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APPLICATION NUMBER:

205934Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA/SDN	205934/SDN 5
Proposed Brand Name	Docetaxel Injection [REDACTED] ^{(b)(4)} , Non-Alcohol Formula
Generic Name	Docetaxel
Submission Date	February 26, 2015
Submission Type	Original, 505(b)(2)
Review Classification	Standard
PDUFA Due Dates	December 26, 2015
Proposed Dosage Form / Strength	20 mg/mL, 80 mg/4 mL, 160 mg/8 mL multi-use vial
Proposed Dosing Regimen	60 to 100 mg/m ² IV over 1 hour every 3 weeks
Proposed Indication	Breast cancer, Non-small cell lung cancer, Hormone refractory prostate cancer, Gastric adenocarcinoma, Squamous cell carcinoma of the head and neck cancer
Listed Drug	One-Vial Taxotere® (docetaxel) Injection, 20 mg/mL and 80 mg/4mL
Applicant	Teikoku Pharma USA, Inc.
OCP Reviewer	Runyan Jin, Ph.D.
OCP Team Leader	Qi Liu, Ph.D.
OCP Division	Division of Clinical Pharmacology V (DCPV)
Clinical Division	Division of Oncology Products 1 (DOP1)

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1 EXECUTIVE SUMMARY

This 505(b)(2) New Drug Application (NDA) submitted by Teikoku Pharma USA, Inc is for Docetaxel Injection [REDACTED] (b)(4), Non-Alcohol Formula. The listed drug (LD) for this 505(b)(2) application is One-Vial Taxotere® (docetaxel) Injection, 20 mg/mL and 80 mg/4mL by Sanofi-Aventis U.S. LLC, which is approved by the FDA under NDA 20449. The dosage form, route of administration, indications, and active ingredient are the same between the proposed drug product (DP) and the LD. However, the proposed DP differs in inactive excipients from the LD.

No clinical study or clinical pharmacology study are included in this application. The applicant is relying on the findings of safety and effectiveness for the approved drug One-Vial Taxotere® (docetaxel) Injection, to support the approval of their product. The applicant is requesting a waiver of in vivo bioequivalence for Docetaxel Injection [REDACTED] (b)(4), Non-Alcohol Formula in accordance with 21 CFR 320.22(b), which is granted by the biopharmaceutics review team.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology V has reviewed the information contained in NDA 205934/SDN 5. The NDA is acceptable from a clinical pharmacology perspective.

1.2 POST-MARKETING REQUIREMENTS (PMRS) AND COMMITMENTS (PMCS)

There are no clinical pharmacology requested PMRs or PMCs.

Signatures:

Runyan Jin, Ph.D.

Clinical Pharmacology Reviewer

Division of Clinical Pharmacology V

Qi Liu, Ph.D.

Team Leader

Division of Clinical Pharmacology V

Cc: DDOPI: MO – Genevieve Schechter; MTL – Amy McKee; RPM – Sakar Wahby

DCP-5: DDD –Brian Booth; DD – Atiqur Nam Rahman

1.3 CLINICAL PHARMACOLOGY SUMMARY

One-Vial Taxotere® (docetaxel) Injection, 20 mg/mL and 80 mg/4mL, is the listed drug (LD) product in this 505(b)(2) submission, which was approved in 2010 for breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, squamous cell carcinoma of the head and neck cancer. The recommended Taxotere dose is 60 to 100 mg/m² intravenously (IV) over one hour every 3 weeks.

Docetaxel Injection (b)(4) Non-Alcohol Formula is the proposed drug product (DP) by Teikoku Pharma USA, Inc. The applicant is seeking approval for the same indication as the LD because the dosage form, route of administration, and active ingredient are identical between the proposed DP and the LD (Table 1). The differences in inactive excipients between two products are listed in Table 1. The comparative quantitative and qualitative compositions of the active ingredient and the inactive excipients are shown in Table 2.

