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RESEARCH**

APPLICATION NUMBER:

022312Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	29-APR-2011
From	Anthony J. Murgu, MD, MS (Acting DDD)
Subject	Division Director Summary Review Sponsor Response to FDA CR dated 12-NOV-2010
NDA/BLA #	22312
Supplement #	
Applicant Name	Apotex, Inc.
Date of Submission	28-MAR-2008 (original); 12-NOV-2010 (re-subm.)
PDUFA Goal Date	12-MAY-2011
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)	<ol style="list-style-type: none"> 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
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	
Statistical Review	
Pharmacology Toxicology Review	
CMC Review/OBP Review	X
Microbiology Review	
Clinical Pharmacology Review	
DDMAC	
DSI	
CDTL Review	X
OSE/DMEPA	
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 resubmission dated 12-NOV-2010, which is a response to FDA CR letter dated 22-SEPT-2010. The current resubmission (12-NOV-2010) 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 not reviewed in this 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, with one exception as noted below. The indications are listed below along with patent exclusivity status:

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 (exclusivity expired)

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 (exclusivity expired)

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

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

The sponsor elected to remove the **Squamous Cell Carcinoma of the Head and Neck Cancer** indication last cycle with the sNDA amendment dated March 24, 2010.

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

This DDD summary encompasses the resubmission dated 12-NOV-2010.

3. CMC/Product Quality Microbiology/ONDQA Biopharmaceutics

CMC

The CMC reviewer could not recommend approval 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 this complete response submission was signed on 21-APR-2011.

I concur with the recommendation of the CMC reviewers that the application cannot be recommended for approval from a CMC perspective because of the existing withhold recommendation from the OC.

PQ-Microbiology

NA: There is no new PQ-M information in this submission.

ONDQA BP

The QONDQA BP review was signed 26-APR-2011. 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

Not applicable this cycle.

11. Other Relevant Regulatory Issues

None

12. Labeling

Due to the intended Complete Response action, labeling discussions will proceed in the next cycle or when the application is otherwise approvable.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** Complete response.

There is an outstanding overall recommendation of withhold from the Office of Compliance.

- Risk Benefit Assessment
The risk benefit relationship for Docetaxel Injection is the same as for the RLD.
- Recommendation for Postmarketing Risk Management Activities
None at this time
- Recommendation for other Postmarketing Study Commitments
None at this time

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/s/

ANTHONY J MURGO
04/29/2011

Cross-Discipline Team Leader Review

Date	27-APR-2011
From	Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22312
Supplement#	
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)	<ol style="list-style-type: none"> 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 adenocarcinoma: 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 RLD used polysorbate 80 in the Injection concentrate; the RLD 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. Murgó:

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.

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/s/

SARAH P MIKSINSKI
04/27/2011

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Submission Number	NDA 22312
Submission Code	Class 2, Resubmission
Letter Date	July 12, 2011
Stamp Date	July 12, 2011
PDUFA Goal Date	January 12, 2012
Reviewer Name	Kristen M. Snyder, MD
Clinical Team Leader	Patricia Cortazar, MD
Review Completion Date	December 19, 2011
Established Name	docetaxel
Trade Name	Docetaxel Injection
Reference NDA	20449
Therapeutic Class	Disruptor of microtubule network
Applicant	Apotex Inc.
Priority Designation	Not Applicable
Formulation	IV
Dosing Regimen	Multiple (see product information, 2.1)
Indication	Multiple (see product information, 2.1)
Intended Population	Multiple (see product information, 2.1)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA for Docetaxel Injection, in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, was submitted to request approval of the therapeutic equivalence of the proposed product to Taxotere®, as defined in the FDA orange book. The sponsor of NDA 20449 for Taxotere® is sanofi-aventis.

The exclusivity of the Taxotere® indications below has expired.

Breast Cancer

- Docetaxel Injection is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.
- Docetaxel Injection in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

Non-Small Cell Lung Cancer

- Docetaxel Injection as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.
- Docetaxel Injection in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

Hormone Refractory Prostate Cancer

- Docetaxel Injection in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

Gastric Adenocarcinoma

- Docetaxel injection in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

Squamous Cell Carcinoma of the Head and Neck Cancer

- Docetaxel injection in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

No new clinical data was submitted for this NDA. The Taxotere NDA 20449 has been previously reviewed for efficacy and safety. The applicant submitted Docetaxel Injection for use in the following indications:

- . **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:** with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction.
- . **Squamous Cell Carcinoma of the Head and Neck Cancer:** with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN.

Therefore, the medical reviewer recommends approval of Docetaxel Injection for the above indications. The recommendation for the application is approval with respect to the chemistry, manufacturing, and controls (CMC). See CMC reviews by Josephine Jee.

1.2 Risk Benefit Assessment

Please refer to NDA 20449.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: docetaxel

Proprietary Name: Docetaxel Injection

Applicant: Apotex, Inc.
c/o Apotex Corporation
2400 North Commerce Parkway, Suite 400
Weston, Florida 33326

Drug Class: Disruptor of microtubule network

Proposed Indications:

- **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:** with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction.
- **Squamous Cell Carcinoma of the Head and Neck Cancer:** with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN.

