CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022534Orig1s000

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 REVIEW AND EVALUATION

Application number:	**22,534**
Supporting document/s:	**None**
Applicant's letter date:	**April 23, 2009**
CDER stamp date:	**April 23, 2009**
Product:	**Docefrez (docetaxel) for Injection**
Indication:	**Breast Cancer, NSCLC, Prostate Cancer** (b) (4) (b) (4)
Applicant:	**Sun Pharma Global FZE**
Review Division:	**Division of Drug Oncology Products**
Reviewer:	**Margaret E. Brower, Ph.D.**
Supervisor/Team Leader:	**Haleh Saber, Ph.D.**
Division Director:	**Robert Justice, M.D.**
Project Manager:	**Alberta Davis-Warren**

Date entered in DARRTS: 2/18/2010

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approval as a 505(b)(2) is recommended.

B. Recommendation for nonclinical studies: None

C. Recommendations on labeling: The content of the pharmacology/toxicology sections of the label is similar to that of the reference drug.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

All Docefrez impurities/degradants were found to be within ICH Q3B(R2) (b) (4) The impurity was qualified in a toxicology study in mice, bridging the reference listed drug (RLD) to Docefrez.

The approval of Docefrez will not be affected by the 2009 Citizen's Petition submitted to the agency by Sanofi (innovator of the Reference Listed Drug, Taxotere). (b) (4)

B. Pharmacologic activity

The anticancer activity of docetaxel has been previously described. Additional data were not submitted with this NDA.

C. Nonclinical safety issues relevant to clinical use

The safety of docetaxel has been previously described.

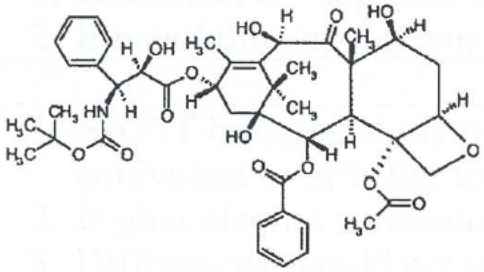
PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 22,534
Review number: 1
Date/type of submission: April 23, 2009/505(b)(2) NDA
Information to Applicant: Yes ( ) No (X)
Applicant and/or agent: Sun Pharma Global FZE (Sun Pharma), Sharjah, United Arab Emirates /Salamandra, Bethesda, MD
Manufacturer: (b) (4)

Reviewer name: Margaret Brower, Ph.D.
Division name: Division of Drug Oncology Products
Review completion date: February 3, 2010

Drug:

Trade name: Docefrez (RLD: Taxotere)
Generic name: docetaxel
Code name: none
Chemical name: (2R,3S)-N-benzoyl-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate
Molecular weight/molecular formula: (b) (4) $C_{43}H_{53}NO_{14}$
CAS No.: 114977-28-5
Structure:



Relevant INDs/NDAs: (b) (4) NDA 20,449 (Reference Listed Drug)

Note: Bridging study for impurity qualification submitted to current NDA.

Pharmacologic class: Microtubule inhibitor

Intended clinical population:
Breast cancer in patients with locally advanced or metastatic cancer following failure of prior chemotherapy. (b) (4)

NSCLC, locally advanced or metastatic, following failure of platinum-based therap (b) (4)

Prostate cancer in combination with prednisolone for treatment of androgen independent (hormone refractory) metastatic cancer

(b) (4)

Clinical formulation:

Comparison of Taxotere and Docefrez following initial dilution/reconstitution

Component	% composition	
	Taxotere RLD	Docefrez
Docetaxel		(b) (4)
Ethanol, USP		
Polysorbate 80		
Water		

Table generated by reviewer.

Final Concentration of components for administration to patients

Component	Taxotere	Docefrez
Docetaxel		(b) (4)
Polysorbate 80		
Ethanol, USP		
Infusion volume		

Reconstitution of Docefrez

Product	Fill Range of the Diluent (35.4% w/w ethanol in polysorbate 80)	Volume of Diluent to be added for the reconstitution	Concentration of initial reconstituted solution
Docetaxel 20 mg vial	1.10 – 1.15 mL	1 mL	20 mg/0.8 mL
Docetaxel 80 mg vial	4.13 – 4.29 mL	4 mL	24 mg/mL

The initially diluted solution is added to 250mL of 0.9% NaCL USP, or 5% dextrose injection USP to provide a docetaxel concentration of 0.3 to 0.74mg/mL. The final concentration of 0.74 mg/ml docetaxel should not be exceeded.

(b) (4)

Route of administration: iv

Disclaimer: Tabular and graphical information is from Applicant's submission unless stated otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA #22,534 are owned by Sun Pharma or are data for which Sun Pharma has obtained a written right of reference. Any information or data necessary for approval of NDA#22,534 that Sun Pharma does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Sun Pharma does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA #22,534.

