DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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Pediatric and Maternal Health Staff Review – Pediatric Team Review

Date: August 31, 2010 **Date Consulted:** August 10, 2010

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, M.D.
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Drug Oncology Products (DDOP)

Drug: Docetaxel Injection (b)(4) Intravenous Infusion, NDA 22-312

Subject: Pediatric Use Labeling

Materials Reviewed:

- Draft Docetaxel labeling, NDA 22-312
- Pediatric Exclusivity Boarrd Minutes for Docataxel, NDA 20-449/S-059 (RLD), March 16, 2010
- Clinical Review, Taxotere (docetaxel), NDA 20-449/S-059, May 3, 2010
- CDTL Review, Taxotere (docetaxel), NDA 20-449/S-059, May 7, 2010
- Orange Book Patent and Exclusivity Information for Taxotere, NDA 20-449

Consult Question:
Determin (b)(4) labeling for this docetaxel product.

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

/s/

JEANINE A BEST
08/31/2010

HARI C SACHS
08/31/2010
I agree with the recommendations in this consult [redacted] (b)(4)

LISA L MATHIS
09/07/2010

Cross-Discipline Team Leader Review

Date	27-APR-2011
From	Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22312
Applicant	Apotex, Inc.
Date of Submission	12-NOV-2010
PDUFA Goal Date	12-MAY-2011
Proprietary Name / Established (USAN) names	Docetaxel Injection
Dosage forms / Strength	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 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:	**Complete Response**

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 fourth cycle for the proposed drug and indications. Specifically, the current resubmission was submitted to the Agency on 12-NOV-2010 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 a "Complete Response" action for this application. All individual discipline reviews may be found in DARRTS. Final container/carton and package insert labeling was not negotiated in the current review cycle, due to the significant outstanding deficiencies.

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 most previous summary review by Dr. T. Murgo delineates the product differences between the innovator and the proposed drug products (see Summary Review dated 22-SEP-2010):

> *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.*

3. CMC

- General product quality considerations
  The CMC reviewer (J. Jee) finalized an updated CMC review on 21-APR-2011. As per that review, the NDA can not be recommended for approval from a CMC perspective due to an existing overall withhold recommendation from the Office of Compliance (see below). The CMC reviewer also details several labeling deficiencies, which were not conveyed during the current cycle due to the significant noncompliance issue.

  The CMC review specifically notes that unsolicited amendments dated 10-DEC-2010 and 11-JAN-2011 were not reviewed in the current cycle. This should be specified in the action letter.

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

- Facilities review/inspection
  An Establishment Evaluation Request (EER) was submitted to the Office of Compliance on 10-JAN-2011. An overall withhold recommendation was issued for the application on 25-MAR-2011. Therefore, this application can not be recommended for approval from a CMC standpoint.

- Microbiology
  There was no new microbiological information contained in the current resubmission. The Microbiology reviewer (Dr. S. Langille) had previously recommended approval of this NDA in a 17-SEP-2010 review.

- Other notable issues (resolved or outstanding)
  None

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology studies provided in this submission. There are no outstanding Pharmacology/Toxicology deficiencies (see 11-DEC-2009 memo 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. The clinical review team was involved briefly in the labeling discussions, prior to the determination that labeling would not be negotiated during the current cycle.

8. Safety

No new clinical data were provided for this submission.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

Reference is made to the previous 31-AUG-2010 review (J. Best). There was no updated review from the Pediatric and Maternal Health Staff in the current cycle. Previous PMHS recommendations are covered in the 22-SEP-2010 Summary Review by Dr. T. Murgo:

> *The Division of Drug Oncology Products consulted the Pediatric Team of the Pediatric and Maternal Health Staff (PMHS) on August 10, 2010, to determine whether protected pediatric use information that appears in RLD Taxotere labeling*

can be carved-out of Docetaxel labeling. Please refer to the PMHS review dated August 31, 2010. Taxotere (NDA 20-449/S-059) labeling was revised to include the study data conducted in response to the PWR. Six months of Pediatric Exclusivity under Best Pharmaceuticals for Children Act (BPCA) (expires November 13, 2010) was granted to Sanofi- Aventis for Taxotere for fairly meeting the terms of the PWR. Sanofi-Aventis was also awarded three years of Waxman-Hatch Exclusivity for revisions to labeling based on data submitted in response to the PWR (expires May 13, 2013). PMHS argued that BPCA does not address the carve-out of protected pediatric information from 505(b)(2) product labeling and that approval of a 505(b)(2) application may be delayed because of patent and exclusivity rights that apply to the listed drug (see 21 CFR 314.50(i), 314.107, 314.108, and section 505(A)(b)(B)(ii) of the Act.

The PMHS-Pediatric team recommended that all protected pediatric use information that appears in subsection 8.4 Pediatric Use of Taxotere labeling be retained in Docetaxel Injection labeling for reasons of safe use. This protected pediatric use information is important safety information for risk/benefit decision making when considering the use of Docetaxel Injection in pediatric cancer patients.

Following further internal discussion conducted during the current review cycle, the multidisciplinary team determined that the pediatric information should be carved out of the labeling of this product because the removal of the language does not present a safety concern for pediatric patients. This is consistent with other related 505(b)(2) applications, and all pertinent disciplines (including the Clinical and PMHS teams) concurred on this recommendation.

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, with the exception of the overall withhold recommendation from the Office of Compliance.

12. Labeling

Due to the intended Complete Response action, labeling discussions were not conducted to an appreciable extent during this review cycle.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  This reviewer recommends a Complete Response action for this NDA. There is an overall recommendation of withhold from the Office of Compliance.

- Risk Benefit Assessment
  The review of this submission is based primarily on chemistry, manufacturing and controls data. However, the overall cGMP status for the application is not acceptable. As a result, none of the proposed manufacturing, testing, packaging or labeling sites can be confirmed as acceptable for commercial production.

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

- Recommendation for other Postmarketing Study Commitments
  None

- Recommended Comments to Applicant

  The following two items need to be inserted into the action letter:
  1. Standard language conveying the lack of cGMP compliance for the appropriate site(s).
  2. Dates of unsolicited and un-reviewed CMC amendments.