Table 1: Comparison between the Proposed DP and the LD

	Docetaxel Injection (b)(4) Non-Alcohol Formula	One-vial Taxotere
Strength	20 mg/mL	20 mg/mL
Dosage form	Injection (b)(4)	Injection concentration
Route of Administration	Intravenous infusion	Intravenous infusion
Inactive Excipients	Soybean oil, Polysorbate 80, Polyethylene glycol 300, Citric acid, (b)(4)	Polysorbate 80, Dehydrated alcohol

Table 2: Comparative Quantitative and Qualitative Compositions of the Proposed DP and the LD

		Docetaxel Injection (b)(4) Non-Alcohol Formula	One-vial Taxotere
Active Ingredient	Docetaxel	20 mg/mL	20 mg/mL
Inactive Excipients	Soybean oil	27.5 mg/mL	N/A
	Polysorbate 80	585 mg/mL	540 mg/mL
	Polyethylene glycol (PEG) 300	442.2 mg/mL	N/A
	Citric acid, (b)(4)	10 mg/mL	N/A
	Dehydrated alcohol	N/A	395 mg/mL

(b)(4)

Of note, all currently marketed docetaxel formulations contain alcohol, with a content ranging from 2.0 to 6.4 g in a 200 mg dose. FDA issued a safety warning on June 20, 2014 to health care professionals and patients that the intravenous chemotherapy drug docetaxel contains ethanol, also known as alcohol, which may cause patients to experience intoxication or feel drunk during and after treatment. The applicant claims that Docetaxel Injection (b)(4) Non-Alcohol formula contains no alcohol and would have an advantage over currently available docetaxel

injections for patients who have experienced hypersensitivity to alcohol. In addition, it would fulfill the need for patients of Asian descent due to a genetic predisposition that accounts for hypersensitivity to ethanol observed in this ethnic group.

Both products are intended to be diluted into either 0.9% sodium chloride solution or in 5% dextrose/glucose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL before IV administration. The concentration of each excipient presenting in the final concentration of proposed DP is below the Inactive Ingredients Database (IID) limit (Table 3).

Table 3: Comparative Composition of Final Diluted Injections

Excipient	Concentration in Docetaxel Infusion Solution (%)	Inactive Ingredients Database (IID) Limit (%)
Soybean oil	(b)(4)	≤ 10
Polysorbate 80	(b)(4)	≤ 50
Polyethylene glycol 300	(b)(4)	≤ 65
Citric Acid	(b)(4)	≤ 0.4

The applicant is requesting a waiver of in vivo bioequivalence for Docetaxel Injection (b)(4), Non-Alcohol formula in accordance with 21 CFR 320.22(b), which is granted by the biopharmaceutics review team.

2 QUESTION BASED REVIEW

For brevity, only QBR questions related to the current submissions are addressed below. Please refer to the clinical pharmacology review for the LD original NDA 20449 submission initially approved by FDA on May 14, 1996 as a two-vial formulation and on August 2, 2010 as a one-vial formulation.

2.1 GENERAL ATTRIBUTES

2.1.1 What are the proposed dosage and route of administration?

Docetaxel Injection (b)(4) Non-Alcohol formula is supplied as a sterile, non-pyrogenic, non-aqueous, non-alcohol formulation, which is presented as 20 mg/mL, 80 mg/4mL and 160 mg/8 mL. The proposed dose is the same as the LD, 60 to 100 mg/m² IV over one hour every 3 weeks.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What is the composition of the to-be-marketed formulation?

The composition and function of the proposed DP is listed in Table 4.

Table 4: Description of Docetaxel Injection (b)(4) Non-Alcohol Formula

Component	Function	Quality Standard	Quantity (mg)			
			Per mL	Per 1 mL/ 2 mL Vial	Per 4 mL/ 8 mL Vial	Per 8 mL/ 10 mL Vial
Docetaxel ¹	Active	USP, EP	20.0	20.0	80.0	160.0
(b)(4) soybean oil	(b)(4)	USP, EP	27.5	27.5	110.0	220.0
Polysorbate 80		NF, EP, JP	585.0	585.0	2340.0	4680.0
Polyethylene glycol 300		NF, EP, JPE	442.2	442.2	(b)(4)	(b)(4)
Citric acid, (b)(4)		USP, EP, JP	10.0	10.0	40.0	80.0
(b)(4)		NF	N/A	N/A	N/A	N/A
Total			1084.7	1084.7	(b)(4)	(b)(4)

Note: EP=European Pharmacopoeia, JP=Japanese Pharmacopoeia, JPE=Japanese Pharmaceutical Excipients, NF=National Formulary, USP=United States Pharmacopoeia
(Source: Table 3 on Page 2 in the applicant's summary of drug product description)

2.2.5 What are the PK characteristics of the drug?

Protein Binding Study

The percent of docetaxel bound to plasma proteins in dog and human was compared between the proposed DP and the LD using Rapid Equilibrium Dialysis (RED). Docetaxel at 5 nominal

concentrations of 0.1, 1, 3, 10 and 100 µg/mL was evaluated. Over the concentration range evaluated, binding of docetaxel in dog plasma dropped from ~93% to ~86%, while binding in human plasma dropped from ~96% to ~93%, indicating a concentration-dependent change in the binding. The finding was similar for both products. Based on the results of this assay and within the limits of error defined by the standard deviation (SD), the protein binding values were similar for the two products in dog and human plasma (Table 5).

