

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022234Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Submission Number	NDA 22234
Submission Code	Class 2, Resubmission
Letter Date	September 23, 2010
Stamp Date	September 23, 2010
PDUFA Goal Date	March 23, 2011
Reviewer Name	Kristen M. Snyder, MD
Clinical Team Leader	Patricia Cortazar, MD
Review Completion Date	February 7, 2011
Established Name	docetaxel
Trade Name	Docetaxel Injection
Reference NDA	20449
Therapeutic Class	Disruptor of microtubule network
Applicant	Hospira, 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)

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT</b>	<b>3</b>
<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT</b>	<b>3</b>
1.1	Recommendation on Regulatory Action	3
1.2	Risk Benefit Assessment	4
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND</b>	<b>4</b>
2.1	Product Information	4
2.2	Availability of Proposed Active Ingredient in the United States	6
2.3	Summary of Presubmission Regulatory Activity Related to Submission	6
2.4	Pediatric Waiver	6
2.5	Other Relevant Background Information	7
<b>3</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES</b>	<b>8</b>
<b>4</b>	<b>SOURCES OF CLINICAL DATA</b>	<b>8</b>
<b>5</b>	<b>REVIEW OF EFFICACY</b>	<b>8</b>
<b>6</b>	<b>REVIEW OF SAFETY</b>	<b>8</b>
<b>7</b>	<b>APPENDICES</b>	<b>8</b>
7.1	Literature Review/References	8
7.2	Labeling Recommendations	8
7.3	Advisory Committee Meeting	8

## List of Tables

Table 1: Patent Data for TAXOTERE Injection Concentrate	7
Table 2: Exclusivity Data* for TAXOTERE Injection Concentrate	7

# 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 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.

### 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.

### 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. Therefore, the medical reviewer recommends approval for all of the above indications. The recommendation for the application is approval with respect to the

Clinical Review  
Kristen M. Snyder, MD  
NDA 22234  
Docetaxel

chemistry, manufacturing, and controls (CMC). See CMC reviews by Josephine Jee and Terrance Ocheltree.

## 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: Hospira, Inc.  
275 North Field Drive  
Bldg. H2-2, Dept. 389  
Lake Forest, IL 60045  
Tel: (224) 212-6158  
Fax: (224) 212-5401

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.

(b) (4)

### Proposed Dosage and Administration

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

- BC, locally advanced or metastatic: 60-100 mg/m<sup>2</sup> single agent
- BC adjuvant: 75 mg/m<sup>2</sup> administered 1 hour after doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> every 3 weeks for 6 cycles
- NSCLC: chemotherapy-naïve: 75 mg/m<sup>2</sup> followed by cisplatin 75 mg/m<sup>2</sup>
- HRPC: 75 mg/m<sup>2</sup> with 5 mg prednisone twice a day continuously

(b) (4)

Reviewer: The pediatric use information for the reference listed product (RLP) is based on data submitted in response to a pediatric written request is protected by Pediatric Exclusivity under the Best Pharmaceuticals for Children Act (BPCA) until May 13, 2013. While the innovator product was issued a pediatric written request, fairly complied with the terms of the WR, and received pediatric exclusivity no pediatric indication was sought. The labeling provides information regarding safety and dosing (including dose-limiting toxicity). Similarly, the question of whether pediatric language in labeling should be “carved-out” or retained in 505(b)(2) applications resulted in a consult to the Pediatric and Maternal Health staff regarding another 505(b)(2) application (NDA 200795) and its RLP (Gemcitabine). The Best Pharmaceuticals for Children Act (BPCA) does not address the protected pediatric information of 505(b)(2) products, only generic products. Therefore, the PMH staff believes omitting pediatric language may be appropriate for a 505b2 product when removal of the language will not result in a safety concern for pediatric patients.

Because the RLP (Taxotere) is not indicated for use in the pediatric population and toxicities seen in pediatric patients were similar to those seen in adults, Docetaxel Injection, if used in the pediatric oncology population, is unlikely to pose a significant or unknown safety risk.

### 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

- 20 mg/2 mL single-dose vial
- 80 mg/8 mL multi-dose vial
- 160 mg/16 mL multi-dose vial

### Contraindications

- Hypersensitivity to docetaxel injection or polysorbate 80
- Neutrophil counts of  $<1500$  cells/mm<sup>3</sup>

### 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

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.

