
-minimal		6	3			4	5	9
-slight			6	7				
-moderate			1					
Secretion depletion								
-slight				4				
-moderate				1				
Thymus								
Cortical atrophy				5				
-slight								
Cortical lymphocytolysis								
-minimal		4	2			2	5	3
-slight		1				1	4	5

Test article	Number of animals affected							
	Docetaxel Injection Concentrate (20 mg/mL)				Taxotere®			
	1	2	3	4	5	6	7	8
Group	1	2	3	4	5	6	7	8
Dose (mg/kg/day)	control	2.5	5	10	control	2.5	5	10
Recovery								
Number/Group	5	0	0	4	5	0	0	5
Epididymides								
Epithelial degeneration/dysplasia								
-slight		-	-	4		-	-	1
-moderate		-	-			-	-	3
Occasional apoptotic cells in epithelium								
-minimal		-	-			-	-	1
Testes								
Partial loss of germinal epithelium								
-slight		-	-	2		-	-	4
-moderate		-	-			-	-	1
Thymus								
Cortical lymphocytolysis								
-minimal	1	-	-			-	-	

Female

Test article	Number of animals affected							
	Docetaxel Injection Concentrate (20 mg/mL)				Taxotere®			
	1	2	3	4	5	6	7	8
Group	1	2	3	4	5	6	7	8
Dose (mg/kg/day)	control	2.5	5	10	control	2.5	5	10
main								
Number/Group	10	10	10	10	10	10	10	10
Thymus								
Cortical atrophy								
-slight								1
Cortical lymphocytolysis								
-minimal		1	2			4	2	2
-slight							1	3
Recovery								
Number/Group	5	0	0	5	5	0	0	5
Thymus								
Cortical atrophy								
-slight		-	-			-	-	1
Cortical lymphocytolysis								
-minimal	1	-	-	1	1	-	-	2

“-“: not applicable

Blank: no related findings

Summary: Treatment related microscopic changes were found in the male reproductive system (testes, epididymides and seminal vesicles) and in the thymus in both males and females. The observed changes in the male reproductive system were still present at the end of recovery period, while the changes in the thymus showed a trend of reversibility.

Toxicokinetics: see "Pharmacokinetics/ADME/Toxicokinetics" section in this review

Study title: Repeat Dose Cyclical Intravenous Infusion Study in the Rat

Study no.: DVC0016
 Study report location: Electronic submission, M4
 Conducting laboratory and location: (b)(4)
 Date of study initiation: June 30, 2011
 GLP compliance: yes
 QA statement: yes (X) no ()
 Drug, lot #, and % purity: kollidon 12 PF, 09845516K0, 99.9%

Key Study Findings

- Rats tolerated Kollidon 12 PF at doses up to 837 mg/kg ;
- The observed toxicities involved the injection sites and the kidney in both males and females, and the reproductive system in males;
- The reversibility of the observed adverse effect was not evaluated in the study.

Methods

Doses: 83.7 and 837 mg/kg*
 * LD was selected as the human equivalent dose, and HD was selected as a 10-fold human equivalent dose of Kollidon present in Docetaxel Injection Concentrate (20 mg/mL) at the recommended therapeutic dose.
 * Female #38 (LD) was only partially dosed on Day 29 due to occlusions and unsuccessful attempts to re-start the infusion. The animal was given approximately 83 % of its nominal dose.

Frequency of dosing: Once every 2 weeks (on days 1, 15, 29, 43, 57 and 71)
 Route of administration: IV (1 hour infusion)
 Dose volume: 5 mL/kg/hour
 Formulation/Vehicle: saline
 Species/Strain: Rat/Crl:CD(SD)
 Number/Sex/Group: 10 animals/sex/group
 Age: approximately 5 to 6 weeks
 Weight: Male: 242 g to 325 g; Female: 194 g to 234 g
 satellite group: none
 Unique study design: none
 Deviation from study protocol: none

Observations and Results**OBSERVATIONS AND TIMES:**

<u>Mortality</u>	Two times daily
<u>Clinical examinations</u>	twice daily for mortality and morbidity; Daily for clinical signs of toxicity or changes in behavior and appearance from the start of treatment
<u>Body weights</u>	weekly
<u>Food consumption</u>	weekly
<u>Ophthalmoscopy</u>	Before the start of treatment and following the final dose
<u>Clinical Pathology:</u>	week 11
<u>Gross pathology:</u>	At death or at scheduled sacrifice (day 72)
<u>Organ weights:</u>	At death or at scheduled sacrifice (day 72)
<u>Histopathology:</u>	At death or at scheduled sacrifice Adequate Battery: yes (x), no (), Peer review: yes (x), no ()
<u>Toxicokinetics:</u>	Not performed

