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RESEARCH**

APPLICATION NUMBER:
201195Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Submission Number	NDA 201195
Submission Code	Class 2, Resubmission
Letter Date	December 7, 2010
Stamp Date	December 10, 2010
PDUFA Goal Date	June 10, 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	Accord Healthcare, 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

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	3
1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	3
1.1	Recommendation on Regulatory Action	3
1.2	Risk Benefit Assessment	4
2	INTRODUCTION AND REGULATORY BACKGROUND	4
2.1	Product Information	4
2.2	Availability of Proposed Active Ingredient in the United States	7
2.3	Summary of Presubmission Regulatory Activity Related to Submission	7
2.4	Pediatric Waiver	7
2.5	Other Relevant Background Information	7
3	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	9
4	SOURCES OF CLINICAL DATA	9
5	REVIEW OF EFFICACY	9
6	REVIEW OF SAFETY	9
7	APPENDICES	9
7.1	Literature Review/References	9
7.2	Labeling Recommendations	9
7.3	Advisory Committee Meeting	9

List of Tables

Table 1:	Patent Data for TAXOTERE Injection Concentrate	7
Table 2:	Exclusivity Data* for TAXOTERE Injection Concentrate	8

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:

Clinical Review
Kristen M. Snyder, MD
NDA 201195
Docetaxel Injection

- . **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

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.

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: Accord Healthcare, Inc.,
1009, Slater Road,
Suite 210-B,
Durham, NC 27703,
USA.

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: 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: 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:

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 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

- 80 mg/2 mL and Diluent for Docetaxel Injection 80 mg
- 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.
- 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 October 22, 2010.

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)

Clinical Review
 Kristen M. Snyder, MD
 NDA 201195
 Docetaxel Injection

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, 2012		X	Paragraph IV	314.50(i)(1)(i)(A)(4)
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 201195 CMC reviews, and the labeling.

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
05/27/2011

PATRICIA CORTAZAR
05/28/2011

DD Summary and CDTL Review for Regulatory Action

Date	(electronic stamp)
From	Anthony J. Murgo, M.D., M.S. Acting Deputy Division Director
Subject	NDA 505(b)(2) review
NDA #	201195
Applicant Name	Accord Healthcare, Inc.
Date of Submission	December 21, 2009
PDUFA Goal Date	October 22, 2010
Proprietary Name / Established (USAN) Name	Docetaxel Injection Docetaxel
Dosage Forms / Strength	20 mg/0.5 mL and 80 mg/2 mL (and diluent)
Proposed Indication(s)	1. Breast cancer 2. Non-small cell lung cancer 3. Prostate cancer 4. Gastric adenocarcinoma 5. Squamous cell carcinoma of the head and neck cancer
Action:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	X
Statistical Review	
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	Product Quality only
Clinical Pharmacology Review	X (Including Biopharmaceutics)
DDMAC	
DSI	
CDTL Review	
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 and CDTL Review

1. Introduction

Accord submitted a 505(b)(2) New Drug Application (NDA 201195) for Docetaxel Injection on December 21, 2009. The reference listed drug (RLD) is Taxotere® for Injection (docetaxel; Sanofi-Aventis), approved by the FDA on May 14, 1996 (NDA 20-449). Taxotere® for Injection is indicated for the treatment of breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck (SCCHN). Accord is seeking approval for all five of these indications.

The major issues with this application pertain to the supporting CMC information, in particular deficiencies in the stability data and unidentified impurities that are above regulatory acceptance limits.

2. Background

Docetaxel is an antineoplastic agent that acts by disrupting microtubular networks essential for normal cell division. The proposed drug product, Docetaxel Injection, was developed as an equivalent to the Reference Listed Drug (RLD) TAXOTERE® Injection Concentrate of Sanofi-Aventis U.S. LLC (NDA 20-449). Taxotere was approved on May 15, 1996, for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy. On December 23, 1999, Taxotere was approved as a single agent for the treatment of advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy at the recommended dose of 60-100mg/m² administered iv once every three weeks. Taxotere was approved on May 19, 2004 in combination with prednisone for the treatment of androgen independent (hormone refractory) metastatic prostate cancer at a recommended dose of 75mg/m² administered once every 3weeks in combination with 5mg oral prednisone BID. In 2005, Taxotere was approved in combination with cisplatin and 5-FU for the treatment of gastric adenocarcinoma. Taxotere (with cisplatin and fluorouracil) is also approved for induction treatment of locally advanced SCCHN.

