CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022534Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Anthony J. Murgo, M.D., M.S.; DDOP, Acting DDD
Subject	Acting Deputy Director Summary
NDA 505(b)(2)	022534
Applicant Name	Sun Pharma Global FZE
Date of Submission	Apr 23, 2009 (original); Nov 3, 2010 (class 2 re-subm.)
PDUFA Goal Date	May 3, 2011
Proprietary Name / Established (USAN) Name	Docefrez™ Injection/Docetaxel Injection
Dosage Forms / Strength	• 20 mg/single-use vial and diluent • 80 mg/vial and diluent
Proposed Indication(s)	. **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
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	X
Statistical Review	
Pharmacology Toxicology Review	
CMC Review/OBP Review	X (Both CMC and OBP)
Microbiology Review (QA)	X
Clinical Pharmacology Review	X
DDMAC	X (labeling)
DSI	
CDTL Review	X
OSE/DMEPA	X
OSE/DDRE	
OSE/DRISK	
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This 505(b)(2) NDA is for DOCEFREZ (docetaxel) for Injection. The sponsor is Sun Pharma and the reference listed drug (RLD) is Taxotere (docetaxel) Injection (NDA 20449; sponsor Sanofi-Aventis). The current 505(b)(2) application does not include clinical studies and relies on the FDA's findings of safety and effectiveness for RLD. Since there are no new clinical data, the review focused on CMC. The non-clinical pharmacology and toxicology information was previously reviewed during the last cycle and found acceptable. The application received Tentative Approval on February 23, 2010. This summary pertains to a November 3, 2010 class 2 Re-submission.

2. Background

Docetaxel is an anti-neoplastic agent with anti-tumor activity against a variety of solid tumors. The proposed labeled indications in this 505(b)(2) application are the same as the approved indications of the RLD but of limited scope. The sponsor is not requesting the Head and Neck cancer and gastric cancer indications and, with this resubmission, is limiting the breast cancer and non-small cell lung cancer indications to the single-agent use, not the combination indications.

The specific indications proposed for DOCEFREZ are as follows:

- **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 patents on the above indications are expired.

3. CMC

OND/QA

Sun Pharma's Docefrez™ Injection product is a different formulation of Docetaxel for Injection containing the same amount of anhydrous docetaxel, 20 mg and 80mg, 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. After reconstitution with diluent, the Sun's Docefrez yields a docetaxel concentration of 20 mg/0.8 mL for the 20 mg strength and 24 mg/mL for the 80 mg strength. The

concentrations differ from that of the 20 and 80 mg strengths of the 2-vial RLD, which is 10 mg/mL for both strengths. Also of note, a new one-vial formulation of Taxotere was approved by the FDA on August 2, 2010. This one vial formulation does not require a two step dilution process, and the drug can be withdrawn from the vial and added directly to the infusion solution. However, whereas the two-vial formulation yielded a concentration of 10 mg/mL before being added to the infusion solution, the new one vial formulation was approved with a concentration of 20 mg/mL. In view of the above, DMEPA has considered the implications of having multiple formulations with varying concentrations on the market and the potential for medication errors (See Section 12 pertaining to the labeling of Docefrez).

In the original submission, the major CMC issue was related to level of one drug substance impurity (b) (4). Sun Pharma has requested the qualification of impurity (b) (4) in the drug substance. However, according to the Pharmacology/Toxicology review signed February 18, 2010, the (b) (4) impurity was adequately qualified in a toxicology study in mice, bridging the reference listed drug (RLD) to Docefrez. The rest of the drug substance impurities at release are controlled at or below ICHQ3A.

In the Amendment (SR 020) submitted on 03-Nov-2010, Sun Pharma provided update on the stability data for Docefrez (docetaxel) for Injection, 20 mg/vial and 80 mg/vial and Diluent for 20 mg and 80 mg strength.

In addition, Sun Pharma proposed the following changes:
1. Intended commercial batches (b) (4) with respect to the exhibit batches (exhibit batches were originally submitted in the initial NDA).

(b) (4)

Given the importance and nature of the changes, the re-submission was considered Class 2.

CMC found the following changes acceptable:
(1) Based on the information provided for the proposed commercial batches for 20 mg Docefrez and Diluent for 20 mg Docefrez, the (b) (4) is acceptable.

(2) Based on drug product stability data, 30 months expiration dating period is granted for drug product (Docefrez 20 mg/vial and 80 mg/vial) and Diluent (for Docefrez 20 mg and for Docefrez 80 mg) when stored at 2°C to 8°C (36°F to 46°F) protected from light. The proposed shelf-life of (b) (4) (when stored between 2°C-8°C [36°F-46°F], protected from bright light) is acceptable.