RESULTS:**Mortality:** none**Clinical Signs:** unremarkable**Body Weights:** unremarkable**Feed Consumption:** unremarkable**Ophthalmoscopy:** No test-article related changes**Hematology:** No test-article related changes**Clinical Chemistry:** No test-article related changes**Urinalysis:** No test-article related changes

Gross Pathology:

Gender	Number of animals affected					
	Male			Female		
	1	2	3	1	2	3
Group	1	2	3	1	2	3
Dose (mg/kg/dose)	0	83.7	837	0	83.7	837
Number/group	10	10	10	10	10	10
Epididymides						
Abnormal size general			1	-	-	-
Lungs						
Abnormal color general			1			
Seminal vesicles						
Abnormal size		1		-	-	-
Testes						
Abnormal consistency			1	-	-	-
Abnormal size			1	-	-	-
Thymus						
Abnormal color		1	1			
Skin/subcutis						
Scab formation, forelimbs			1			
Hair loss, forelimbs			1			

Blank-no related findings

“-“: not applicable

Organ Weights: Unremarkable**Histopathology:**

Gender	Number of animals affected					
	Male			Female		
	1	2	3	1	2	3
Group	1	2	3	1	2	3
Dose (mg/kg/dose)	0	83.7	837	0	83.7	837
Number/group	10	10	10	10	10	10
Duodenum						
Epithelial hyperplasia			1			
-slight						
Epididymides						
Reduced spermatozoa			1	-	-	-
-marked						
Injection site						
Perivascular fibroplasia		1	1			1
-minimal						
-slight			2			1
Tendon fibroplasia			1			
-slight						
Tendonitis		1	2			
-minimal						
Thrombus			1			
Kidney						
Vacuolated tubular epithelium			2			1
-minimal						
-slight			1			

Gender Group Dose (mg/kg/dose) Number/group	Number of animals affected					
	Male			Female		
	1	2	3	1	2	3
	0	83.7	837	0	83.7	837
	10	10	10	10	10	10
Lacrimal glands						
Periductal inflammatory cell infiltration						
-minimal			1			1
Granulomatous inflammation, focal						
-minimal						1
Pancreas						
Exocrine acinar atrophy	1	3	3	1	1	
-minimal						
-slight						1
-moderate		1				
Islet cell hypertroplasia		1	1			
-slight						
Seminal vesicles						
Secretion depletion		1		-	-	-
-marked						
Skin/subcutis						
Dermal inflammation			1			
-moderate						
Epidermal hyperplasia			1			
-moderate						
Scab formation			1			
-moderate						
Submandibular lymph nodes						
Plasmacytosis	2	2	2			
-slight						
-moderate		2	3			
-marked		1				
Sciatic nerve						
Nerve fibres degeneration				1	2	2
-minimal						
Testes						
Tubular atrophy, unilateral			1	-	-	-
-severe						
Germinal epithelium degeneration, focal			1	-	-	-
-moderate						

Blank-no related findings

“-“: not applicable

Summary: Major treatment-related microscopic findings were seen at the injection sites, in the kidneys (vacuolated tubular epithelium), and in the male reproductive system (reduced spermatozoa in the epididymides, tubular atrophy, germinal epithelium degeneration in the testes).

Histopathology inventory

Study	DVC0016	DVC0002
Species	Rat	Rat
Adrenals	x*	x*
Aorta	x	x
Bone Marrow smear	x	x
Bone (femur)	x	x
Brain	x*	x*
Cecum	x	x
Cervix	x	x
Colon	x	x
Duodenum	x	x
Epididymis	x*	x
Esophagus	x	x
Eye	x	x
Fallopian tube		
Gall bladder		
Gross lesions	x	x
Harderian gland	x	x
Heart	x*	x*
Ileum	x	x
Injection site	x	x
Jejunum	x	x
Kidneys	x*	x*
Lachrymal gland	x	x
Larynx		
Liver	x*	x*
Lungs	x	x*
Lymph nodes, cervical		
Lymph nodes mandibular		
Lymph nodes, mesenteric	x	x
Lymph nodes, submandibular	x	x
Mammary Gland	x	x
Nasal cavity		
Optic nerves		
Ovaries	x	x*
oviducts	x	x
Pancreas	x	x
Parathyroid		

Peripheral nerve		
Peyer's patches		
Pharynx		
Pituitary	X*	X*
Prostate	X*	X*
Rectum	X	X
Salivary gland	X	X*
Sciatic nerve	X	X
Seminal vesicles	X	X*
Skeletal muscle	X	X
Skin	X	X
Spinal cord	X	X
Spleen	X*	X*
Sternum	X	X
Stomach	X	X
Teeth		
Testes	X*	X*
Thymus	X*	X*
Thyroid	X*	X*
Tongue	X	X
Trachea	X	X
Ureters	X	X
Urinary bladder	X	X
Uterus	X	X*
Vagina	X	X
Zymbal gland		