This Docetaxel Injection 505(b)(2) NDA application submitted by Accord Healthcare, Inc. proposes the same indications as the RLD Taxotere.

As mentioned above and in Section 3 below, there are outstanding deficiencies in the CMC information. The sponsor has not adequately addressed several IRs pertaining to deficiencies in the stability data and unidentified impurities above acceptance limits.

3. CMC/Product Quality and PQ Microbiology

Docetaxel Injection will be supplied in two presentations and one strength: 20 mg/0.5 mL and 80 mg/2 mL (40 mg/mL). Each presentation is a two-vial formulation intended for single-dose administration. For each presentation, one carton contains two vials packed together in a

blister. One vial is Docetaxel Injection (“Concentrate”) and the other accompanying vial is Diluent for Docetaxel Injection (“Diluent”).

Drug Product Docetaxel Injection—Two-Vial Formulation

Strength	Vial #1: Docetaxel Injection Concentrate	Vial #2: Diluent for Docetaxel Injection
Docetaxel Injection 20 mg/0.5 mL	20 mg/0.5 mL Docetaxel in Dehydrated Alcohol and Polysorbate 80	1.5 mL of PEG 400 in Water for Injection
Docetaxel Injection 80 mg/2 mL	80 mg/2 mL Docetaxel in Dehydrated Alcohol and Polysorbate 80	6.0 mL of PEG 400 in Water for Injection

Docetaxel Injection has the same active ingredient, drug concentration, dosage form, route of administration, and dosing regime, and is intended for the same indications as TAXOTERE. Accord’s proposed drug product is formulated slightly different from TAXOTERE. The proposed product contains two additional inactive ingredients not found in TAXOTERE. Citric acid, which acts as a pH modifying agent, is present in the Docetaxel Injection, and polyethylene glycol 400, (b) (4), is present in the Diluent. Dehydrated alcohol is present in the concentrate in Accord’s drug product, but is a component of the Diluent in TAXOTERE. These inactive ingredients are listed in the Inactive Ingredient Database (IIG) and have been previously approved for use in the same route of administration, and at levels higher than those in the proposed product.

The applicant states that the proposed drug product is considered equivalent to the reference drug and requests a biowaiver of *in-vivo* studies. The request was granted by Biopharmaceutics on Jul. 21, 2010.

The CMC/Product Quality review was signed by the primary team on October 19, 2010, and the CMC branch chief summary memo was also signed on October 19, 2010. The deficiencies are summarized as follows:

- Revisions to and justification of criteria in the drug product specification for various impurities and degradation products are needed (please see Section 4 below for details pertaining to unidentified impurities that are at levels above acceptable limits).
- Updated long term drug product stability data to support the label storage statement and proposed expiry period should be submitted.
- Revision of the drug product established name (b) (4) is recommended.
- Revision of the comparability protocol for change of drug substance supplier to submit the change as a prior approval supplement is recommended.

I concur with the conclusions reached by the CMC reviewers that the application is unacceptable from a CMC perspective for the reasons summarized above.

The Product Quality Microbiology review was signed October 5, 2010. I concur with the conclusion of the reviewers that the application is approval on the basis of issues pertaining to product quality microbiology.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology review was signed on September 9, 2010. That review noted that there are two impurities above the threshold defined in ICH Q3B(R2). The Applicant did not respond to the information request addressing this issue, which is summarized below.

Using the analytical method in the NDA, there are two new impurity peaks identified as RRT (b)(4) and RRT (b)(4). The acceptance criteria for these two compounds are set at NMT (b)(4). This acceptance criterion is above the threshold of 0.2% set by ICH Q3B (R2) based on the maximum daily dose of 180 mg/person. The identification of these two impurity peaks is needed.

If the impurity peaks at RRT (b)(4) and RRT (b)(4) cannot be identified, their levels should be adequately justified (e.g. based on nonclinical studies), or reduced to meet the ICH Q3B(R2) threshold. If the impurity peaks at RRT (b)(4) and RRT (b)(4) are identified to be an impurity in the RLD, their levels should be reduced not to exceed the levels in the RLD; levels above the RLD should be adequately justified based on nonclinical or clinical studies.