Proposed Dosage and Administration

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

- BC: locally advanced or metastatic: 60 mg/m² to 100 mg/m² single agent
- BC adjuvant: 75 mg/m² administered 1 hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks for 6 cycles
- NSCLC, after platinum therapy failure: 75 mg/m² single agent
- NSCLC, chemotherapy-naive: 75 mg/m² followed by cisplatin 75 mg/m²
- HRPC: 75 mg/m² with 5 mg prednisone twice a day continuously
- GC: 75 mg/m² followed by cisplatin 75 mg/m² (both on day 1 only) followed by fluorouracil 750 mg/m² per day as a 24-hr intravenous infusion (days 1 to 5), starting at end of cisplatin infusion
- SCCHN, locally advanced inoperable, induction chemotherapy followed by radiotherapy: 75 mg/m² followed by cisplatin 75 mg/m² intravenously (day 1), followed by fluorouracil 750 mg/m² per day as a 24-hr intravenous infusion (days 1 to 5), starting at end of cisplatin infusion; for 4 cycles
- SCCHN, induction treatment for locally advanced unresectable, low surgical cur, organ preservation, induction chemotherapy followed by chemoradiotherapy: 75 mg/m² followed by cisplatin 100 mg/m² intravenously (day 1), followed by fluorouracil 1000 mg/m² per day as a 24-hr intravenous infusion (days 1 to 4); for 3 cycles

Reviewer's Comments:

Premedication Regimen

- Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice a day) for 3 days starting 1 day before administration
- HRPC: oral dexamethasone 8 mg at 12, 3, and 1 hr before treatment

For dosage adjustments during treatment see full prescribing information.

Dosage Forms and Strengths

- 80 mg/2 mL and Diluent for Docetaxel Injection
- 20 mg/0.5 mL and Diluent for Docetaxel Injection 20 mg

Contraindications

- Hypersensitivity to docetaxel injection or polysorbate 80
- Neutrophil counts of <1500 cells/mm³

Warnings and Precautions

- Acute myeloid leukemia: In patients who received docetaxel, doxorubicin and cyclophosphamide, monitor for delayed myelodysplasia or myeloid leukemia.
- Cutaneous reactions: Reactions including erythema of the extremities with edema followed by desquamation may occur. Severe skin toxicity may require dose adjustment
- Neurologic reactions: Reactions including paresthesia, dysesthesia, and pain may occur. Severe neurosensory symptoms require dose adjustment or discontinuation if persistent.
- Asthenia: Severe asthenia may occur and may require treatment discontinuation.

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 Kristen M. Snyder, MD
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 Docetaxel Injection

- **Pregnancy:** Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant when receiving Docetaxel Injection

Adverse Reactions

The most common adverse reactions are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

2.2 Availability of Proposed Active Ingredient in the United States

Taxotere® (docetaxel) is marketed in the US. Docetaxel Injection is to be marketed in the US.

2.3 Summary of Resubmission Regulatory Activity Related to Submission

The applicant received a complete response letter on May 4, 2011.

2.4 Pediatric Waiver

Pediatric exclusivity of Taxotere® ended on November 14, 2010.

2.5 Other Relevant Background Information

Table 1: Patent Data for TAXOTERE Injection Concentrate

Patent Number	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Certification	21 CFR Reference
4814470	May 14, 2010	X	X	Paragraph II	314.50(i)(1)(i)(A)(3)
4814470*PED	Nov 14, 2010				
5438072	Nov 22, 2013		X	Paragraph IV	314.50(i)(1)(i)(A)(4)
5438072*PED	May 22, 2014				
5698582	Jul 03, 2012		X	Paragraph IV	314:50(i)(1)(i)(A)(4)
5698582*PED	Jan 03, 2013				
5714512	Jul 03,		X	Paragraph	314.50(i)(1)(i)(A)(4)

Clinical Review
 Kristen M. Snyder, MD
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	2012			IV	
5714512*PED	Jan 03, 2013				
5750561	Jul 03, 2012		X	Paragraph IV	314.50(i)(1)(i)(A)(4)
5750561*PED	Jan 3, 2013				

Table 2: Exclusivity Data* for TAXOTERE Injection Concentrate

Exclusivity Code	Exclusivity Definition	Exclusivity Expiration	Action if not Expired
I-429	For use in combination with prednisone for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.	May 19, 2007	Expired
I-436	For use in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.	Aug 18, 2007	Expired
I-490	For use in combination with Cisplatin and 5-FU for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease	Mar 22, 2009	Expired
I-519	For use in combination with Cisplatin and 5-FU in patients with inoperable HNSCC prior to definitive treatment.	Oct 17, 2009	Expired
I-542	Expansion of patient population for head and neck cancer from “inoperable” patients to all patients.	Sep 28, 2010	Expired
I-543	For use in combination with Cisplatin and 5-FU in patients with advanced HNSCC prior to definitive treatment.	Sep 28, 2010	Expired
PED	Pediatric exclusivity	Mar 28, 2011	Expired

(b) (4)

3 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to NDA 20449 CMC, Pharmacology/Toxicology, and Clinical Pharmacology reviews, NDA 22312 CMC reviews, and the labeling.

