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RESEARCH**

APPLICATION NUMBER:
022534Orig1s000

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

BIOPHARMACEUTICS REVIEW

Office of New Drugs Quality Assessment

Application No.:	NDA 22-534	Reviewer: Angelica Dorantes, Ph.D	
Submission Date:	November 3, 2010	Supervisor: Patrick J. Marroum, Ph.D	
Division:	DDOP	Date Assigned:	February 10, 2011
Sponsor:	Sun Pharma Global FZE	Date of Review:	March 28, 2011
Trade Name:	Docefrez™ Injection	Type of Submission: 505 (b)(2) NDA Re-Submission Class 2	
Generic Name:	Docetaxel Injection		
Indication:	Docetaxel is used for the treatment of various types of cancers like breast cancer, non-small cell lung cancer, prostate cancer (b)(4)		
Formulation/strengths	Injectable Solution 20 mg/vial or 80 mg/vial		
Route of Administration	Intravenous		
Type of Review:	BIOWAIVER REQUEST		

SUBMISSION:

Sun Pharma Global FZE (Sun Pharma) submitted the Original NDA 22-534 for Docefrez™ Injection (20 mg/vial or 80 mg/vial) on April 23, 2009 under 505 (b) (2) of the Federal Food, Drug, and Cosmetic Act. The Re-submission for this NDA was submitted on November 3, 2010.

This 505 (b) (2) application relies for approval on the FDA's findings of safety and effectiveness for the Reference Listed Drug. This product has the same dosage form (i.e., injectable solution) as the Reference Listed Drug Taxotere® of Sanofi-Aventis U.S L.L.C. RLD product. This product is intended for the same indications, dosage regimen and route of administration as Taxotere®. The proposed indication for Docetaxel injection is the treatment of various types of cancers like breast cancer, non-small cell lung cancer, prostate cancer (b)(4).

BIOPHARMACEUTICS:

Formulation: Sun Pharma's Docefrez™ Injection product is a different formulation of Docetaxel for Injection containing the same amount of anhydrous docetaxel, 20 mg and 80 mg, as Taxotere®. Docefrez™ is packaged in a similar manner to Taxotere® with two vials, one containing the active ingredient and the other containing a diluent. The active ingredient is provided as a sterile, lyophilized white powder rather than as a concentrated solution. The diluent is ethanol (35.4%, w/w) in polysorbate 80 provided in (b)(4) vials with fill volumes of either 1 mL or 4 mL.

The quantitative composition in the Drug product vial and Diluent vial is listed in the following table.

Vial 1- Ingredient	Docefrez Injection Lyophilized Powder 20mg ^{(b) (4)}	Docefrez Injection Lyophilized Powder 80 mg ^{(b) (4)}
Docetaxel (anhydrous)	20 mg	80 mg
Vial 2 - Diluent		
Ethanol	(b) (4) (35.4% w/w)	(b) (4) (35.4% w/w)
Polysorbate 80		(b) (4)
Volume of Diluent		
Volume used for reconstitution (including overages)	1.00 ml	4.00 mL

A comparison of the RLD and proposed Docetaxel for Injection is provided in Table 1. The quantities of active ingredient (expressed as the base equivalent) are the same in the proposed formulation and the RLD formulation (Taxotere®).

Product	Taxotere® (Docetaxel) Injection Concentrate	Docefrez (Docetaxel for Injection)	Taxotere® (Docetaxel) Injection Concentrate	Docefrez (Docetaxel for Injection)
	20 mg strength		80 mg strength	
	RLD (Aventis Pharmaceuticals Inc.)	Proposed Product	RLD (Aventis Pharmaceuticals Inc.)	Proposed Product
Dosage Form	Injection Concentrate	Injection Lyophilized Powder	Injection Concentrate	Injection Lyophilized Powder
Route of Administration	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion
HOW SUPPLIED				
Product Vial				
Docetaxel trihydrate	20 mg (base eq.)	--	80 mg (base eq.)	--
Docetaxel (anhydrous)	--	20 mg	--	80 mg
Polysorbate 80	(b) (4)			
Volume	0.5 mL	--	2.0 mL	--
Diluent Vial				
Ethanol	(b) (4) (13% w/w)	(b) (4) (35.4% w/w)	(b) (4) (13% w/w)	(b) (4) (35.4% w/w)
Polysorbate 80	(b) (4)			
Water for Injection	(b) (4)			
Volume of Diluent	(b) (4)			
Volume used for reconstitution (including overages)	1.80 mL	1.00 mL	7.10 mL	4.00 mL