In June, 2009, Sanofi submitted a Citizen's Petition (CP) to the Agency which indicated that changes in the ratio of docetaxel:PS80 different from that of Taxotere may affect the release of the unbound fraction of docetaxel (i.e. pharmacokinetics), which may change the safety profile and effectiveness of the drug product compared to Taxotere. Sanofi requested that the Agency require a clinical pharmacokinetic study for these 505(b)(2) or ANDA drug formulations. The ratio of docetaxel:PS80 for the marketed Taxotere 1- and 2-vial formulations is (b)(4). The ratio of docetaxel: PS80 for the proposed Accord 505(b)(2) formulation is (b)(4). The Clinical Pharmacology review of the Applicant formulation indicated that differences in the ratio of docetaxel:PS80 between Taxotere and Docetaxel Injection are not likely to have a significant clinical impact on the pharmacokinetics of docetaxel.

I concur with the Nonclinical Pharmacology/Toxicology reviewers that this NDA cannot be approved until the impurity issue is adequately addressed.

5. Clinical Pharmacology/Biopharmaceutics

As noted in the Clinical Pharmacology review signed by the primary reviewer and team leader on September 8 and September 10, 2010, respectively, the applicant was informed by the Division on June 4, 2008 that a bioequivalence study with the RLD is not needed. The current application thus does not include clinical studies and relies on the FDA's findings of safety and effectiveness for RLD Taxotere® for Injection (NDA 20-449).

See previous section regarding a Citizen's Petition (CP) related to the ratio of docetaxel:PS80. As noted above, the Clinical Pharmacology review of the Accord formulation indicated that

differences in the ratio of docetaxel:PS80 between Taxotere and Docetaxel Injection are not likely to have a significant clinical impact on the pharmacokinetics of docetaxel.

The Biopharmaceutics review was signed on July 21 and July 22, 2010, by the primary reviewer and team leader, respectively. The reviewers note that Accord Healthcare is requesting that the Agency's requirement for the submission of in vivo BA/BE data to support the approval of Docetaxel Injection 20 mg and 80 mg be waived. The reviewers recommended that the sponsor's request for a biowaiver for Docetaxel Injection 20 mg/0.5 ml and 80 mg/2 ml is acceptable and that the biowaiver be granted.

I concur with the conclusions of the reviewers that the application is acceptable from a Clinical Pharmacology/Biopharmaceutics perspective.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

As noted in the Clinical Review signed on July 1 and July 2, 2010, by the primary review and team leader, respectively, no new clinical data were submitted for this NDA. The RLD Taxotere (NDA 20449) has been previously reviewed for efficacy and safety. I concur with the conclusions of the clinical reviewers that there are no outstanding clinical deficiencies.

8. Safety

NA

9. Advisory Committee Meeting

NA

10. Pediatrics

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. 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. The PMHS-Pediatric team concluded that the protected pediatric use information is important safety information for risk/benefit decision making when considering the use of Docetaxel Injection in pediatric cancer patients. The final disposition of this matter (i.e., whether the information can be “carved-out”) is pending further discussion within the Agency.

11. Other Relevant Regulatory Issues

None

12. Labeling

Review of the labeling will be completed during the next cycle or when the application is otherwise approvable.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: **COMPLETE RESPONSE**
- Deficiencies (all pertaining to nonclinical/ product Quality) to be conveyed to the sponsor in the CR letter are as follows:
 1. Revise the drug product release specification to include a single criterion for purity and related substances to be used both at release and on stability. Include a justification for the proposed criteria.
 2. In section 3.2.P.2 Table 18, Comparator Comparison Stability Study, the levels of impurity (b) (4) at 3 and 6 months are lower at $40\pm 2^{\circ}\text{C}/75\pm 5\% \text{ RH}$ than at $25\pm 2^{\circ}\text{C}/60\pm 5\% \text{ RH}$. However, other impurity levels are generally higher at the higher temperature than at the lower temperature. Explain this apparent discrepancy.
 3. Either provide additional stability data and information to support the proposed storage condition (b) (4) in the absence of light) or revise the proposed label storage statement to indicate a condition supported by the submitted long-term stability studies. The current stability information is not sufficient to support storage (b) (4)
 4. Provide additional long term stability data to support the proposed initial drug product expiry period. The submitted 6 month data is not sufficient to support approval (b) (4)
 5. Using the analytical method in your NDA, there are two new impurity peaks identified as RRT (b) (4) and RRT (b) (4). The acceptance criteria for these two compounds are set at NMT (b) (4). This acceptance criteria is above the threshold of 0.2% set by ICH Q3B (R2) based on the maximum daily dose of 180 mg/person. Please identify these two impurity peaks.