Table 5: Summary of Docetaxel Plasma Protein Binding

Species	Target Concentration (µg/mL)	%Bound (Mean ± SD)	
		TPU-004DO	Taxotere®
Dog	0.100	93.5 ± 0.737	92.6 ± 0.902
	1.00	92.6 ± 0.451	90.6 ± 1.28
	3.00	92.8 ± 0.361	91.1 ± 0.0577
	10.0	92.4 ± 0.529	90.4 ± 2.03
	100	86.7 ± 1.06	85.1 ± 1.44
Human	0.100	96.3 ± 0.458	95.0 ± 0.493
	1.00	96.3 ± 0.173	95.9 ± 0.141
	3.00	95.6 ± 0.265	95.0 ± 0.702
	10.0	93.2 ± 1.65	94.2 ± 1.01
	100	91.8 ± 0.907	93.1 ± 0.781

(Source: Table 11 on Page 23 in the applicant's protein binding report)

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections of the Applicant’s proposed labeling and the LD labeling are included. The only changes are made to replace the brand name “TAXOTERE” with the generic name “Docetaxel Injection (b)(4)” or “docetaxel”, wherever applicable. FDA clinical pharmacology team agrees with the clinical team to delete “(b)(4)” in the generic name.

LD Labeling	Proposed Labeling
<p>5. WARNINGS AND PRECAUTIONS 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)].</p>	<p>5. WARNINGS AND PRECAUTIONS Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with Docetaxel Injection (b)(4) [see Boxed Warning, Use in Specific Populations (8.6), Clinical studies (14)].</p>
<p>7. DRUG INTERACTIONS Docetaxel is a CYP3A4 substrate. <i>In vitro</i> 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. <i>In vivo</i> 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 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)].</p>	<p>7. DRUG INTERACTIONS Docetaxel is a CYP3A4 substrate. <i>In vitro</i> 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. <i>In vivo</i> 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 (b)(4) and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel Injection (b)(4), close monitoring for toxicity and a Docetaxel Injection (b)(4) 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)].</p>
<p>8. USE IN SPECIFIC POPULATIONS 8.6 Hepatic Impairment Patients with bilirubin >ULN should not receive TAXOTERE. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive TAXOTERE [see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]. The alcohol content in TAXOTERE Injection should be taken into account when given to patients with hepatic impairment [see Warnings and Precautions (5.11)].</p>	<p>8.6 Hepatic Impairment Patients with bilirubin >ULN should not receive docetaxel. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive docetaxel [see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)].</p>
<p>12. CLINICAL PHARMACOLOGY</p>	<p>12. CLINICAL PHARMACOLOGY</p>

12.3 Human Pharmacokinetics

Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m² to 115 mg/m² in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m² to 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. Mean total body clearance was 21 L/h/m².

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 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 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.

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<p>Effect of Age: A population pharmacokinetic analysis was carried out after TAXOTERE 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.</p> <p>Effect of Gender: The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel.</p>	<p>Effect of Age: 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.</p> <p>Effect of Gender: The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel.</p>
<p>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. <i>[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]</i></p>	<p>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 Docetaxel Injection (b)(4). Patients with severe hepatic impairment have not been studied. <i>[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]</i></p>
<p>Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/m² to 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.</p> <p>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 with ketoconazole <i>[see Dosage and Administration (2.7) and Drug-Drug Interactions (7)]</i>.</p>	<p>Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/m² to 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.</p> <p>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 with ketoconazole <i>[see Dosage and</i></p>

	<i>Administration (2.7) and Drug-Drug Interactions (7)].</i>
<p>Effect of Combination Therapies:</p> <ul style="list-style-type: none"> • 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 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. 	<p>Effect of Combination Therapies:</p> <ul style="list-style-type: none"> • 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 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/