## **2.3 Summary of Resubmission Regulatory Activity Related to Submission**

None

## **2.4 Pediatric Waiver**

Pediatric exclusivity of Taxotere ended on November 14, 2010.

## 2.5 Other Relevant Background Information

### Patent Infringement Case

At the time of NDA filing with the FDA Hospira cited “Paragraph IV” alleging that U.S. Patent Numbers 5438072, 5698582, 5714512, and 5750561 were invalid, not infringed, and/or not enforceable. In court proceedings sanofi-aventis sued Hospira for infringement of patents ‘512 and ‘561 and lost. They did not challenge Hospira’s paragraph IV citations for patents ‘072 or ‘582 (see Appendix 7.4)

**Table 1: Patent Data for TAXOTERE Injection Concentrate**

Patent Number	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Certification	21 CFR Reference	Result following September 2011 Ruling
4814470	May 14, 2010	X	X	Paragraph II	314.50(i)(1)(i)(A)(3)	Expired
4814470*PED	Nov 14, 2010					Expired
5438072	Nov 22, 2013		X	Paragraph IV	314.50(i)(1)(i)(A)( 4)	Hospira cited paragraph IV and sanofi-aventis did not challenge.
5438072*PED	May 22, 2014					
5698582	Jul 03, 2012		X	Paragraph IV	314.50(i)(1)(i)(A)( 4)	Hospira cited paragraph IV and sanofi-aventis did not challenge.
5698582*PED	Jan 03, 2013					
5714512	Jul 03, 2012		X	Paragraph IV	314.50(i)(1)(i)(A)( 4)	Hospira cited paragraph IV. Sanofi-aventis sued for infringement and lost.
5714512*PED	Jan 03, 2013					
5750561	Jul 03, 2012		X	Paragraph IV	314.50(i)(1)(i)(A)( 4)	Hospira cited paragraph IV. Sanofi-aventis sued for infringement and lost.
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

Clinical Review  
Kristen M. Snyder, MD  
NDA 22234  
Docetaxel

PED	Pediatric exclusivity	Mar 28, 2011	Carved Out
M-61	Revisions to labeling based on data submitted in response to pediatric written request	May 13, 2013	Carved Out
PED	Pediatric exclusivity	Nov 13, 2013	Carved Out

### **3 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

Please refer to NDA 20449 CMC, Pharmacology/Toxicology, and Clinical Pharmacology reviews, NDA 201525 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. The clinical safety and efficacy are based on the Taxotere (NDA 20449) label. The clinical team is in agreement with the final approved labeling, carton and container labels.

#### **7.3 Advisory Committee Meeting**

None

#### **7.4 Patent Infringement Case**

##### **Sanofi's initial case<sup>1</sup>:**

[http://www.orangebookblog.com/Aventis\\_20v.\\_20Hospira\\_20\\_28Taxotere\\_29\\_20complaint.pdf](http://www.orangebookblog.com/Aventis_20v._20Hospira_20_28Taxotere_29_20complaint.pdf)

**Outcome:** Sanofi's Taxotere Patents Found Invalid<sup>2</sup>

Clinical Review  
Kristen M. Snyder, MD  
NDA 22234  
Docetaxel

Sanofi filed an infringement action against Hospira and Apotex in November 2007 alleging that the companies infringed U.S. Patent Nos. [5,714,512](#) and [5,750,561](#) by filing NDAs for docetaxel (*see* "[Court Report](#)," November 18, 2007). In November 2009, following a bench trial in the U.S. District Court for the District of Delaware, the parties were ordered to present post-trial proposed findings of fact and conclusions of law concerning the validity and enforceability of the '512 and '561 patents.

On September 27, 2010 Judge Gregory Sleet ruled that the defendants had established by clear and convincing evidence that Sanofi's '512 and '561 patents were invalid due to indefiniteness and obviousness, and unenforceable due to inequitable conduct. In a lengthy opinion, Judge Sleet found that the specific formula for Taxotere was obvious in view of U.S. Patent No. [4,814,470](#), which issued in 1989. Judge Sleet also found that Sanofi did not disclose two highly material prior art references to the Patent Office during the prosecution of the '512 and '561 patents, thus rendering them unenforceable<sup>3</sup>.