INTRODUCTION/DRUG HISTORY/IMPURITY CONCERN:
Taxotere (docetaxel) for Injection Concentrate, NDA 20,449, was approved on May 15, 1996 for the treatment of refractory, locally advanced or metastatic breast cancer. On December 23, 1999, Taxotere was approved as a single agent for the treatment of advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy at the recommended dose of 60-100mg/m^2 administered iv once every three weeks. As an adjuvant therapy, Taxotere was approved on May 19, 2004 in combination with prednisone for the treatment of androgen independent (hormone refractory) metastatic prostate cancer at a recommended dose of 75mg/m^2 administered once every 3weeks in combination with 5mg oral prednisone BID. In 2005, Taxotere was approved in combination with cisplatin and 5-FU for the treatment of gastric adenocarcinoma. Taxotere (with cisplatin and flurouracil) is also approved for induction treatment of locally advanced SCCHN. As mentioned above, the Sun Pharma 505(b)(2) NDA application for Docefrez is indicated for the same clinical patient population as Taxotere.

Several drug product batches of Docefrez (batches JK70373, JK80098, and JK80099) were tested in stability studies up to 24 months at 2 to 8 degrees C. All Docefrez impurities/degradants were found to be within ICH Q3B(2) (b) (4) in batch #JK80098, 20mg vial concentration (NDA section 2.3.P. Drug Product description and composition). When considering all batches, levels of (b) (4) ranged from (b) (4) As a result of these stability studies, Sun Pharma proposes (b) (4) in the drug product (see comparative table below), and has qualified the impurity in a toxicology study bridging the RLD to Docefrez, as recommended by the Division.

Sun Pharma proposed acceptance criteria for individual impurities

Impurity identification	Release Specification	Shelf life (stability) specification
(b) (4)		

Table generated by reviewer.

CITIZEN'S PETITION FROM INNOVATOR OF REFERENCE LISTED DRUG:
In June, 2009, Sanofi submitted a Citizen's Petition (CP) to the Agency (b) (4)

(b) (4)

(b) (4) The approval of Docefrez will not be effected by the Citizen's Petition.

DATA REVIEW

PHARMACOLOGY – None

SAFETY PHARMACOLOGY - None

PHARMACOKINETICS/TOXICOKINETICS - None

GENERAL TOXICOLOGY (Tables in this section were generated by the reviewer.)

Study title: **Acute toxicity study of Docetaxel for Injection with (b) (4), placebo and Taxotere in CD-1 mice by intravenous route**

Key study findings:
- Toxicities of Docefrez (b) (4) are comparable to Taxotere

Study no: BRT/08/097
Volume #, and page #: electronic submission (Module 4)
Conducting laboratory and location: Biological Research Toxicology, Sun Pharma Advanced Research Company, Vadodara, India
Date of study initiation: November 10, 2008
GLP compliance: Y OECD Principles of Good Laboratory Practice, 1997
QA report: yes (X) no ( )
Drug, lot #, and % purity: Docefrez 20mg/vial: Batch # JK80098A, 98.43% pure (study author name of study material: Docetaxel for Injection); Taxotere RLD 80mg/vial: D6D399

Note 1: Study conducted with the marketed formulation of Docefrez. Study report description of test material: "use/reconstitute just before use Docetaxel for Injection".

Note 2: The concentration of the (b) (4) degradate in the Analytical Report for the test material was noted as (b) (4). The comparative concentration of the same degradate in the Reference Listed Drug was (b) (4).

Formulation/vehicle: Saline control for Taxotere; diluent control for Docefrez

Methods: Mice were observed for 15 days prior to sacrifice. On days 2/3, and 15, separate mice/sex/dose (5/analysis) were used for hematological and biochemical evaluation.

Dosing:

Species/strain: CD-1 mice
#/sex/group (main study): 20
Satellite groups: none
Age: 4-6w
Weight: 30-35g, males; 25-28g, females
Doses in administered units: 40, 80 mg/kg Docefrez; 40, 80 Taxotere
Route and infusion rate: iv bolus: 8mL/kg dose volume for controls and high-dose, 4mL/kg dose volume for low-dose (concentration of 10mg/mL)

Observation	Time of assessment
Mortality	.5, 1-4, 6h post dose followed by 2x/d to 14d
Clinical observations	.5, 1-4, 6h post dose, followed by 2x/d to 14d
Body weight	d1,4,7, 10,14,15 post dose
Food consumption	d1,7,14
Hematology	d2/3, 15
Clinical chemistry	d2/3, 15
Organ weights	d2/3, 15
Gross pathology	d2/3, 15
Histopathology	d2/3, 15