X, histopathology performed

*, organ weight obtained

7 Genetic Toxicology

No studies conducted

8 Carcinogenicity

No studies conducted

9 Reproductive and Developmental Toxicology

No studies conducted

10 Special Toxicology Studies

No studies conducted

12 Integrated Summary and Safety Evaluation

- **Nonclinical safety and pharmacological evaluation of the new formulation.** A bridging study comparing the toxicity and TK profiles between Docetaxel Injection Concentrate (20mg/mL) and Taxotere® was conducted in rats. The study was adequately conducted, and the study results suggested that the new formulation did not result in any notable differences in the pharmacological or toxicological profiles compared to the listed drug.
- **Safety evaluation for Kollidon 12 PF:** Docetaxel Injection Concentrate (20 mg/mL) contains Kollidon 12 PF, a low-molecular weight povidone, as a (b)(4) To qualify the safety of Povidone (Kollidon PF 12) for intravenous use at the concentration present in a dose of 100 mg/m² Docetaxel Injection Concentrate, a repeat-dose toxicology study with Kollidon 12 PF was conducted in rats. Kollidon 12 PF was administered via cyclical intravenous infusion at doses of 83.7 mg/kg and 837 mg/kg for 3 months (twice per month for a total of 6 doses). The human equivalent dose of the 837 mg/kg high dose used in this study is approximately 10 times the dose of Kollidon 12 PF administered to patients receiving Docetaxel Injection Concentrate (20 mg/mL) at the recommended therapeutic dose. There were no premature deaths or treatment related clinical observations seen during the study. There were no apparent treatment related effects on bodyweight gain, food consumption, clinical pathological parameters, or organ weights. Microscopic changes were observed at the high dose in the kidney (vacuolated tubular epithelium) in both male and female rats, and in the male reproductive system (epididymides-reduced spermatozoa; testes-tubular atrophy and germinal epithelium degeneration; and seminal vesicles-secretion depletion). The conducted 3-month toxicology study with Kollidon 12 PF did not provide information on the reversibility of the observed toxicities and plasma exposure of Kollidon 12 PF associated with the toxicities.

Considering that 1) the Kollidon 12 PF associated toxicities were observed at the high dose with a 10-fold safety margin; 2) the dosing schedule used in the study was more frequent than the recommended dosing schedule of docetaxel;

3) the intended indications are for treating advanced cancer patients; 4) There is available human experience with Kollidon 12 PF, since it is used as an inactive ingredient in FDA approved drugs with the intravenous injection or infusion route of administration (e.g. (b)(4)[®]); therefore, the specified level of Kollidon 12 PF (100 mg/mL) in the proposed formulation of Docetaxel Injection Concentrate (20 mg/mL) is acceptable from a pharmacology/toxicology perspective.

- **Concerns raised by CMC:** The following concerns were raised by the CMC review team.

1) *Kollidon 12 PF as a excipient for intravenous administration:*

From a pharmacology/toxicology perspective, the level of Kollidon 12 PF in the proposed formulation of docetaxel is acceptable based on the submitted nonclinical data. See discussion above.

2) *The acceptability of the level of the potential genotoxic impurity with RRT = 1.12 in the drug product.*

From pharmacology/toxicology perspective, the potential daily exposure of 18 µg is acceptable for the proposed indications, especially considering docetaxel itself is genotoxic.

3) *The ethanol content in the drug product prior to dilution for IV administration of 400 mg/mL:*

Based on the results from the conducted comparative toxicology study in rats, the fact that ethanol is classified as a Class 3 solvent in ICH Q3C, and that the maximum expected amount of ethanol that would be administered to a patient receiving a 200 mg dose of docetaxel (100 mg/m² administered to a 74 kg patient) is 4 g over 1 hour, which is comparable to the amount of ethanol administered in other approved docetaxel formulations, the proposed level of ethanol in the Docetaxel Injection Concentrate is acceptable.

4) *The osmolarity of Docetaxel Injection Concentrate (20 mg/mL) when diluted to 0.74 mg/mL docetaxel in infusion solutions with NaCl 0.9% and glucose 5% ranges from 0.597 to 0.687, while the osmolarity for the reference listed drug, Taxotere, in these two diluents is 0.325 and 0.327, respectively:*

The conducted comparative nonclinical study in rats did not show any toxicities associated with the increased osmolarity. However, infusion of a solution with high osmolarity may be a safety concern for cancer patients. The Pharmacology/Toxicology team defers to the clinical team for the acceptability of the osmolarity of the proposed product for use in patients with advanced cancer.

Conclusions

The nonclinical studies submitted to this NDA adequately support the safety of the proposed formulation of Docetaxel Injection Concentrate (20mg/mL) administered by intravenous infusion for the proposed indications. See the EXECUTVE SUMMARY, Page 3, for an overall summary of nonclinical findings.

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

/s/

WEI CHEN
02/26/2013

TODD R PALMBY
02/26/2013