## References

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<sup>1</sup> Complaint for patent infringement. Aventis Pharma S.A., sanofi-aventis U.S., LLC v. Hospira, Inc. November 9, 2007. [http://www.orangebookblog.com/Aventis\\_20v.\\_20Hospira\\_20\\_28Taxotere\\_29\\_20complaint.pdf](http://www.orangebookblog.com/Aventis_20v._20Hospira_20_28Taxotere_29_20complaint.pdf) Accessed February 7, 2011.

<sup>2</sup> Sanofi's Taxotere patents found invalid. <http://www.patentdocs.org/2010/09/index.html>. Accessed February 7, 2011.

<sup>3</sup> Honorable Gregory Sleet ruling in Aventis Pharma S.A., sanofi-aventis U.S., LLC v Hospira, Inc case. September 27, 2010. <http://patentdocs.typepad.com/files/taxotere-order.pdf> Accessed February 7, 2011.

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/s/  
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KRISTEN M SNYDER  
02/07/2011

PATRICIA CORTAZAR  
02/08/2011

## Summary Review for Regulatory Action

<b>Date</b>	August 11, 2008
<b>From</b>	Ramzi Dagher, M.D.
<b>Subject</b>	Deputy Division Director Summary Review
<b>NDA #</b>	22-234 new NDA 505(b)(2)
<b>Applicant Name</b>	Hospira, Inc.
<b>Date of Submission</b>	7/11/07
<b>PDUFA Goal Date</b>	5/11/08 revised to 8/11/08 due to a major CMC microbiology amendment
<b>Proprietary Name / Established (USAN) Name</b>	No proprietary name / Docetaxel
<b>Dosage Forms / Strength</b>	Docetaxel injection 20 mg/2mL Docetaxel injection 80 mg/8 mL Docetaxel injection 160 mg/16 mL
<b>Proposed Indications</b>	<p>Breast Cancer</p> <ul style="list-style-type: none"> <li>• Docetaxel Injection is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.</li> <li>• Docetaxel Injection in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.</li> </ul> <p>Non-Small Cell Lung Cancer</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> </ul> <p>Prostate Cancer</p> <ul style="list-style-type: none"> <li>• Docetaxel Injection in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.</li> </ul>
<b>Action :</b>	Tentative Approval

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	X
Pharmacology Toxicology Review	X
CMC Review	X
Microbiology Review	X
Clinical Pharmacology Review	X
SEALD	X
OSE/DMEPA	X

SEALD=Study Endpoints and Labeling  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA= Division of Medication Error Prevention and Analysis  
 DDRE= Division of Drug Risk Evaluation  
 CMC=chemistry manufacturing and controls

# Signatory Authority Review

## 1. Introduction

This is a 505(b)(2) application for docetaxel injection submitted by Hospira, Inc. The major differences between Sanofi-Aventis' Taxotere® and Hospira's product are as follows:

- a) The Hospira product can be directly diluted into infusion solutions, as compared to Taxotere®, which must be diluted to a strength of 10 mg/mL prior to addition into infusion solutions.
- b) Hospira, Inc. is registering an additional presentation (160 mg/16 mL) that the innovator does not have.
- c) Hospira, Inc. is proposing a multi-dose application for the 80 mg/8 mL and 160 mg/16mL presentations as compared to Taxotere® which is supplied as single-dose vials.

Although Taxotere® is approved for indications in the treatment of breast cancer, non-small cell lung cancer, prostate cancer, squamous cell carcinoma of the head/neck, and gastric/GE junction adenocarcinoma, exclusivity for the head/neck cancer and gastric/GE junction indications does not expire until 2009. Therefore, the Hospira indications in the tentative approval letter will be limited to breast cancer, lung cancer, and prostate cancer.

## 2. Background

Please see above.

### 3. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance.

The CMC primary review was completed and archived by Terrance Ocheltree, R.Ph., Ph.D. and also signed by Ravi Harapanhalli, Ph.D. on 7/24/08.