Clinical Review
Kristen M. Snyder, MD
NDA 22312
Docetaxel Injection

4 Sources of Clinical Data

Refer to NDA 20449.

5 Review of Efficacy

Refer to NDA 20449.

6 Review of Safety

Refer to NDA 20449.

7 Appendices

7.1 Literature Review/References

Refer to NDA 20449.

7.2 Labeling Recommendations

See final labeling and carton and container labels. The clinical safety and efficacy are based on the Taxotere® (NDA 20449) labeling. The clinical team is in agreement with the final approved labeling, carton and container labels.

7.3 Advisory Committee Meeting

None

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/s/

KRISTEN M SNYDER
12/19/2011

PATRICIA CORTAZAR
12/19/2011

Summary Review for Regulatory Action

Date	September 22, 2010
From	Anthony J. Murgu, MD, MS (Acting DDD)
Subject	Division Director Summary Review Sponsor Response to FDA CR dated January 29, 2010
NDA/BLA #	NDA 22-312
Supplement #	Cycle 3 review
Applicant Name	Apotex, Inc.
Date of Submission	March 24, 2010 (re-submission)
PDUFA Goal Date	September 24, 2010
Proprietary Name / Established (USAN) Name	N/A / Docetaxel Injection
Dosage Forms / Strength	Injectable/40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL)
Proposed Indication(s)	<ol style="list-style-type: none"> 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: in combination with CP and 5-FU 5. Squamous cell carcinoma of Head/Neck: in combination with CP and 5-FU (amended this cycle to remove this indication)
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	
Statistical Review	
Pharmacology Toxicology Review	
CMC Review/OBP Review	X
Microbiology Review	X (Product Quality)
Clinical Pharmacology Review	
DDMAC	
DSI	
CDTL Review	
OSE/DMEPA	
OSE/DDRE	
OSE/DRISK	
Other	Pediatric and Maternal Health Consult

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 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 March 28, 2008. This review comprises cycle 3 and considers a resubmission of NDA 22-312 dated March 24, 2010, which is a response to FDA CR letter dated January 29, 2010. This resubmission also amends the proposed indications removing the Head and Neck indication. The FDA has determined that the amended application is not approvable because of outstanding product quality and labeling deficiencies.

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 along with patent exclusivity status:

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 (exclusivity expired)

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 (exclusivity expired)

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

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

Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN (exclusivity will expire September 28, 2010). **The sponsor amended the sNDA on March 24, 2010 to remove this indication.**

Please refer to DDD summary reviews dated April 29, 2009 and January 29, 2010 for the salient issues in the original application and the first resubmission.

This DDD summary encompasses salient components of the CMC product review, Product Quality Microbiology review, and Pediatric and Maternal Health Staff (PMHS) review.

3. CMC/Product Quality Microbiology

The Chemistry Review for this complete response submission was signed on September 22, 2010 by the primary reviewer and team leader. Also see Product Quality Microbiology Reviews dated September 1 and September 17, 2010. Summary of the CMC concerns and recommendations, which include those of Product Quality, are as follows:

The Chemistry review noted a list of outstanding deficiencies regarding the Sponsor's proposed established name and other elements of the carton and container labels. In addition, the CMC review notes that several drug product manufacturing facilities are cited for not meeting current GMP requirements. These deficiencies are outlined below.

The application cannot be recommended for approval under section 505 of the Act from a chemistry, manufacturing and controls perspective until acceptable container/carton and PI labeling are submitted. Also note that a withhold overall recommendation dated 16-SEP-2010 was issued by the Office of Compliance. GMP status of the manufacturing and controls facilities are as follows:

1. Apotex, Signet Campus, Toronto, Canada – Withhold and Warning Letter issued on 29-MAR-2010
2. Apotex, 3701 Weston Road, Toronto, Canada – Withhold and Warning Letter issued on 29-MAR-2010
3. Apotex, 380 Elgin Mills Road, Richmond Hill, Ontario, Canada – Withhold on 25-MAY-2010 based on DO recommendation.
4. Apotex, 50 Steinway, Etobicoke, Ontario, Canada – Withhold and Warning Letter issued on 25-JUN-2009

(b) (4)
(b) (4)
(b) (4)
(b) (4)

The CMC reviews recommend that the application cannot be approved from CMC perspective (see Section 13, below, for the deficiencies to be included in the action letter).

I concur with the recommendation of the CMC reviewers.

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 December 21, 2009 for more information).

5. Clinical Pharmacology/Biopharmaceutics

No formal review applicable this cycle.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

No formal review applicable this cycle. Clinical team participated in labeling review.

8. Safety

Not applicable.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The Division of Drug Oncology Products consulted the Pediatric Team of the Pediatric and Maternal Health Staff (PMHS) on August 10, 2010, (b) (4)

Please refer to the PMHS review dated August 31, 2010.

(b) (4)

(b) (4)

The final disposition of this matter is pending further discussion within the Agency.

11. Other Relevant Regulatory Issues

The originator's patent has not expired on the head and neck indication. However, the applicant has amended the application this cycle removing this indication.