Observation (time)	Docefrez (40mg/kg) + (b) (4)		Docefrez (80mg/kg) + (b) (4)		RLD (40mg/kg)		RLD (80mg/kg)	
	M	F	M	F	M	F	M	F
Mortality	None							
Clinical observations	Piloerection was observed in all groups, with a higher incidence in HD mice administered the RLD. Ataxia, abdominal breathing, and injection site inflammation were observed at the HD in the RLD and docetaxel + (b) (4). Lethargy was observed at the HD RLD.							
Body weight	UR							
Food consumption	UR							
Hematology[a] WBC (Day 2) Platelet (Day 2) Reticulocyte (Day 2)	 ↓40 ↓53	 ↓40 ↓11 ↓47	 ↓28 ↓33	 ↓33 ↓9 ↓42	 ↓31 ↓17 ↓48	 ↓36 ↓60	 ↓38 ↓10 ↓57	 ↓36 ↓13 ↓62
Clinical chemistry[a] AST (Day 2)			 ↑51				 ↑48	
Organ wt (abs) [a] Epididymis Testes	 ↓15		 ↓43 ↓44		 ↓10		 ↓32	
Gross pathology	Small thymus: 2/8 HD examined with Docefrez + (b) (4); 1/8 HD examined RLD Small dark spots on lungs: 1/8 HD examined RLD							
Histopathology [N=10]	See table below							

Abbreviations: UR = unremarkable when compared to concurrent placebo control; d = day; M = male; F = female; HD = high-dose; RLD = Reference Listed Drug

[a]Percent change compared to concurrent placebo control

Hematological indices recovered by D15 following dosing.

Histopathology (male mice; N=10)

Organ/finding	Placebo control	Docefrez (40mg/kg) + (b) (4)	Docefrez (80mg/kg) + (b) (4)	RLD (40mg/kg)	RLD (80mg/kg)
Cerebrum/hemorrhage (minimal-mild)	3		4		4
/congestion (min-mild)	1		6		5
Cerebellum/hemorrhage (minimal)	1		3		3
/congestion (minimal)	2		4		4
/ hemorrhage (minimal)	3		1		6
Thymus/Lymphoid atrophy (minimal-severe)		6 (minimal-mild)	10 (mild-severe)	5(minimal-mild)	10 (minimal-severe)
Testes/degenerated sperm (moderate-severe)			10		9
/atrophy (mod-severe)			10		8
Epididymes/degenerated sperm (minimal-mod)			6		8
/oligospermia			4		2
Colon/lymphoid hyperplasia (minimal)			2		1

Abbreviations: min = minimal; mod = moderate; RLD = Reference Listed Drug

Histopathology Females (N=10)

Organ/finding	Placebo control	Docefrez(40mg/kg) + (b) (4)	Docefrez(80mg/kg) + (b) (4)	RLD (40mg/kg)	RLD (80mg/kg)
Cerebellum/hemorrhage (minimal)	3				4
/congestion (min)	4		3		6
Rectum/lymphoid hyperplasia (minimal)			1		2
Ovaries/↓#follicles (minimal-severe)			8		9
/hypoplasia (minimal-severe)			6		7
Thymus/lymphoid atrophy (min-severe)		10	10	10	10

Abbreviations: min = minimal; RLD = Reference Listed Drug

Histopathology inventory for NDA 22,534

Study	BRT/08/097
Species	Mouse
Adrenals	*
Aorta	
Bone Marrow smear	
Bone (femur)	
Brain	*
Cecum	
Cervix	
Colon	
Duodenum	
Epididymis	*
Esophagus	
Eye	

Fallopian tube	
Gall bladder	*
Gross lesions	
Harderian gland	
Heart	*
Ileum	
Injection site	
Jejunum	
Kidneys	*
Lachrymal gland	
Larynx	
Liver	*
Lungs	
Lymph nodes, cervical	
Lymph nodes mandibular	
Lymph nodes, mesenteric	
Mammary Gland	
Nasal cavity	
Optic nerves	
Ovaries	*
Pancreas	
Parathyroid	
Peripheral nerve	
Pharynx	
Pituitary	
Prostate	
Rectum	
Salivary gland	
Sciatic nerve	
Seminal vesicles	
Skeletal muscle	
Skin	
Spinal cord	
Spleen	*
Sternum	
Stomach	
Testes	*
Thymus	
Thyroid	
Tongue	
Trachea	
Urinary bladder	
Uterus	
Vagina	
Zymbal gland	
Standard List	X

X, histopathology performed
*, organ weight obtained

There were no additional toxicology studies submitted.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

All Docefrez impurities/degradants were found to be within ICH Q3B(R2) (b) (4) The impurity was qualified in a toxicology study in mice, bridging the Reference Listed Drug (Taxotere) to Docefrez. Toxicities of Docefrez at the 40

and 80 mg/kg dose [redacted] (b) (4) were generally comparable to those observed with Taxotere at the same doses.

The approval of Docefrez will not be affected by the 2009 Citizen's Petition submitted to the agency by Sanofi (innovator of the RLD, Taxotere). [redacted] (b) (4)

There were no other non-clinical issues for this 505(b)(2).

Recommendations:
There are no pharmacology/toxicology issues which preclude approval of Docefrez as a 505(b)(2).

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

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/s/

MARGARET E BROWER
02/18/2010

HALEH SABER
02/18/2010