The following is excerpted from the CMC review:

“The recommendation for the application is approval with respect to the chemistry, manufacturing, and controls (CMC). The sites recommendation from the Office of Compliance is listed in EES as acceptable. The applicant and Holder of the Type II Drug Master File (DMF) referenced in the NDA have adequately responded to all CMC issues outlined in either this review or the review for DMF (b)(4). All CMC comments related to the carton and container labels have either been implemented or satisfactorily addressed.

The following comment should be included in the action letter.

1. An expiration dating period of (b)(4) is granted to your product. You may extend the expiration date based on satisfactory accrual of real time stability data and report it in the annual report.
2. We remind you of your letter dated 11-MAR-2008 in which you have indicated that the (b)(4) has been withdrawn. Therefore, any future site change should be submitted as a prior-approval supplement to the NDA.”

### 4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharm/tox issues that preclude approval. The review was completed and archived by Margaret Brower, Ph.D. and Haleh Saber, Ph.D. on 6/9/08.

## 5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval. The review was completed by Sophia Abraham, Ph.D. and also signed by Brian Booth, Ph.D. on 10/1/07.

## 6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewers that there are no outstanding clinical microbiology or sterility issues that preclude approval.

The initial microbiology review, completed by Anastasia G. Lolas, Ph.D. on 4/11/08 identified several deficiencies. Specifically, additional information was required and requested for the process of depyrogenation of vials (b) (4), efficacy of the (b) (4) to remove bacterial endotoxins, procedures and specifications for media fills, (b) (4) and for the summary of antimicrobial effectiveness test results. The request was sent on 4/11/08 and a response was received on 4/25/08. The response was considered to be a major amendment.

A subsequent review recommending approval was completed and archived by Anastasia Lolas, Ph.D. and Bryan Riley, Ph.D. on 6/9/08. The applicant's responses were considered acceptable. (b) (4)

## 7. Clinical/Statistical-Efficacy

There were no new clinical data submitted with this 505(b)(2) application.

The medical review, archived by Qin Ryan, M.D., Ph.D. on 8/7/08 recommends "...approval ...when the exclusivity for Taxotere® expires."

The medical review team had several labeling recommendations including minor changes to section headings for breast cancer and prostate cancer to more specifically reflect the approved indications, rounding off estimates of adverse reactions to the nearest whole number, and changing "Docetaxel injection" to "docetaxel" throughout the proposed label.

The medical review team agreed with the recommendation to add a patient counseling section as recommended by the SEALD team.

## **8. Safety**

The office of surveillance and epidemiology recommended strategies to reduce the potential risk of medication errors arising from the differences in preparation between this final product and Taxotere®. However, it should be noted that this product can be directly diluted into infusion solutions, as compared to Taxotere® which must be diluted to a strength of 10 mg/mL prior to addition into infusion solutions. Therefore, the risk of a medication error is small, and an error is not likely to result in a change in dosing.

After internal discussion between OSE staff, the CMC review team, and the clinical review team, the following approach was adopted:

- a. propose that the applicant further enhance the prominence of the route of administration statement “For IV infusion only” on the carton labeling. (This was agreed to by the applicant on 8/8/08)
- b. propose that the applicant agree to inform healthcare practitioners about the differences in the preparation of the proposed Docetaxel Injection versus other docetaxel products (e.g., Dear Healthcare Professional letter). (This was agreed to by the applicant on 8/8/08)

## **9. Advisory Committee Meeting**

An advisory committee meeting was not considered necessary given the substantial evidence of safety and effectiveness and post-marketing information available on the active ingredient, docetaxel.

## **10. Pediatrics**

Pediatric waivers for the proposed indications have been submitted. The PeRC will discuss these at the next scheduled PeRC and approval of the waivers is anticipated.

## **11. Other Relevant Regulatory Issues**

There are no other unresolved relevant regulatory issues.

## **12. Labeling**

See specific discipline reviews.

## **13. Decision/Action/Risk Benefit Assessment**

The application is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed upon labeling. This determination is contingent upon information available to the Agency at this time and is, therefore, subject to change on the basis of any new information that may come to our attention.

The listed reference drug product is subject to a period of patent protection and exclusivity protection and therefore, final approval of the application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired, i.e., September 28, 2010.

