

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022534Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	02-MAY-2011
From	Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22534
Supplement#	
Applicant	Sun Pharma Global FZE
Dates of Submissions	21-APR-2009 (original NDA submission) 23-FEB-2010 (tentative approval) 03-NOV-2010 (request for full approval) 21-DEC-2010 (CMC amendment)
PDUFA Goal Date	03-MAY-2011 (based on request for full approval)
Proprietary Name / Established (USAN) names	DOCEFREZ Docetaxel for injection
Dosage forms / Strength	20 mg (b) (4) vial and 80 mg (b) (4) vial (both with diluent)
Proposed Indication(s)	1. Breast cancer 2. Non-small cell lung cancer 3. Prostate cancer
Recommended:	Approval

1. Introduction

Sun Pharma submitted NDA 22534 for DOCEFREZ (docetaxel) for Injection on 21-APR-2009. The NDA was subsequently filed on 02-JUL-2009, and the application was tentatively approved on 23-FEB-2010. The Applicant submitted a request for full approval on 03-NOV-2010, and in a 24-NOV-2010 letter, the Agency deemed the submission a Class 2 resubmission. The PDUFA date is 03-MAY-2011.

This CDTL memo serves to highlight the critical approvability issues discussed in all review disciplines and recommends an “Approval” action for this application. All individual discipline reviews may be found in DARRTS. Final container labels were provided on 02-MAY-2011. Final PI labeling was received on 29-APR-2011. This labeling was confirmed as acceptable for all disciplines.

2. Background

The Reference Listed Drug for this submission is Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), which is currently marketed by Sanofi Aventis. The proposed drug product is a co-packaged product containing an active lyophilized powder in one vial, and a product-specific diluent in a second vial. The active powder is intended for reconstitution with the supplied diluent, followed by intravenous injection. DOCEFREZ is supplied in two dosages (20 mg and 80 mg, based on the free base) in two respective vial

sizes (b) (4). With the exception of the amount of ethanol, the proposed drug product contains the same active and inactive ingredients (b) (4) as the RLD, but the supplied active formulations differ in dosage form (lyophilized powder for dilution vs. injection concentrate).

Dosing Regimen and Administration

Administered IV over 1 hr every 3 weeks for the following cancers:

- BC, locally advanced or metastatic: 60-100 mg/m² single agent
- NSCLC: after platinum therapy failure: 75 mg/m² single agent
- HRPC: 75 mg/m² with 5 mg prednisone twice a day continuously

3. CMC

NDA 22534 was initially submitted on 21-APR-2009 as a 505(b)(2) application. The NDA included a full dossier of CMC information, along with proposed container/carton and PI labeling. In a review dated 17-FEB-2010, the Chemistry Reviewer (Dr. D. Ghosh) recommended approval from a CMC perspective. A shelf life of (b) (4) is recommended for the drug product, when stored at 2°-8°C (36°F-46 F) and protected from light.

The current submission contained minimal new CMC information to review. Briefly, the submitted information is as follows:

- (b) (4)
The proposed commercial batches (b) (4) relative to the exhibit batches. Exhibit batch data were provided in the initial NDA submission, and further supporting batch data are located in the current resubmission. Additional manufacturing equipment changes (b) (4) are detailed in the Chemist's 24-MAR-2011 review. Note that several of the proposed changes were subsequently withdrawn by the Applicant in a 21-DEC-2010 amendment.
- **Updated stability data**
The Applicant submitted updated stability data for both proposed dosage strengths. The Chemistry reviewer has assessed this updated data and now recommends the approval of a 30-month expiration dating period for the drug product, when stored at 2°-8°C (36°F-46°F) and protected from light (see 24-MAR-2011 review by Dr. D. Ghosh). This should be captured in the action letter.

This resubmission to NDA 22534 did not include any new Biopharmaceutics data. However, a review was filed in DARRTS (see review dated 01-APR-2011, by Dr. A. Dorantes), which further confirms the Applicant's previous request for a biowaiver.