RUNYAN JIN
10/16/2015

QI LIU
10/16/2015

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA 205934**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

Teikoku Pharma USA, Inc. (TPU) submitted an original New Drug Application (NDA 205934/SDN 5) for Docetaxel Injection (b)(4) Non-Alcohol Formula (20 mg/mL, 80 mg/4mL, and 160 mg/8mL) in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. This 505 (b)(2) application intends to rely on the FDA's findings of safety and effectiveness for the Reference Listed Drug (RLD) One-Vial Taxotere® (docetaxel) Injection, 20 mg/mL and 80 mg/4mL, of Sanofi-Aventis, U.S., LLC as the holder of the approved application NDA 020449 because the active ingredient, route of administration (IV infusion) and indications for the TPU drug product are the same as the RLD. Reference is made to 21 CFR Section 320.22 (a) and (b)(I) for the waiver of the requirement for the submission of in vivo Bioavailability/Bioequivalence data of a drug product. No bioequivalence studies are included in this application.

The applicant claims that Docetaxel Injection (b)(4) Non-Alcohol Formula would address FDA's safety concerns for the current marketed docetaxel formulations containing alcohol with a range from 2.0 to 6.4 g in a 200 mg dose, which may cause patients to experience intoxication or feel drunk during and after treatment. In addition, the applicant states that the non-alcohol formula would fulfill an unmet need for patients who have a known hypersensitivity to alcohol, who have experience hypersensitivity to alcohol in docetaxel injections, or who prefer not to use formulations containing alcohol. It also could benefit patients of Asian descent due to a genetic predisposition that accounts for hypersensitivity to ethanol.

The active ingredient of Docetaxel Injection (b)(4) Non-Alcohol Formula is the same as that of the approved RLD Taxotere. All inactive ingredients used in the Docetaxel Injection (b)(4) Non-Alcohol Formula, which are different from those in One-vial Taxotere, are shown in the following table.

Ingredient	Docetaxel Injection (b)(4) Non-Alcohol Formula	One-vial Taxotere
Docetaxel ¹	20 mg/mL	20 mg/mL
Soybean oil	27.5 mg/mL	N/A
Polysorbate 80	585 mg/mL	540 mg/mL
Citric acid (b)(4)	10 mg/mL	N/A
Polyethylene glycol (PEG) 300	442.2 mg/mL	N/A
Dehydrated alcohol	N/A	395 mg/mL

The applicant claims that the different inactive ingredients in Docetaxel Injection (b)(4) Non-Alcohol Formula are not expected to affect the amount of drug delivered at the site of action.

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA 205934**

NDA/BLA Number	205934/SDN 5	Brand Name	Docetaxel Injection (b)(4) Non-Alcohol Formula
OCP Division (I, II, III, IV, V)	V	Generic Name	Docetaxel
Medical Division	DOP1	Drug Class	Microtubule Inhibitor
OCP Reviewers	Runyan Jin, Ph.D.	Indication(s)	Breast cancer, Non-small cell lung cancer, Hormone refractory prostate cancer, Gastric adenocarcinoma, Squamous cell carcinoma of the head and neck cancer
OCP Team Leaders	Qi Liu, Ph.D.	Dosage Form	20 mg/mL, 80 mg/4 mL, 160 mg/8 mL multi-use vial
Date of Submission	2/26/15	Dosing Regimen	60 to 100 mg/m ² IV over 1 hours every 3 weeks
Estimated Due Date of OCP Review	TBD	Route of Administration	IV
Medical Division (CDTL) Due Date	TBD	Sponsor	Teikoku Pharma USA, Inc.
PDUFA Due Date		Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	x			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	x	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
QT assessment				

NDA 205934_Docetaxel Injection (b)(4)

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA 205934**

Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Preclinical study in mice:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Immunogenicity assessment				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	505(b)(2)
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	IV administration
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			x	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			x	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions,			x	

NDA 205934_Docetaxel Injection (b)(4)

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA 205934**

	submitted in the appropriate format (e.g., CDISC)?				
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			x	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Runyan Jin 4/22/2015

 Reviewing Clinical Pharmacologists Date

Qi Liu 4/22/2015

 Acting Team Leader/Team Leader Date

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

/s/

RUNYAN JIN
05/05/2015

QI LIU
05/05/2015