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APPLICATION NUMBER:

201525Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Submission Number	NDA 201525
Letter Date	September 16, 2010
Stamp Date	September 17, 2010
PDUFA Goal Date	July 17, 2011
Reviewer Name	Kristen M. Snyder, MD
Clinical Team Leader	Patricia Cortazar, MD
Review Completion Date	May 25, 2011
Established Name	docetaxel
Trade Name	Docetaxel Injection
Reference NDA	20449
Therapeutic Class	Disruptor of microtubule network
Applicant	Sandoz, 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

- Taxotere is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.
- Taxotere 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

- Taxotere 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.
- Taxotere 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

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

Gastric Adenocarcinoma

- Taxotere 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

- Taxotere 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:

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- . **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

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.

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: Sandoz, Inc.,
506 Carnegie Center
Suite 400
Princeton, NJ 08540

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 (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 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

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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:

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 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 505(b)(2) 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

Multiple dose vial 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL

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.

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- **Asthenia:** Severe asthenia may occur and may require treatment discontinuation.
- **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

This is the original submission.

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)

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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	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 reviews, and the labeling.

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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
06/01/2011

PATRICIA CORTAZAR
06/09/2011