CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022312Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	9-JAN-2012
From	Haripada Sarker, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22312
Applicant	Apotex, Inc.
Date of Submission	3-MARCH-2008 (original)
	4-May-2011 (CR letter)
	12-July-2011 (Resubmission-2, current review cycle)
PDUFA Goal Date	12-JAN-2012
Proprietary Name / Established (USAN) names	Docetaxel Injection
Dosage forms / Strength	40 mg/mL
Proposed Indication(s)	1. Breast cancer: locally advanced or metastatic, or in combination with doxorubicin and cyclophosphamide as adjuvant treatment 2. Non-small cell lung cancer: locally advanced or metastatic following failure of platinum-based therapy, or in combination with cisplatin in patients not previously receiving chemotherapy 3. Prostate cancer: in combination with prednisolone for hormone refractory chemotherapy 4. Gastric adenocarcinmoa: in combination with cisplatin and 5-FU
Recommended:	**Approval**

1. Introduction

Apotex, Inc. originally submitted NDA 22312 for Docetaxel Injection on 28-MAR-2008. The NDA is a 505(b)(2) submission which seeks approval of Docetaxel Injection (40 mg/mL). The current review is the fifth cycle for the proposed drug and indications. Specifically, the current resubmission is a response to CR that contained several CMC issues. This NDA was submitted to the Agency on 12-July-2011 and was granted a 6-month review clock (Class 2).

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/carton and Package Insert (PI) labeling have been received and reviewed.

2. Background

The Reference Listed Drug for this submission is Taxotere® (docetaxel) Injection (NDA 20-371). The proposed drug product is an aqueous injectable dosage form intended for dilution and intravenous injection. It is supplied at a concentration of 40 mg/mL docetaxel (b) (4) in two dosing volumes (0.5 mL and 2 mL). The previous CDTL review by Dr. S. Pope Miksinski delineates the product differences between the innovator and the proposed drug products (see CDTL Review dated 27-APR-2011):

> *Compared to the RLD Taxotere (docetaxel) Injection, the Apotex formulation contains reduced amounts of alcohol and has a different execipient (polyethylene glycol (b) (4)) added to the Docetaxel Injection (b) (4) The added polyethylene glycol (b) (4) for the drug substance. In addition, the Apotex formulation uses polysorbate 80 in the diluent (b) (4) whereas the RDL used polysorbate 80 in the Injection concentrate; the RDL diluent is composed entirely of ethyl alcohol.*

3. CMC

- General product quality considerations
  The CMC reviewer (J. Jee) finalized an updated CMC review on 2-DEC-2011. As per that review, the NDA is recommended for approval from a CMC perspective. An overall acceptable recommendation from the Office of Compliance was received on September 25, 2012, which effectively resolves the only outstanding issue from the previous review cycle. Final labeling was also negotiated during this cycle, and acceptable labeling was submitted by the Applicant on November 25, 2011 for both container/carton and PI.

  A. Biopharmaceutics review was finalized on 26-APR-2011. The Biopharmaceutics reviewer (Dr. A. Dorantes) confirmed the granting of a biowaiver for this application during the previous review cycle.

- Facilities review/inspection
  Inspections requested on 01-AUG-2011 by D. Mesmer, PM. An overall OC recommendation for all manufacturing facilities used NDA 22-312 is acceptable on 22-AUG-2011.

- **Microbiology**
  NDA 22-312 is recommended for approval from the standpoint of product quality microbiology. See microbiology review (Dr. S. Langille) in DARRTS for this NDA dated 1-Dec-2011.

- Other notable issues (resolved or outstanding)
  None

4. Nonclinical Pharmacology/Toxicology

No Pharmacology/Toxicology (P/T) review applicable this cycle. There are no outstanding P/T deficiencies (See P/T review signed dated 21-DEC-2009 by Dr. M. Brower).

5. Clinical Pharmacology

There was no clinical pharmacology data submitted in this submission. The clinical pharmacology reviewer (Dr. J. Fourie) recommended approval of this NDA in her review dated 12-FEB-2009.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

There are no new clinical data provided in the current submission. An updated clinical review recommends approval of this NDA. See memo in DARRTS dated 19-DEC-2011 by Dr. K. Snyder.

8. Safety

No new clinical data were provided for this submission.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

(b) (4)

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP): This was not raised during the pre-approval inspections for this NDA.

12. Labeling

General:

The product labeling including the package insert and carton and container labels was reviewed by various disciplines, and deficiencies were communicated with the applicant during the review cycle. See section 10 regarding pediatric information. Acceptable labeling was received on November 25, 2011 for PI and container/carton. Details are captured in the respective discipline reviews. There are two additional minor comments from DMEPA, which will be submitted to the applicant in the approval letter.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action:
  Approval

- Risk Benefit Assessment:
  The risk benefit relationship for Docetaxel Injection is the same as for the RLD.

- Recommendation for Postmarketing Risk Management Activities:
  This does not apply to this NDA.

- Recommendation for other Postmarketing Study Commitments:
  None

- Recommended Comments to Applicant:
  Based on the stability data provided, a 24-month expiration dating period is granted for the drug product when stored at controlled room temperature, 20°C to 25°C (59°F to 86°F), excursions permitted from 15°C to 30°C (68°F to 77°F) [See USP Controlled Room Temperature].

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/s/

HARIPADA SARKER
01/10/2012

SARAH P MIKSINSKI
01/10/2012