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this page is the manifestation of the electronic signature.**  
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/s/

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Ramzi Dagher  
8/11/2008 09:37:17 AM  
MEDICAL OFFICER

## CLINICAL REVIEW

Application Type	NDA 505(2)(b)
Submission Number	22234
Submission Code	000
Letter Date	July 9, 2007
Stamp Date	July 9, 2007
PDUFA Goal Date	August 11, 2008
Reviewer Name	Qin Ryan, MD, PhD
Clinical Team Leader	Amna Ibrahim, MD Ramzi Dagher MD
Review Completion Date	August 7, 2008
Established Name	docetaxel
Trade Name	Docetaxel Injection
Reference NDA	20449
Therapeutic Class	Microtubule disregulator and antineoplastic
Applicant	Hospira
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)

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>3</b>
1.1	Recommendation on Regulatory Action.....	3
1.2	Risk Benefit Assessment .....	3
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND.....</b>	<b>3</b>
2.1	Product Information.....	3
2.2	Availability of Proposed Active Ingredient in the United States.....	5
2.3	Summary of Presubmission Regulatory Activity Related to Submission.....	5
2.4	Pediatric Waiver .....	5
2.5	Other Relevant Background Information .....	5
<b>3</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....</b>	<b>6</b>
<b>4</b>	<b>SOURCES OF CLINICAL DATA .....</b>	<b>6</b>
<b>5</b>	<b>REVIEW OF EFFICACY .....</b>	<b>6</b>
<b>6</b>	<b>REVIEW OF SAFETY.....</b>	<b>6</b>
<b>7</b>	<b>APPENDICES .....</b>	<b>6</b>
7.1	Literature Review/References .....	6
7.2	Labeling Recommendations .....	6
7.3	Advisory Committee Meeting .....	7

## List of Tables

Table 1: Patent Data for TAXOTERE Injection Concentrate .....	5
Table 2: Exclusivity Data* for TAXOTERE Injection Concentrate .....	6

## **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 will be expired on August 10, 2008:

#### 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.

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<sup>®</sup> expires.

### **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: Hospira  
275 N. Field Dr.  
D-0389, Bldg. H2-2N  
Lake Forest, IL 60045-5046

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.

Proposed Dosage and Administration

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

- BC, locally advanced or metastatic: 60-100 mg/m<sup>2</sup> single agent.
- BC adjuvant: 75 mg/m<sup>2</sup> administered 1 hour after doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> every 3 weeks for 6 cycles.
- NSCLC: after platinum therapy failure: 75 mg/m<sup>2</sup> single agent
- NSCLC: chemotherapy-naïve: 75 mg/m<sup>2</sup> followed by cisplatin 75 mg/m<sup>2</sup>
- HRPC: 75 mg/m<sup>2</sup> with 5 mg prednisone twice a day continuously

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/2 mL single-dose vial
- 80 mg/8 mL multi-dose vial
- 160 mg/16 mL multi-dose vial

#### Contraindications

- Hypersensitivity to Docetaxel Injection or polysorbate 80
- Neutrophil counts of  $<1500$  cells/mm<sup>3</sup>

#### 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**

Feb 2, 2007: Hospira acquired Mayne Pharma Limited.

July 9, 2007: Hospira submitted NDA 22234.

## **2.4 Pediatric Waiver**

A full pediatric waiver request was submitted with NDA 22234 submission. The waiver is granted because there are very few pediatric patients, if any, that 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**

Clinical Review  
 {Insert Reviewer Name}  
 {Insert Application and Submission Number}  
 {Insert Product Trade and Generic Name}

---

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

\* No exclusivity information remain in Orange Book for NSCLC indication.

### **3 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

Please refer to NDA 20449 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**

The clinical recommendations for the label are as follows:

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

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- Administrative revision of adverse reaction observed during treatment for breast cancer
- Round off adverse event incidence.
- 14.1 title [REDACTED]<sup>(b)(4)</sup> changed to “locally advanced or metastatic breast cancer”.
- (NSCLC) was removed from 14.3 title.
- 14.4 title [REDACTED]<sup>(b)(4)</sup> changed to “Hormone refractory prostate cancer”
- All “Docetaxel Injection” phrases changed to “docetaxel”.
- Please also see chemistry and clinical pharmacology reviews for relevant label changes.

### **7.3 Advisory Committee Meeting**

None

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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.**  
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/s/

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