12. Labeling

Please refer to Sections 3 and 10, above, and Section 13, below, for comments regarding the labeling. Complete review of the labeling, including the package insert, container and carton labels, is deferred until the next cycle or when the application is otherwise adequate.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** Complete response.

The following deficiencies will be communicated in the CR action letter:

- 1) The proposed established name “Docetaxel Injection (b)(4) is not acceptable in that (b)(4) is not a recognized name by the United States Pharmacopeia. We recommend that you revise your established name to “Docetaxel Injection” in the package insert, container labels and carton labels.
- 2) Revise your labels as follows:

Container Labels

A. Active Drug

- a. On the 80 mg/2 mL vial, the statement of strength and “Before Initial Dilution” statement are (b)(4) difficult to read. Revise accordingly (e.g., increase the font weight) to improve readability.
- b. Add the statement “For Intravenous Infusion Only After Final Dilution” and place it below the statement “Before Initial Dilution” on the principal display panel.
Consider deleting (b)(4) to provide additional space, if needed.
- c. Increase the prominence of the statement of strength on the 20 mg/0.5 mL and 80 mg/2 mL vials.

B. Diluent

- a. Decrease the prominence of the Docetaxel Injection strength (i.e., “20 mg” and “80 mg”) to be commensurate with the statement “for Docetaxel Injection”.
- b. The diluent ingredients are not stated on the label. State the diluent ingredients.

Carton Labels:

- A. Increase the prominence of the statement of strength on the 20 mg/0.5 mL and 80 mg/2 mL vials.
 - B. On the side panel, expand the box around the caution statement to include the “10 mg/mL docetaxel after initial dilution...to prepare the final dilution for infusion” statement.
- 3) The proposed sites for the manufacturing and control of the drug product do not meet current GMP requirements. Specifically, the Apotex facility at Richmond Hill has unresolved GMP issues from a recent inspection; and the sites at Weston Road, Signet Campus, and Etobicoke have unresolved GMP issues addressed in Warning Letters dated 25-JUN-2009 and 29-MAR-2010. Satisfactory resolution of these deficiencies is required before this application may be approved.

- 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

09/22/2010

Anthony J.Murgo, M.D. signing for:
Robert Justice, M.D., M.S.

Summary Review for Regulatory Action

Date	January 28, 2010
From	Anthony J. Murgu, MD, MS (Acting DDD)
Subject	Division Director Summary Review
NDA/BLA #	NDA 22-312
Supplement #	
Applicant Name	Apotex, Inc.
Date of Submission	July 29, 2009
PDUFA Goal Date	January 29, 2010
Proprietary Name / Established (USAN) Name	N/A / Docetaxel Injection
Dosage Forms / Strength	Injectable/40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL)
Proposed Indication(s)	<ol style="list-style-type: none"> 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: in combination with CP and 5-FU 5. Squamous cell carcinoma of Head/Neck: in combination with CP and 5-FU
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	N/A
Statistical Review	N/A
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X (Product Quality)
Clinical Pharmacology Review	N/A
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 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. This review considers a resubmission of NDA 22-312 received July 29, 2009 and amendments dated August 14 and September 10, 2009. The resubmission is in response to a Complete Response action sent to the sponsor on April 28, 2009. The sponsor's amendments dated November 24, 2009 and January 15, 2010 are not reviewed or considered during this cycle. The FDA has determined that the amended application is not approvable because of outstanding product quality and labeling deficiencies.

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 along with patent exclusivity status:

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 (exclusivity expired)

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 (exclusivity expired)

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

Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction (exclusivity will expire on March 22, 2009)

Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN (exclusivity will expire September 28, 2010)

The salient issues in the original application that led to the CR related to the CMC and Pharmacology/Toxicology information. The following were specific deficiencies noted in the April 28, 2009 CR Action:

Nonclinical

The proposed acceptance criteria for the following impurities (b) (4) in the Docetaxel Injection drug product exceed the ICH Q3B(R2) qualification limit of 0.2%.

Furthermore, the sponsor needed to demonstrate that (b) (4) in their drug product both during release as well as during stability is below the ICH Q3B(R2) proposed limit of 0.2%.

Impurity specifications that exceed the qualification limit must be lowered to meet the current ICH Q3B(R2) guidance or the impurities will need to be qualified in nonclinical toxicology studies.

Product Quality

DMF (b) (4) was inadequate to support the NDA. Deficiencies had been communicated to the DMF Holder; these deficiencies need to be adequately resolved.

The sponsor needed to demonstrate the adequacy of the proposed analytical (Method No. DOCE-SINJ-CB-90-RH) method in terms of precision, linearity, accuracy and robustness for all the degradants monitored in the docetaxel injection (b) (4) that are over 0.2%.

Considering that all vials are for single use, the Sponsor needed to revise the 'Volume of Injection' acceptance criteria for docetaxel injection diluent to represent the actual fill volumes, as listed in table 3 of the package insert (for 1.8mL the range is 1.83-2.43mL while for 7.1mL the range is 7.3-7.9mL).