The proposed drug product, Docetaxel for Injection (Docefrez™), will be packaged in two (2) packaging presentations, each consisting of the following:

- a single use drug product vial containing docetaxel lyophilized powder (20 mg or 80 mg, amounts expressed in base equivalents)
- a single use diluent vial containing 35.4% w/w ethanol in polysorbate 80

Taxotere® is the Reference Listed Drug (RLD) and it is also provided as two vials, one containing the active ingredient and the other the diluent, each containing the following:

- a single use drug product vial containing docetaxel 20 mg/0.5 mL or 80 mg/2 mL in polysorbate 80
- a single use diluent vial containing 13% w/w ethanol in water for injection

Initial Stage Dilution (Diluent Vial): The first dilution step for Docetaxel for Injection and Taxotere® RLD is with the single-use, sterile, non-pyrogenic diluent provided with each corresponding drug product vial. The final concentrations of the two products following the initial stage dilution [REDACTED] (b) (4) are provided in the Table below.

Comparison of RLD and Docetaxel for Injection after Initial Dilution/Reconstitution

Composition	Taxotere – RLD	Docefrez - Docetaxel for Injection
20mg strength		
Docetaxel	20 mg	20 mg
Ethanol	[REDACTED] (b) (4)	
Polysorbate 80	[REDACTED]	
Water	[REDACTED]	
Final Volume (approximate)	[REDACTED]	
80mg strength		
Docetaxel	80 mg	80 mg
Ethanol	[REDACTED] (b) (4)	
Polysorbate 80	[REDACTED]	
Water	[REDACTED]	
Final Volume (approximate)	[REDACTED]	
Docetaxel concentration after initial reconstitution/ dilution (approximate)	10 mg/ml	24 mg/ml

After initial dilution, the quantity of docetaxel and polysorbate 80 per vial is [REDACTED] (b) (4) [REDACTED] whereas the ethanol content is slightly higher in Sun Pharma's proposed formulation.

Second Stage Dilution (Admixture In Commercially Available Infusion Bottle/Bag):

After initial dilution, both Docetaxel for Injection and Taxotere® RLD preparations are further diluted in intravenous solutions before administration to a patient. The diluted/reconstituted solution is added to bags or bottles with 250 mL of 0.9% sodium chloride injection, USP or 5% dextrose injection, USP to give a docetaxel concentration of 0.3 to 0.74 mg/mL, which is then administered by intravenous infusion. The next Table provides a comparison of Sun Pharma's proposed Docetaxel for Injection and Taxotere® RLD after admixture with intravenous solution, i.e., the solution that is to be given to the patient.

Comparison of RLD and Docetaxel for Injection after Admixture with Intravenous Solution (Second Dilution): Solution to be administered to Patients

	Taxotere RLD	Docetaxel for Injection
Composition	Docetaxel – 80 mg	Docetaxel – 80 mg (b) (4)
Infusion volume (5% Dextrose injection or 0.9% Sodium chloride injection)		(b) (4)
Drug concentration after admixture		(b) (4)
Polysorbate 80 concentration after admixture		(b) (4)
Alcohol concentration after admixture		(b) (4)

BIOWAIVER:

In this submission, Sun Pharma is requesting that the Agency’s requirement for the submission of in vivo Bioavailability/Bioequivalence (BA/BE) data to support the approval of Docefrez™ Injection (20 mg/vial or 80 mg/vial) be waived.

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:

- 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.

Sun Pharma’s Docetaxel for Injection (Docefrez™) is intended solely for administration as an intravenous infusion, following reconstitution with diluent and admixture in either 0.9% sodium chloride (normal saline) or 5% dextrose in water (D5W). As described below, Docetaxel for Injection and the RLD, Taxotere®, contain the same amount of docetaxel in the single use drug product vials but differ in presentations (dosage forms). However, from a BA/BE perspective, the (b) (4) active and inactive ingredients to be delivered to the patient are similar to those in the RLD. The amount of docetaxel and polysorbate 80 to be administered is (b) (4); the amount of ethanol is higher to achieve a solution but would not affect bioavailability of the product once it is in solution and also the proposed quantity to be used is within the IIG limits of intravenous use.