If the impurity peaks at RRT (b) (4) and RRT (b) (4) cannot be identified, their levels should be adequately justified (e.g., based on nonclinical studies), or reduced to meet the ICHQ3B (R2) threshold. If the impurity peaks at RRT (b) (4) and RRT (b) (4) are identified to be an impurity in the RLD, their levels should be reduced to less than the levels observed in the RLD; levels above the RLD should be adequately justified based on nonclinical or clinical studies.

- Risk Benefit Assessment
NA

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/s/

ANTHONY J MURGO
10/22/2010

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Submission Number	201195
Submission Code	000
Letter Date	December 21, 2009
Stamp Date	December 28, 2009
PDUFA Goal Date	October 22, 2010
Reviewer Name	Qin Ryan, MD, PhD
Clinical Team Leader	V. Ellen Maher, MD
Review Completion Date	May 29, 2010
Established Name	docetaxel
Trade Name	Docetaxel Injection
Reference NDA	20449
Therapeutic Class	Disruptor of microtubule network
Applicant	Accord Healthcare, Inc.
Priority Designation	S
Formulation	IV
Dosing Regimen	Multiple (see product information, 2.1)
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2.5	Other Relevant Background Information	6
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4	SOURCES OF CLINICAL DATA	7
5	REVIEW OF EFFICACY	7
6	REVIEW OF SAFETY	7
7	APPENDICES	8
7.1	Literature Review/References	8
7.2	Labeling Recommendations	8
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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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.

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).

Clinical Review
Qin Rayn MD, PhD
NDA 201195
Docetaxel

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 (if pharmacological equivalence is established) for all of the above indications.

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: Accord Healthcare, Inc.
1009 Slater Rd, Suite 210-B
Durham, ND 27703, USA
Tel: (919) 941-7878
Fax: (919) 941-7881

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: 60-100 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: 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.

Reviewer: The applicant applied for the following indications, still under exclusivity at the time of review.

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 hr before treatment

For dosage adjustments during treatment see full prescribing information.

Clinical Review
Qin Rayn MD, PhD
NDA 201195
Docetaxel

Dosage Forms and Strengths

- (b) (4) single-dose vial and diluent
- (b) (4) single-dose vial and diluent

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

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 Presubmission Regulatory Activity Related to Submission

May 6, 2008, Pre-IND meeting was held to discuss CMC issues. IND 101904 was subsequently filled.

June 4, 2008: FDA pre-IND meeting minutes regarding NDA submission plan were conveyed to the applicant.

December 21, 2009: Accord Healthcare Inc. submitted NDA 201195.

2.4 Pediatric Waiver

A full pediatric waiver request was submitted with NDA 22534 submission. The waiver is granted because there are very few pediatric patients, if any, who would have breast cancer, lung cancer, prostate cancer, gastric cancer or head and neck squamous cell carcinoma.

2.5 Other Relevant Background Information

Refer to NDA 20449

Clinical Review
 Qin Rayn MD, PhD
 NDA 201195
 Docetaxel

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.	May 19, 2007
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
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
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 use in combination with Cisplatin and 5-FU in patients with advanced HNSCC prior to definitive treatment.	Sep 28, 2010

* Exclusivity information was not found in recent Orange Book for NSCLC indication, since it expired in 2005.

3 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to NDA 20449 CMC, Pharmacology/Toxicology, and Clinical Pharmacology reviews, NDA 22534 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.

Clinical Review
Qin Rayn MD, PhD
NDA 201195
Docetaxel

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 (NDA20449) label.

7.3 Advisory Committee Meeting

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201195	ORIG-1	ACCORD HEALTHCARE INC	DOCETAXEL INJECTION 20 MG and 80 MG
NDA-201195	GI-1	ACCORD HEALTHCARE INC	DOCETAXEL INJECTION 20 MG and 80 MG

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/s/

QIN C RYAN
07/01/2010
Clinical NDA review

VIRGINIA E MAHER
07/02/2010