CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022312Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	15- DEC-2011
From	Anthony J. Murgo, MD, MS (Acting DDD)
Subject	Division Director Summary Review Sponsor Response to FDA CR dated 04-MAY-2011
NDA/BLA # **Supplement #**	22312
Applicant Name	Apotex, Inc.
Date of Submission	28-MAR-2008 (original); 12-JUL-2011 (re-subm. 4)
PDUFA Goal Date	12-JAN-2012
Proprietary Name / **Established (USAN) Name**	Docetaxel Injection
Dosage Forms / Strength	Injectable/40 mg/mL (20 mg/0.5 mL and 80 mg/2 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 (CP) in patients not previously received chemotherapy 3. Prostate cancer: in combination with prednisolone for hormone refractory metastatic cancer 4. Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction 5. Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted (this cycle) OND Action Package, including:	
Medical Officer Review	
Statistical Review	
Pharmacology Toxicology Review	
CMC Review/OBP Review	X (including product micro)
Microbiology Review	
Clinical Pharmacology Review	
DDMAC	
DSI	
CDTL Review	
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) application (NDA 22312) seeks approval of Docetaxel Injection, 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL). The reference listed drug (RLD) is Taxotere (docetaxel) Injection, 20 and 80 mg vials, Sanofi Aventis. The original submission for this 505(b)(2) application is dated 28-MAR-2008. This review considers a Class 2 resubmission (no. 4) dated 12-JUL-2011, which is a response to FDA CR letter dated 04-MAY-2011. The current resubmission was granted a 6-month review clock (Class 2). Apotex submitted two Gratuitous Amendments dated 10-DEC-2010 and 27-JAN-2011, respectively; these were reviewed during the current cycle.

2. Background

Compared to the RLD Taxotere (docetaxel) Injection, the Apotex formulation contains reduced amounts of alcohol and has a different expedient (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.

The proposed labeled indications are the same as the RLD.
The indications are listed below:

Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC

Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC

Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer

Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction

Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN (In the current submission, the sponsor added back the Squamous Cell Carcinoma of the Head and Neck Cancer indication).

Please refer to DDD summary reviews dated 29-APR-2009, 29-JAN-2010, 22-SEPT-2010, and 29-APR-2011 for the salient issues in the original application and the first, second and third resubmissions.

This DDD summary encompasses the fourth resubmission (dated 12-JUL-2011).

3. CMC/Product Quality Microbiology/ONDQA Biopharmaceutics

CMC

The CMC reviewer could not recommend approval of the previous submission (resubmission #3) because of an extant withhold recommendation issued by the Office of Compliance (OC) on 11-MAR-2011 related to manufacturing and controls facilities inspection findings. The Chemistry Review for that complete response submission was signed on 21-APR-2011.

The CMC review of the current submission was signed by the primary and secondary reviewers on 30-NOV-2011 and 02-DEC-2011, respectively. An acceptable OC recommendation was received on 22-AUG-2011. I concur with the recommendation of the CMC reviewers that the prior deficiencies are resolved and that the application is now approvable from a CMC perspective.

Based on the stability data provided, a 24-month expiration dating period is granted for this 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).

PQ-Microbiology

The applicant has provided a resubmission of NDA 22-312 to support changes to the (b) (4) and process for docetaxel concentrate at the Weston, Ontario manufacturing facility. I concur with the conclusion of the PQ-Microbiology review signed 30-NOV-2011 and 01-DEC-2011 by the primary and secondary reviewers, respectively, that the application is approvable.

ONDQA BP

The QONDQA BP review was signed 26-APR-2011 during the previous cycle. Based on this review, a biowaiver for this drug was granted.

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 21-DEC-2009 for more information).

5. Clinical Pharmacology

Not applicable.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Not applicable.

8. Safety

Not applicable.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

(b) (4)

11. Other Relevant Regulatory Issues

None

12. Labeling

The product labeling including the package insert and carton and container labels were reviewed by various disciplines, including DMEPA, with communication with the applicant. See section 10 regarding pediatric information.

13. Decision/Action/Risk Benefit Assessment

- **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**
  None
- **Recommendation for other Postmarketing Study Commitments**
  None

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/s/

ANTHONY J MURGO
12/15/2011