RECOMMENDATION:

The ONDQA-Biopharmaceutics has reviewed the information included in NDA 22-534 for Docefrez™ Injection 20 mg/vial or 80 mg/vial. Based on the Agency's CFR 320.22(b)(1) regulations and the information showing that **1)** their product contains the same active ingredient as the reference listed drug product and all the inactive ingredients are within IIG limits, **2)** the route of administration, dosage form and indications of their product are the same as the RLD product, ONDQA-Biopharmaceutics considers that the in vivo BA/BE of Sum Pharma's Docetaxel Injection is self-evident. Therefore, the sponsor's request for a biowaiver for Docefrez™ Injection 20 mg/vial or 80 mg/vial is acceptable and the biowaiver is granted.

Angelica Dorantes, Ph. D.

Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.

Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 22-534, Debbie Mesmer

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/s/

ANGELICA DORANTES
04/01/2011

PATRICK J MARROUM
04/01/2011

Clinical Pharmacology Review

NDA 22534/Serial Number 18
Submission Date: 10/19/10
Brand Name: Docefrez for Injection™
Generic Name: Docetaxel
Formulation: (b) (4) 80 mg vial with diluent and (b) (4) 20 mg vial with diluent
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: Sun Pharma Global FZE
Submission Type; Code: Request for final approval and labeling supplement
Dosing regimen: IV over 1 hr every 3 weeks.
Breast Cancer: 60-100 mg/m²,
Non-small cell lung cancer: 75 mg/m²,
Hormone Refractory Prostate cancer: 75 mg/m²
Indication: Breast cancer, non-small cell lung cancer and hormone refractory prostate cancer.

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1 EXECUTIVE SUMMARY

The original submission for the current application was reviewed previously by the Office of Clinical Pharmacology (NDA 22534/S-001; letter date: 4/23/09). Based on the original review, the submission was found to be acceptable from a clinical pharmacology perspective. The current review summarizes the relevant Clinical Pharmacology labeling recommendations for this 505(b)(2) application.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 reviewed the information contained in NDA 22534 (Serial number 18). This submission is considered acceptable from a clinical pharmacology perspective.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

1.2 PHASE IV COMMITMENTS

None.

1.3 REGULATORY BACKGROUND

The original submission for the current 505(b)(2) application was reviewed previously by the Office of Clinical Pharmacology (NDA 22534/S-001; letter date: 4/23/09). Based on the original review, the submission (including labeling recommendations) was found to be acceptable from a clinical pharmacology perspective. FDA issued a tentative approval to this NDA on 2/23/10.

The indications sought by the applicant are:

- Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure.
- Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure.
- Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer.

The current submission comprises of a request for final approval and the final updated labeling based on the most recently approved label for the two-vial formulation of Taxotere (listed drug NDA 20449) which was approved on 5/13/10.

The purpose of the current review is to summarize the relevant Clinical Pharmacology labeling recommendations for this 505(b)(2) application.

1.4 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Signatures:

Reviewer: Jeanne Fourie Zirkelbach, PhD
Division of Clinical Pharmacology 5

Team Leader: Qi Liu, PhD
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - J Mwidau; MTL - P Cortazar; MO - K Snyder,
DCP- Reviewers - J Fourie Zirkelbach,
5: DDD - B Booth
PM TL -
PG TL -
DD - A Rahman

2 QUESTION BASED REVIEW

Note: Only relevant sections were completed.

2.1 GENERAL ATTRIBUTES

- 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?**
- 2.1.2 What are the proposed mechanisms of action and therapeutic indications?**
- 2.1.3 What are the proposed dosage(s) and route(s) of administration?**

2.2 GENERAL CLINICAL PHARMACOLOGY

- 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**
- 2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?**
- 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**
- 2.2.4 Exposure-response**

2.3 INTRINSIC FACTORS

- 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?**
- 2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**
- 2.3.2.1 Pediatric patients**
- 2.3.2.2 Renal impairment**
- 2.3.2.3 Hepatic impairment**
- 2.3.2.4 What pregnancy and lactation use information is there in the application?**

2.4 EXTRINSIC FACTORS

- 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?**
- 2.4.2 Drug-drug interactions**

2.5 GENERAL BIOPHARMACEUTICS

- 2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**
- 2.5.2 What is the composition of the to-be-marketed formulation?**
- 2.5.3 What moieties should be assessed in bioequivalence studies?**
- 2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**
- 2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?**

2.6 ANALYTICAL SECTION

- 2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?
- 2.6.2 Which metabolites have been selected for analysis and why?
- 2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?
- 2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, <http://www.fda.gov/cder/guidance/4252fnl.pdf>)
- 2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?
- 2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?
- 2.6.4.3 What are the accuracy, precision, and selectivity at these limits?
- 2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?
- 2.6.4.5 What is the QC sample plan?