The FDA requested that the Sponsor describe their plans to scale up in order to meet the commercial requirement.

The FDA also noted the following two comments regarding the application:

- “Given the breadth of information provided in the March 31, 2009 amendment, as well as the timing of the submission, this amendment was not reviewed during this cycle.
- Due to the outstanding Chemistry, Manufacturing and Controls deficiencies, it is not possible to confirm the acceptability of your proposed (b) (4) Protocol.”

Finally, the Sponsor was asked to submit a draft labeling that incorporates revisions to the labeling (attached with the CR letter).

Summaries of the reviews of the July 29, 2009 resubmission are noted below by discipline.

3. CMC/Product Quality Microbiology

CMC

The Chemistry Review for this complete response submission was signed on January 22, 2010 by the primary reviewer and team leader. Summary of the CMC concerns and recommendations are as follows:

The Chemistry review noted a list of outstanding deficiencies regarding the Sponsor's proposed carton and container labels, and the package insert. The review also noted that due to the timing of the submission and breadth of information in the November 24, 2009 amendment a review was not done during this cycle. This amendment includes the use of (b) (4) [redacted] at the Richmond Hill facility (b) (4) [redacted] of Docetaxel Diluent, 1.8 mL and 7.1 mL package sizes).

Microbiology

The Product Quality Microbiology review was completed and signed by the primary reviewer and team leader on January 11, 2010 and January 12, 2010, respectively. The review found deficiencies in a (b) (4) [redacted] protocol submitted by the applican (b) (4) [redacted]

[redacted] The review concluded that failure to address the microbiology deficiencies could result in microbial and/or endotoxin contamination of the drug product. The review also noted that due to the timing of the submission and breadth of information in the November 24, 2009 amendment a review was not done during this cycle (see CMC review, above).

I concur with the conclusions reached by the CMC and Microbiology reviews that satisfactory resolution of all the CMC and Microbiology deficiencies outlined above is required before an approval recommendation can be made.

Areas of disagreement – There are areas of disagreement between CMC and DMEPA regarding the review of carton and container labels. As noted in a CMC Memo dated January 28, 2010, several DMEPA-generated comments appear to contradict the CMC reviewer's recommendations. Internal discussion to reconcile the differences was not possible due to the timing of the review. Therefore, due to the pending action date for this submission, as well as the recommended "Complete Response" action for the submission, CMC recommended, and the Review Division concurred, that all container/carton and PI labeling deficiencies be deferred during this review cycle. (see section on Labeling, below).

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review is complete and was signed on December 21, 2009 by the primary reviewer and team leader. The following is a brief overview of their findings:

All 505(b)2 impurities noted in the Background section concerning the original Apotex NDA submission have been qualified.

Another subject in the Pharmacology/Toxicology review pertains to the levels of polysorbate 80 (PS80). In June 2009, Sanofi submitted a Citizen's petition (CP) to the Agency requesting the Agency require a clinical pharmacokinetic study for proposed new drug products [505(b)(2) or ANDA] containing a ratio of docetaxel:PS80 different from that of Taxotere. Sanofi claims that docetaxel binds with high affinity to AAG in plasma, and increased concentrations of PS80 may result in increased levels of unbound docetaxel, which may have a greater effect on overall safety and pharmacodynamics, than the total docetaxel drug level. As a result, this variability in unbound docetaxel plasma concentration may cause significant differences in the safety and efficacy of the drug product. After FDA review of data submitted by Sanofi, it was decided by the Center Director that the petitioner did not submit adequate data to justify their position. The ratio of docetaxel:PS80 is (b) (4) for the 2-vial Sanofi Taxotere formulation and is (b) (4) for the present 505(b)(2) docetaxel. At this time there are no data to suggest that the minor change in the docetaxel:PS80 ratio will affect either the safety or the efficacy of Apotex's Docetaxel Injection.

I concur with the conclusions reached by the Pharmacology/Toxicology reviewer that the impurity concerns are adequately resolved and that the concern about the docetaxel:PS80 ratio brought forth in the Citizen's petition is not relevant to this particular 505(b)(2) application.

5. Clinical Pharmacology/Biopharmaceutics

No formal review applicable this cycle.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

No formal review applicable this cycle. Clinical team participated in labeling review.

8. Safety

Not applicable.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

The originator's patent has not expired on the head and neck indication.

12. Labeling

The Sponsor's proposed carton labels, container labels and package insert were reviewed by various disciplines, and a number of deficiencies were noted (see CMC review dated January 22, 2010, DMEPA review dated January 26, 2010, and CMC Memo dated January 28, 2010). As noted in a CMC Memo dated January 28, 2010, several DMEPA-generated comments appear to contradict the CMC reviewer's recommendations. Internal discussion to reconcile the differences was not possible due to the timing of the reviews. Therefore, due to the pending action date for this submission, as well as the recommended "Complete Response" action for the submission, CMC recommended (with the concurrence of the Review Division) that all container/carton and PI labeling deficiencies be deferred during this review cycle. Labeling deficiencies captured in both reviews will need to be revisited during a subsequent review cycle and prior to approval of this NDA.

