CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201525Orig1s000

SUMMARY REVIEW

DD Summary Review for Regulatory Action

Date	(electronic stamp)
From	Anthony J. Murgo, M.D., M.S. Acting Deputy Division Director
Subject	NDA 505(b)(2) review
NDA #	201525
Applicant Name	Sandoz, Inc.
Date of Submission	17-SEP-2010
PDUFA Goal Date	17-JUL-2011
Proprietary Name / Established (USAN) Name	Docetaxel Injection
Dosage Forms / Strength	10 mg/mL (20 mg/2 mL, 80 mg/8 mL, 160 mg/16 mL)
Proposed Indication(s)	1. Breast cancer 2. Non-small cell lung cancer 3. Prostate cancer 4. Gastric adenocarcinoma 5. Squamous cell carcinoma of the head and neck cancer
Action:	**Approval**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	X
Statistical Review	
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	
Clinical Pharmacology Review	X
DDMAC	
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

Sandoz, Inc. submitted a 505(b)(2) New Drug Application (NDA 201195) for Docetaxel Injection on 17-SEP-2010. The reference listed drug (RLD) is Taxotere® for Injection (docetaxel; Sanofi-Aventis), initially approved by the FDA on 14-MAY-1996 (NDA 20-449). Taxotere® for Injection is indicated for the treatment of breast cancer (as a single-agent for metastatic disease and in combination as adjuvant treatment), non-small cell lung cancer (as a single-agent and in combination), hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck. Sandoz, Inc. is seeking approval for all five of these indications.

2. Background

This Docetaxel Injection 505(b)(2) NDA application was submitted by Sandoz, Inc. on 17-SEP-2010. The applicant is seeking the same indications as the RLD Taxotere. The proposed drug product is a "ready to use" product containing the drug substance (in solution) in one vial. The solution is intended for reconstitution and subsequent intravenous injection. Docetaxel Injection is supplied in three presentations (20 mg/2 mL, 80 mg/8 mL, 160 mg/16 mL). All three presentations utilize the same concentration of 10 mg/mL. With the exception of two added excipients (polyethylene glycol 300 and citric acid), the proposed drug product contains the same active and inactive ingredients as the RLD. Variations are present relative to the innovator product, including small variations in concentration for both polysorbate 80 and ethanol.

3. CMC/Product Quality and PQ Microbiology

The three "ready to use" presentations are described in Section 2 above. The CMC review (signed 12-May-2011 and 16-May-2011 by the primary and secondary reviewers, respectively) recommends approval of this NDA, with language regarding the granted expiration dating period to be captured in the action letter as indicated below:

> ***"Based on the stability data provided, an 18-month expiration dating period is granted for the drug product, when stored at the proposed conditions (between 2^{o}C and 25^{o}C)"***

I concur with the conclusions reached by the CMC reviewers that the application is acceptable from a CMC perspective.

See Section 4 (below) regarding the (b) (4) impurity and the (b) (4) levels, and non-clinical review and resolution.

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The Product Quality Microbiology review was signed 08-APR-2011. I concur with the conclusion of the reviewers that the application is approvable from a product quality microbiology perspective.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted to support this application. However, two concerns were identified during the review process that required input from the pharmacology/toxicology team. First, as a result of a change in formulation between the RLD and the Sandoz product, there was an increase in the level of the [redacted] (b) (4) impurity. At a pre-NDA applicant meeting, the FDA informed Sandoz that if the levels of impurity were higher than those of the RLD then an additional nonclinical study might be required for qualification. However, during the interim between the pre-NDA meeting and the review of the NDA, there was a publication showing that [redacted] (b) (4) is a metabolite of docetaxel and is found at high levels in human plasma. Consequently, the sponsor was not required to do further qualification studies for this impurity. Secondly, the FDA also asked the sponsor to justify the [redacted] (b) (4) specification level for [redacted] (b) (4) in their product. The sponsor provided data from the literature to show that the level of clinical [redacted] (b) (4) exposure resulting from administration of Sandoz docetaxel is significantly lower than the documented no observed effect level (NOEL) in 2 species, thus, the specification was considered to be justified.

The non-clinical pharmacology/toxicology reviewers concluded (review signed 09-JUN-2011) that the level of [redacted] (b) (4) in the Sandoz product does not require further qualification and that the sponsor provided sufficient data to justify the level of [redacted] (b) (4) in their product.

I concur with the nonclinical pharmacology/toxicology reviewers that this NDA is approvable from a nonclinical pharmacology/toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology or biopharmaceutics data was submitted and a waiver of the bioequivalence requirements was granted (see ONDQA OBP review signed 26-APR-2011). The Clinical Pharmacology reviewers concluded (review signed 08-APR-2011) that the change in the unbound docetaxel fraction caused by the decreased amount of PS80 in the Sandoz formulation compared to Taxotere is not likely to have a significant effect on the pharmacokinetics of docetaxel.

I concur with the conclusions of the reviewers that the application is acceptable from a Clinical Pharmacology/Biopharmaceutics.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

No new clinical information is included in the application. However, the clinical team participated in the review of the labeling. I concur with the conclusions of the clinical reviewers (review signed 01-JUN-2011 and 09-JUN-2011 by the primary reviewer and team leader, respectively) that the application is approvable.

8. Safety

NA

9. Advisory Committee Meeting

NA

10. Pediatrics

New pediatric information in the RLD labeling is carved out of the labeling of this product, consistent with the handling of other 505(b)(2) docetaxel labels. For a more detailed explanation, please refer to the Clinical Review signed 01-JUN-2011 and 09-JUN-2011 by the primary reviewer and team leader, respectively.

11. Other Relevant Regulatory Issues

None

12. Labeling

The labeling was reviewed by a multidisciplinary team, including DMEPA (signed 27-MAY-2011). The FDA and applicant agreed upon the final PI labeling (received 01-JUN-2011).

13. Decision/Action/Risk Benefit Assessment

I concur with the recommendation by the CDTL (review signed 24-JUN-2011) that the application is approvable.

- Regulatory Action: **Approval**

The following comment regarding the granted expiration dating period should be included in the action letter:

> ***"Based on the stability data provided, an 18-month expiration dating period is granted for the drug product, when stored at the proposed conditions (between 2^{o}C and 25^{o}C)"***

- Risk Benefit Assessment

  Similar to the RLD

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/s/

ANTHONY J MURGO
06/27/2011