3 DETAILED LABELING RECOMMENDATIONS

All of the applicant's proposed labeling for the Clinical Pharmacology Sections of the label were acceptable and identical to the most recent approved language found in the reference product label.

Only relevant clinical pharmacology sections are shown in track change format below. The sponsor's proposed changes from the most recent Taxotere label are underlined. FDA recommended changes are **underlined and bolded**.

SPONSOR PROPOSED PACKAGE INSERT

-----DRUG INTERACTIONS-----

- Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism. (7)

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 DOCEFREZ and drugs that inhibit CYP3A4 may increase exposure to docetaxel and

should be avoided. In patients receiving treatment with DOCEFREZ, close monitoring for toxicity and a DOCEFREZ 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 USE IN SPECIFIC POPULATIONS

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)]

12.3 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.

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.

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 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 DOCEFREZ. 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/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.

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 [*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.

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.

4 APPENDICES

4.1 NDA FILING AND REVIEW FORM

General Information About the Submission				
NDA Number	22534	Brand Name	Docefrez®	
DCP Division (I, II, III, IV, V)	V	Generic Name	Docetaxel	
Medical Division	Oncology	Drug Class	Microtubule Stabilizer	
OCP Reviewer	Jeanne Fourie Zirkelbach, PhD	Indication(s)	Breast cancer, non-small cell lung cancer and hormone refractory prostate cancer.	
OCP Team Leader	Qi Liu, PhD	Dosage Form	(b) (4) 80 mg vial with diluent and (b) (4) 20 mg vial with diluent	
Date of Submission	10/19/2010	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 , (b) (4)	
Due Date of OCP Review		Route of Administration	Intravenous infusion	
Standard PDUFA Due Date		Sponsor	Sun Pharma Global FZE	
Clinical Pharmacology 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:				
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:				
geriatrics:				
renal impairment:				
hepatic impairment:				
pediatrics:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
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:				
QTC studies:				
In-Vitro Release BE				
(IVVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References				
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm?				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	J Fourie Zirkelbach, Ph.D.			
Secondary reviewer Signature and Date	Q Liu, Ph.D.			

CC: HFD-150 (CSO – D Hanner; MTL– P Cortazar; MO –K Snyder)

HFD-860 (Reviewer – J Fourie Zirkelbach; TL – Q Liu; DDD - B Booth; DD - A Rahman)

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/s/

JEANNE FOURIE
03/31/2011

QI LIU
04/01/2011

Clinical Pharmacology Review

NDA 22-534/S-001
Submission Date: 23-Apr-2009
Brand Name: Docefrez™
Generic Name: Docetaxel
Formulation: 20 mg (b) (4) and 80 mg (b) (4) and diluent
OCP Reviewer: Young Jin Moon, Ph.D.
OCP Deputy Division Director: Brian P. Booth, Ph.D.
OCP Division: Division of Clinical Pharmacology V
ORM Division: Division of Drug Oncology Products
Sponsor: Sun Pharma
Submission Type; Code: 505 (b) (2) NDA
Indication: Breast cancer, Non-small cell lung cancer, Prostate cancer (b) (4)
(b) (4)

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1 EXECUTIVE SUMMARY

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Sun Pharma submitted an original New Drug Application (NDA 22-534/S-001) for DocefrezTM. The reference listed drug is Taxotere[®] for Injection (docetaxel; Sanofi-Aventis). The following (b)(4) indications have been approved for Taxotere[®] for Injection[®] (NDA 20-449):

For the treatment of breast cancer; non-small cell lung cancer; hormone refractory prostate cancer; gastric adenocarcinoma; squamous cell carcinoma of the head and neck cancer.

The applicant was informed by the Division on 16 January 2008 that a bioequivalence study with the RLD is not needed. The current application thus does not include clinical studies and relies on the FDA's findings of safety and effectiveness for Taxotere[®] for Injection (NDA 20-449).