I concur that the container/carton and PI labeling deficiencies be deferred during this review cycle and revisited during a subsequent review cycle.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: **Complete Response**

The following deficiencies will be communicated in the CR action letter:

CMC

Given the breadth of information provided in the November 24, 2009, amendment, as well as the timing of this submission, this amendment (which includes the use of (b) (4) (b) (4) at the Richmond Hill facility (b) (4) of Docetaxel Diluent, 1.8 mL and 7.1 mL package sizes) was not reviewed during this cycle.

Your (b) (4) protocol submitted in the July 29, 2009, amendment (b) (4) is inadequate based on the Microbiology evaluation. (Refer to Microbiology deficiencies).

CMC Microbiology

Although a (b) (4) protocol does not require the inclusion of data, sufficient detail regarding the manufacturing process, the methods by which validation studies will be conducted, and the acceptance criteria for validation studies should be provided prior to approval of the (b) (4) protocol. The following is a list of information required for

approval of a (b) (4) protoco (b) (4)

Facility Inspections

During a recent inspection of the Apotex, Inc. (Etobicoke and Toronto, Canada) manufacturing facilities for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

- 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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22312

ORIG-1

DOCETAXEL INJECTION 40 MG
ML

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/s/

ANTHONY J MURGO
01/29/2010

Summary Review for Regulatory Action

Date	March 28, 2009
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA #	NDA 22-312
Supplement #	
Applicant Name	Apotex, Inc.
Date of Submission	March 28, 2008
PDUFA Goal Date	April 28, 2009
Proprietary Name / Established (USAN) Name	N/A / Docetaxel Injection
Dosage Forms / Strength	Injectable/40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL)
Proposed Indication(s)	<ol style="list-style-type: none"> 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: in combination with CP and 5-FU 5. Head/Neck cancer: in combination with CP and 5-FU
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	X
Statistical Review	N/A
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X
Clinical Pharmacology Review	X
DDMAC	X
DSI	N/A
CDTL Review	N/A
OSE/DMEPA	X
OSE/DDRE	N/A
OSE/DRISK	N/A
Other	X

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 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. This review considers NDA 22-312 received March 28, 2008 and amendments dated September 17, December 3, 2008 and March 5 and March 12, 2009, but not the major amendment dated March 31, 2009.

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 listed below are abbreviated for conciseness (see proposed package insert for full text).

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 (exclusivity expired)

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 (exclusivity expired)

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

Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction (exclusivity will expire on March 22, 2009)

Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN (exclusivity will expire September 28, 2010)

The salient issues in the application relate to the CMC and Pharmacology/Toxicology information. There are no areas of disagreement between various discipline reviewers.

3. CMC/Device

The Chemistry Review for this complete response summary was signed on April 23, 2009. Relevant concerns and recommendations are as follows:

The injection concentrate specifications include quality tests for appearance, identity, assay, degradation products, and microbiology. In the original submission, it was noted that the

specifications for release were (b) (4)

(b) (4) the sponsor proposed the same set of specifications for both release and stability. It is noted from the specifications that four of the impurities are above the ICH Q3B(R2) limit of 0.2% and would thus have to be qualified. These are: (b) (4), (b) (4), and Apotex impurity at (b) (4). In addition, it is not clear from the March 12, 2009 amendment whether the impurity (b) (4) is at all present in the product and if so at what levels. The sponsor also has to demonstrate the adequacy of the proposed analytical (Method No. DOCE-SINJ-CB-90-RH) method in terms of precision, linearity, accuracy and robustness for all the degradants monitored in the docetaxel injection (b) (4) that are over 0.2%. Please refer to the Pharmacology/Toxicology review dated April 21, 2009 for further details regarding impurity qualification.

The current NDA submission also included a proposed (b) (4) protocol. This protocol allowed for the (b) (4)

(b) (4) Due to the pending CMC deficiencies, it is not possible to confirm the acceptability of the proposed (b) (4) protocol at this time. This will be communicated in the action letter.

On evaluation of the stability data, it was decided to grant the sponsor only 12 months of expiration, if the application were to be approved at this time. (b) (4)

(b) (4) In addition, granting the 12 month expiration per the 12 month data provided is in accordance with ICH guidance Q1E, which states that no extrapolation be allowed if significant changes are observed during storage.

Complete review of labeling has been deferred at this time for this submission given the outstanding CMC deficiencies. Comments based on the proposed container/carton label were communicated to DMEPA.

DMF (b) (4) is currently inadequate to support the NDA. Deficiencies have been communicated to the DMF Holder; these deficiencies are not yet adequately resolved.

I concur with the conclusions reached by the chemistry review that satisfactory resolution of all the CMC deficiencies outlined above, as well as a review of the proposed (b) (4) protocol provided in the original NDA and scale up, information provided in the amendment dated March 31, 2009 (not reviewed for this action), is required before an approval recommendation can be made from the CMC standpoint.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review is complete and signed on April 21st and April 22nd, 2009 by the primary reviewer and team leader, respectively. The following is a brief overview of their findings:

The proposed acceptance criteria for impurities (b) (4) in the Docetaxel Injection drug product exceed the ICH Q3B(R2) qualification limit of 0.2%. Impurity specifications that exceed the qualification limit must be lowered to meet the current ICH Q3B(R2) guidance, or the impurities will need to be qualified in nonclinical toxicology bridging studies. Alternatively, justifications for impurity levels may be provided based on appropriate literature citations.