I concur with the conclusions reached by the chemistry reviewer and team leader signed March 3 and April 5, 2011, respectively that the submission is acceptable for approval (the "pending satisfactory resolution of labeling issues" noted in the CMC review have been adequately addressed as noted below).

Product Quality Microbiology

The Product Quality Microbiology reviewer recommended approval of the original NDA in a review dated November 13, 2009. However, the Class 2 resubmission submitted by applicant on November 3, 2010 provided changes to the manufacturing process. Subsequently, the applicant submitted an amendment on December 21, 2010 withdrawing some of the major changes which were provided in the November 3, 2010 submission. The changes which were withdrawn include the following: (b) (4) (Cover Letter dated December 21, 2010).

I concur with the Product Quality Microbiology review of the resubmission (signed by the primary reviewer and team leader on March 1, 2011) that application is approvable from the perspective of product quality microbiology.

4. Nonclinical Pharmacology/Toxicology

There is no non-clinical pharmacology/toxicology review of this resubmission because it does not contain any changes or new information pertaining to this discipline since it was last reviewed, and existing information was previously considered acceptable for approval (review signed February 18, 2010).

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

The original submission for the current application was previously reviewed previously by the Office of Clinical Pharmacology (signed January 15, 2010). Based on that review, the submission was found to be acceptable from a clinical pharmacology perspective. The current Clinical Pharmacology review signed by the primary reviewer and team leader on March 31 and April 1, 2011, respectively, focused on the Clinical Pharmacology labeling. I concur with the reviewers that the submission is acceptable from a clinical pharmacology perspective.

ONDQA Biopharmaceutics

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.

The ONDQA-Biopharmaceutics has reviewed the information included in NDA 22-534 for Docefrez™ Injection 20 mg/vial or 80 mg/vial (review signed April 4, 2011). 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 the in vivo BA/BE of Sum Pharma's Docetaxel Injection to be self-evident. OBP concluded that the sponsor's request for a biowaiver for Docefrez ™ Injection 20 mg/vial or 80 mg/vial is acceptable and granted the biowaiver. I concur with this conclusion.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

Not applicable

8. Safety

Not applicable

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

The pediatric use information for the RLP is based on data submitted in response to a pediatric written request is protected by Pediatric Exclusivity under the Best Pharmaceuticals for Children Act (BPCA) until May 13, 2013. The labeling in the RLP provides information regarding safety and dosing in pediatric patients but does not include a pediatric indication. Consistent with other 505(b)(2) applications, the pediatric information is carved out of the labeling of the Sun Pharma product because the removal of the language should not present a safety concern for pediatric patients.

11. Other Relevant Regulatory Issues

None

12. Labeling

Multiple FDA disciplines have reviewed the drug labeling, including the package insert, patient PPI, and carton and container labels. The team also reviewed the applicant's proposed Dear Health Care Professional letter alerting them that the concentration and preparation procedures of their product differs from that of other docetaxel products on the market. Recommended revisions have been shared with the sponsor for comment. Final revisions of the labeling will be attached to the action letter.

Division of Medication Error Prevention and Analysis (DMEPA)
Review of the labeling was signed by primary reviewer and team leader on April 5, 2011 and by the DMEPA Division Director on April 6, 2011.

Due to the availability of multiple formulations of docetaxel in varying concentrations that require differing instructions for drug preparation, the potential for confusion among these products is a significant safety concern for DMEPA. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized. One important feature of the container labels and carton labeling, that may help to differentiate these products, is color. Thus, in an effort to help minimize the potential for confusion that can lead to dosing errors due to similarities or overlaps in color between the products DMEPA takes into consideration the use of colors that do not overlap.

DMEPA proposed two additional recommendations for the DHCP which are the following:

1. Under A.1. revise (b) (4) to "46ºF" so that it matches the insert labeling.
2. In the last paragraph of the letter, revise the second sentence to read "If you need further information about this product, please contact our distributor Caraco Pharmaceutical Laboratories, Ltd at 1-800-818-4555."

Sun Pharma Global FZE submitted revised container labels, carton labeling, and Dear Healthcare Professional (DHCP) letter on 29-April-2011 that incorporated all of DMEPA's previous recommendations. In a memo signed 02-May-2011, DMEPA indicated that the revised container labels and carton labeling acceptable.

The conclusion of the DMEPA review of the proprietary name (signed March 23, 2011) was that the name Docefrez was acceptable.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action: Approval

The CDTL review signed 02-May-2011 recommended the following comment be conveyed in the action letter:

- "Based on the stability data provided, a 30-month expiration dating period is granted for the drug product, when stored at 2^{o}C -8^{o}C (36^{o}F -46^{o}F) and protected from light."

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

/s/

ANTHONY J MURGO
05/02/2011