1.1 RECOMMENDATIONS

This application is acceptable from a clinical pharmacology perspective.

Phase IV commitments

None.

Labeling Recommendations

The Clinical Pharmacology sections of the labeling for DocefrezTM have been reproduced within the Detailed Labeling Recommendations Section below.

Signatures:

Reviewer: Young Jin Moon, Ph.D.
Division of Clinical Pharmacology
5

Deputy Division Director: Brian P. Booth, Ph.D.
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - A Davis-Warren ; MTL - E Maher; MO - Q Ryan
DCP-5: Reviewer - Y Moon
DDD - B Booth
DD - A Rahman

1.2 CLINICAL PHARMACOLOGY SUMMARY

Taxotere[®] for Injection (docetaxel) is a product of Sanofi-Aventis and was approved by the FDA on May 14, 1996 (NDA 20-449). Taxotere[®] for Injection is indicated for the treatment of breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck cancer.

Taxotere[®] for Injection is provided as two vials, one containing the active ingredient and the other the diluent, in a blister pack in one carton. The dosage form and two strengths of Taxotere[®] (docetaxel) Injection Concentrate are described in the approved labeling as follows:

- 20 mg/0.5 mL: 20 mg docetaxel in 0.5 mL polysorbate 80 and Diluent for Taxotere[®] 20 mg (13% w/w) ethanol in water for injection
- 80 mg/2 mL: 80 mg docetaxel in 2 mL polysorbate 80 and Diluent for Taxotere[®] 80 mg (13% w/w) ethanol in water for injection.

Taxotere[®] is typically administered as a 1-hour infusion once every 3 weeks over a 10-cycle course. Doses range from 60 to 100 mg/m², alone or in combination with other chemotherapeutic agents. In the current application, Taxotere[®] for Injection is designated as the reference listed drug (RLD).

Sun Pharma submitted the current application to market a new drug product, Docefrez[™] as an alternative to the RLD. The indications for which the applicant is seeking approval are:

- The treatment of breast cancer, non-small cell lung cancer, hormone refractory prostate cancer (b) (4)

These (b) (4) are (b) (4) approved indications for the RLD. The applicant is not seeking approval for the squamous cell carcinoma of the head and neck cancer indication of the RLD.

Sun Pharma's product is a different formulation of Docetaxel for Injection. It contains the same amount of anhydrous docetaxel, 20 mg or 80 mg, as Taxotere[®]. Docefrez[™] is packaged in a similar manner to Taxotere[®] with two vials, one containing the active ingredient and the other containing a diluent. The active ingredient is provided as a sterile, lyophilized white powder rather than as a concentrated solution. The diluent is ethanol (35.4%, w/w) in polysorbate 80 provided in (b) (4) vials with fill volumes of either 1 mL or 4 mL. A comparison of the RLD and Docefrez[™] is provided in table below. The quantities of active ingredient (expressed as the base equivalent) are the same in the proposed formulation and the RLD formulation (Taxotere[®]). Dose and dosage regimen of Docefrez[™] are same as ones of Taxotere[®] (1-hour infusion once every 3 weeks).

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Table 1 Comparison of RLD Taxotere[®] and Docefrez[™] for Injection Dosage Forms

Product	Taxotere [®] (Docetaxel) Injection Concentrate	Docefrez (Docetaxel for Injection)	Taxotere [®] (Docetaxel) Injection Concentrate	Docefrez (Docetaxel for Injection)
	20 mg strength		80 mg strength	
	RLD (Aventis Pharmaceuticals Inc.)	Proposed Product	RLD (Aventis Pharmaceuticals Inc.)	Proposed Product
Dosage Form	Injection Concentrate	Injection Lyophilized Powder	Injection Concentrate	Injection Lyophilized Powder
Route of Administration	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion
HOW SUPPLIED				
Product Vial				
Docetaxel trihydrate	20 mg (base eq.)	--	80 mg (base eq.)	--
Docetaxel (anhydrous)	--	20 mg	--	80 mg
Polysorbate 80	(b) (4)			
Volume	0.5 mL	--	2.0 mL	--
Diluent Vial				
Ethanol	(b) (4) (13% w/w)	(b) (4) (35.4% w/w)	(b) (4) (13% w/w)	(b) (4) (35.4% w/w)
Polysorbate 80	(b) (4)			
Water for Injection	(b) (4)			
Volume of Diluent	(b) (4)			
Volume used for reconstitution (including overages)	1.80 mL	1.00 mL	7.10 mL	4.00 mL

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

Refer to the RLD original NDA 20-449 (Approval Date: 5/14/96) for the issues listed in Section 2.1.2 to Section 2.4.