The sponsor has interchangeably referred to (b) (4). These degradates are not equal. The sponsor will need to demonstrate that (b) (4) both during release as well as during stability, is below the ICH Q3B(R2) proposed limit of 0.2%. Alternatively, the sponsor may qualify this impurity, or provide justification for the impurity level of (b) (4).

Other than impurity qualification as indicated above, there are no outstanding nonclinical safety issues relevant to clinical use of Docetaxel Injection. Adverse reactions associated with Docetaxel Injection are expected to be comparable to those reported for the RLD.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that impurity concerns must be resolved as indicated in this review.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review of this complete response dated February 12, 2009 noted that there is no new clinical pharmacology information in this submission. I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics review team that there are no outstanding clinical pharmacology issues.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

A clinical review of the application signed by the Medical Reviewer (February 27, 2009) and the Medical Team Leader (March 10, 2009) is included in the package. This review noted that there were no clinical data submitted and made reference to the CMC and Pharmacology/Toxicology reviews for safety issues related to those disciplines.

8. Safety

Not applicable. No clinical data were submitted.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

During a recent inspection of the Apotex, Inc. (Etobicoke, Canada) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. An additional manufacturing site (Apotex, Inc., Toronto, Canada) was also determined to be unacceptable. Satisfactory resolution of any related deficiencies is required before this application may be approved.

12. Labeling

The statement of strengths on the container and carton labeling is not expressed in accordance with USP recommendations for the labeling of injectable drug products. Several other deficiencies in the container and carton label wording and design have been noted in the review. These have been conveyed to the sponsor for revision. Complete review of labeling has been deferred at this time for this submission given the outstanding CMC deficiencies.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete response. The following deficiencies will be communicated in the letter:

Your proposed acceptance criteria for the following impurities (b) (4) in the Docetaxel Injection drug product exceed the ICH Q3B(R2) qualification limit of 0.2%.

Furthermore, you will need to demonstrate that (b) (4) in your drug product both during release as well as during stability is below the ICH Q3B(R2) proposed limit of 0.2%.

Impurity specifications that exceed the qualification limit must be lowered to meet the current ICH Q3B(R2) guidance or the impurities will need to be qualified in nonclinical toxicology studies. Alternatively, justifications for impurity levels may be provided based on appropriate literature citations.

DMF (b) (4) is currently inadequate to support your NDA. Deficiencies have been communicated to the DMF Holder; these deficiencies need to be adequately resolved.

During a recent inspection of the Apotex, Inc. (Etobicoke, Canada) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. An additional manufacturing site (Apotex, Inc., Toronto, Canada) was also determined to be unacceptable. Satisfactory resolution of any related deficiencies is required before this application may be approved.

Due to the outstanding Chemistry, Manufacturing and Controls deficiencies, it is not possible to confirm the acceptability of your proposed (b) (4) Protocol.

Given the timing of the submission as well, as the breadth of information provided, the March 31, 2009 amendment was not reviewed during this cycle.

- 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 Murgo
4/28/2009 02:43:01 PM
MEDICAL OFFICER
For Robert Justice, M.D.

CLINICAL REVIEW

Application Type NDA 505(2)(b)
Submission Number 22312
Submission Code 000

Letter Date Mar 23, 2008
Stamp Date Mar 28, 2008
PDUFA Goal Date April 28, 2009

Reviewer Name Qin Ryan, MD, PhD
Clinical Team Leader Robert Justice, MD, MS
Review Completion Date Feb. 27, 2009

Established Name docetaxel
Trade Name Docetaxel Injection
Reference NDA 20449
Therapeutic Class Microtubule disregulator and
antineoplastic
Applicant Apotex Inc

Priority Designation S

Formulation IV
Dosing Regimen Multiple (see product information, 2.1)
Indication Multiple (see product information, 2.1)
Intended Population Multiple (see product information, 2.1)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA for docetaxel injection in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act was submitted to request approval of therapeutic equivalence of the proposed product to Taxotere, as defined in the FDA orange book. The sponsor of NDA 20449 for Taxotere is sanofi-aventis. The exclusivity of indications below has expired:

Breast Cancer

- Docetaxel Injection is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.
- Docetaxel Injection in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

Non-Small Cell Lung Cancer

- Docetaxel Injection as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.
- Docetaxel Injection in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

Prostate Cancer

- Docetaxel Injection in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

The exclusivity for the following indication will expire on March 22, 2009.

Gastric Adenocarcinoma

- Docetaxel injection in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

The exclusivity for the following indication will expire on September 28, 2010.

Head and Neck Cancer

- Docetaxel injection in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

No new clinical data was submitted for this NDA. Taxotere NDA 20449 has been previously reviewed for efficacy and safety. Therefore, the medical reviewer recommends approval (if pharmacological equivalence is supported adequately) for all of the above indications when the exclusivity for Taxotere[®] expires. However, only 3 of 5 cancer indications (breast cancer, non-small cell lung cancer and hormone refractory prostate cancers) will be eligible for approval at the time of PDUFA date for this NDA submission.