- **Facilities review/inspection**
An Establishment Evaluation Request (EER) was submitted to the Office of Compliance in a previous review cycle. An overall acceptable recommendation was issued for the application on 05-JUN-2009. The request was not re-entered, as all sites

were previously determined to be acceptable within a two-year timeframe from the overall recommendation date.

- Microbiology
The Microbiology reviewer (Dr. J. Metcalfe) conducted an updated review of this submission and recommended approval in a 01-MAR-2011 review.
- Other notable issues (resolved or outstanding)
None

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology studies provided in this submission. The final Pharmacology/Toxicology memo was finalized (Dr. M. Brower) in DARRTS on 18-FEB-2010 and captures a recommendation of approval for the NDA. Labeling recommendations for the proposed PI are also captured in the review.

5. Clinical Pharmacology

There was no clinical pharmacology data submitted to this NDA. The clinical pharmacology reviewer (Dr. Y. Moon) recommended approval of this NDA in her review dated 15-JAN-2010. This review also captures related revisions to the PI.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

There are no new clinical data provided in the current submission. The clinical reviewer (Dr. K. Snyder) recommends approval of this NDA in her 13-APR-2011 memo.

8. Safety

No new clinical data were provided for this submission.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

Not applicable

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): This was not raised during the pre-approval inspections for this NDA.
- Exclusivity or patent issues of concern: No issues were noted for this NDA.
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None
- Any other outstanding regulatory issues: None

12. Labeling

General:

All disciplines participated in internal labeling meetings held throughout the review clock. Specific labeling recommendations are captured in each discipline-specific review.

Proprietary name:

In a 23-MAR-2011 review, the Division of Medication Error and Prevention Analysis (DMEPA) reviewer (Dr. C. Baksh) finds the proposed trade name of “DOCEFREZ” acceptable.

DMEPA/DDMAC comments:

Previous reviews dated 22-FEB-2010 and 23-FEB-2010 (L. Holmes) detail several internal discussion points (ONDQA/DMEPA) applicable to the proposed container/carton labeling. An updated review (05-APR-2011) outlines a comprehensive list of updated deficiencies related to DMEPA’s review of the currently proposed container/carton and PI labeling. Following internal team discussion, these comments were issued to the Applicant.

Overlapping container/carton labeling comments were initially covered in the 16-FEB-2010 CMC review, which also confirmed that the labeling to date effectively incorporated all recommendations from the CMC reviewer. In a 02-MAY-2011 updated review, the DMEPA reviewer (L. Holmes) also confirmed that the Applicant’s proposed labeling (received 29-APR-2011) was acceptable.

A review was filed on 23-MAR-2011 by the Division of Drug Marketing, Advertising, and Communications (DDMAC). The identified recommendations were discussed internally and incorporated into the labeling accordingly.

Carton and immediate container labels:

See above section titled “DMEPA comments.” Overlapping container/carton labeling comments were also covered in the 16-FEB-2010 CMC review. There were no substantial CMC-recommended edits of the container/carton labels in the current review cycle, and the labeling remains acceptable.

Patient labeling/Medication guide:

This is not required for this product.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**
This reviewer recommends approval of this NDA. There are no outstanding deficiencies for any disciplines involved in the review of this submission. All disciplines were involved in labeling discussions. The final proposed labeling reflects the recommended revisions from all disciplines and is acceptable.
- **Risk Benefit Assessment**
The review of this NDA is based primarily on chemistry, manufacturing and controls data. However, the NDA is recommended for approval from all disciplines.
- **Recommendation for Postmarketing Risk Management Activities**
This does not apply to this NDA.
- **Recommendation for other Postmarketing Study Commitments**
None
- **Recommended Comments to Applicant**
The following language confirming the granted expiration dating period should be placed 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°C -8°C (36°F -46°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/

SARAH P MIKSINSKI
05/02/2011