Section 2.6 is not applicable to this application.

- 2.1.1** What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?
- 2.1.2** What are the proposed mechanisms of action and therapeutic indications?
- 2.1.3** What are the proposed dosage and route of administration?
- 2.2** GENERAL CLINICAL PHARMACOLOGY
 - 2.2.1** What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?
 - 2.2.2** What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?
 - 2.2.3** Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?
 - 2.2.4** Exposure-response
 - 2.2.4.1** What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?
 - 2.2.4.2** What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?
 - 2.2.4.3** Does this drug prolong the QT or QTc interval?
 - 2.2.4.4** Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?
 - 2.2.5** Pharmacokinetic characteristics of the drug and its major metabolites
 - 2.2.5.1** What are the single dose and multiple dose PK parameters?
 - 2.2.5.2** How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
 - 2.2.5.3** What are the characteristics of drug absorption?
 - 2.2.5.4** What are the characteristics of drug distribution?
 - 2.2.5.5** Does the mass balance study suggest renal or hepatic as the major route of elimination?
 - 2.2.5.6** What are the characteristics of drug metabolism?
 - 2.2.5.7** What are the characteristics of drug excretion?
 - 2.2.5.8** Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?
 - 2.2.5.9** How do the PK parameters change with time following chronic dosing?

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients

2.3.2.2 Renal impairment

2.3.2.3 Hepatic impairment

2.3.2.4 What pregnancy and lactation use information is there in the application?

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

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

See General Clinical Pharmacology Section 1.2, for the quantitative and qualitative comparisons between Docefrez™ and the RLD.

2.5.3 What moieties should be assessed in bioequivalence studies?

The applicant was informed by the Division on 16 January 2008 that a bioequivalence study with the RLD is not needed. This submission did not include clinical studies and relies on the FDA's findings of safety and effectiveness for Taxotere® for Injection (NDA 20-449).

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

3 DETAILED LABELING RECOMMENDATIONS

Only relevant Clinical Pharmacology sections are included below.

1) Page 1

CONTRAINDICATIONS
| • Hypersensitivity to (b) (4) locetaxel or polysorbate 80 (4)

2) Page 1, 3, 8, 12, and 13

Replace (b) (4) to "ALT" and (b) (4) to "AST".

3) Page 7

2.8 Preparation and Administration

| Between 2- and 8°C

44 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS)
immediately following this page

Office of Clinical Pharmacology

5 NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information about the Submission

NDA Number	22-534/000	Brand Name	Docefrez™
DCP Division (I, II, III, IV, V)	V	Generic Name	Docetaxel
Medical Division	Oncology	Drug Class	Antineoplastic agent that acts by disrupting the microtubular network
OCP Reviewer	Young-Jin Moon, Ph.D.	Indication(s)	Breast cancer Non-small cell lung cancer Prostate cancer (b) (4)
OCP Deputy Division Director	Brian Booth, Ph.D.	Dosage Form	IV injection
Date of Submission	April 23, 2009	Dosing Regimen	Varies depending on indications. Doses ranging from 60 to 100 mg/m ² given as a 1-hour infusion every 3 weeks, alone or in combination with other chemotherapeutic agent
Due Date of OCP Review	January 18, 2010	Route of Administration	IV infusion
Standard PDUFA Due Date	October 18, 2009	Sponsor	Sun Pharma

Clinical Pharmacology 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:				
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:				
geriatrics:				
renal impairment:				
hepatic impairment:				
pediatrics:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
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:				
QTC studies:				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS	X			
BCS class				
III. Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References	X			
Total Number of Studies				

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		
2	Has the applicant provided metabolism and drug-drug interaction information?		X		
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
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			Information of Reference Listed Drug (RLD)
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			Information of RLD
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			Information of RLD

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
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.

Young-Jin Moon

Reviewing Clinical Pharmacologist

Date

Brian P. Booth
Deputy Division Director

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22534	ORIG-1	SUN PHARMA GLOBAL FZE	DOCEFREZ INJECTION (20/80 MG/VIAL)

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

/s/

YOUNG J MOON
01/07/2010

BRIAN P BOOTH
01/15/2010