1.2 Risk Benefit Assessment

Please refer to NDA 20449.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: docetaxel

Proprietary Name: Docetaxel Injection

Applicant: Apotex
150 Signet Drive
Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300
Fax: (416) 401-3849
www.apotex.com

Drug Class: Microtubule disregulator and antineoplastic

Proposed Indications:

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.

Proposed Dosage 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.
- BC adjuvant: 75 mg/m² administered 1 hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks for 6 cycles.
- NSCLC: after platinum therapy failure: 75 mg/m² single agent
- NSCLC: chemotherapy-naïve: 75 mg/m² followed by cisplatin 75 mg/m²
- HRPC: 75 mg/m² with 5 mg prednisone twice a day continuously
- GC: 75 mg/m² followed by cisplatin 75 mg/m² (both on day 1 only) followed by fluorouracil 750 mg/m² per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion
- Induction chemotherapy of inoperable SCCHN followed by radiotherapy: 75 mg/m² followed by cisplatin 75 mg/m² IV (day 1), followed by fluorouracil 750 mg/m² per day as a continuous 24-hr IV infusion (days 1-5) for 4 cycles.
- Induction chemotherapy followed by chemoradiotherapy of locally advanced SCCHN: 75 mg/m² followed by cisplatin 100 mg/m² IV (day 1), followed by fluorouracil 1000 mg/m² per day as a continuous 24-hr IV infusion (days 1-4) for 3 cycles.

Premedication Regimen

- Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice a day) for 3 days starting 1 day before administration
- HRPC: oral dexamethasone 8 mg, at 12, 3, and 1 hrs before treatment

Dosage adjustments during treatment see full prescribing information

Dosage Forms and Strengths

- 20 mg/ (b) (4) single-dose vial
- 80 mg/ (b) (4) dose vial

(b)

Contraindications

- Hypersensitivity to Docetaxel Injection or polysorbate 80
- Neutrophil counts of <1500 cells/mm³

Warnings and Precautions

- Acute myeloid leukemia
- Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant when taking Docetaxel Injection
- Asthenia

Adverse Reactions

Most common adverse reactions are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, myalgia

2.2 Availability of Proposed Active Ingredient in the United States

Taxotere is marketed in the US.

2.3 Summary of Presubmission Regulatory Activity Related to Submission

Sep 24, 2007: Pre-IND meeting to discuss NDA submission plan

Mar 27, 2008: Apotex submitted NDA 22312.

2.4 Pediatric Waiver

A full pediatric waiver request was submitted with NDA 22312 submission. The waiver is granted because there are very few pediatric patients, if any, which would have breast cancer, lung cancer or prostate cancer.

2.5 Other Relevant Background Information

Refer to NDA 20449

Table 1: Patent Data for TAXOTERE Injection Concentrate

Patent Number	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Certification	21 CFR Reference
4814470	14 May 2010	X	X	Paragraph II	314.50(i)(1)(i)(A)(3)
5438072	22 Nov 2013	X		Paragraph IV	314.50(i)(1)(i)(A)(4)
5698582	03 Jul 2012	X		Paragraph IV	314.50(i)(1)(i)(A)(4)
5714512	03 Jul 2012	X		Paragraph IV	314.50(i)(1)(i)(A)(4)
5750561	03 Jul 2012	X		Paragraph IV	314.50(i)(1)(i)(A)(4)

Table 2: Exclusivity Data* for TAXOTERE Injection Concentrate

Exclusivity Code	Exclusivity Definition	Exclusivity Expiration
I-429	For use in combination with prednisone for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.	19 May 2007
I-436	For use in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.	18 Aug 2007
I-490	For use in combination with Cisplatin and 5-FU for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of prior chemotherapy for advanced disease	Mar 22,2009
I-519	For use in combination with Cisplatin and 5-FU in patients with inoperable HNSCC prior to definitive treatment.	OCT 17,2009
I-542	Expansion of patient population for head and neck cancer from “inoperable” patients to all patients.	SEP 28,2010
I-543	For in combination with Cisplatin and 5-FU in patients with advanced HNSCC prior to definitive treatment.	SEP 28,2010

* No exclusivity information remains in Orange Book for NSCLC indication.

3 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to NDA 20449 CMC, Pharmacology/Toxicology, and Clinical Pharmacology reviews, NDA 22312 CMC review, and the label.

4 Sources of Clinical Data

Refer to NDA 20449.

5 Review of Efficacy

Refer to NDA 20449.

6 Review of Safety

Refer to NDA 20449.

7 Appendices

7.1 Literature Review/References

Refer to NDA 20449

7.2 Labeling Recommendations

See final label.

7.3 Advisory Committee Meeting

None

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

/s/

Qin Ryan
2/27/2009 01:36:25 PM
MEDICAL OFFICER

All your suggestion were taken, thanks!

Robert Justice
3/10/2009 06:06:44 PM
MEDICAL OFFICER