

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201195Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

| | |
|-------------------------------|---|
| NDA | 201195/SDN 14 |
| Submission Date: | 7 Dec., 2010 |
| Brand Name: | Docetaxel Injection™ |
| Generic Name: | Docetaxel |
| Formulation: | 20 mg/0.5 mL and 80 mg/2 mL and diluent |
| OCP Reviewer: | Jeanne Fourie Zirkelbach, PhD |
| OCP Team Leader: | Qi Liu, PhD |
| OCP Division: | Division of Clinical Pharmacology V |
| ORM Division: | Division of Drug Oncology Products |
| Sponsor: | Accord Healthcare Inc. |
| Submission Type; Code: | Complete Response, labeling supplement |
| Dosing regimen: | IV over 1 hr every 3 weeks. Breast Cancer: 60-100 mg/m ² , Non-small cell lung cancer: 75 mg/m ² , Prostate cancer: 75 mg/m ² , Gastric adenocarcinoma: 75 mg/m ² , Head and Neck Cancer: 75 mg/m ² . |
| Indication: | Breast cancer, non-small cell lung cancer, hormone refractory prostate cancer and gastric adenocarcinoma, head and neck cancer. |

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1 EXECUTIVE SUMMARY

The original submission for the current application was reviewed previously by the Office of Clinical Pharmacology (NDA 201195/000; letter date: 12/21/09). Based on the original review, the submission was found to be acceptable from a clinical pharmacology perspective. The current review summarizes the relevant Clinical Pharmacology labeling recommendations for this 505(b)(2) application.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 201195 (SDN14). This submission is considered acceptable from a clinical pharmacology perspective.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

1.2 PHASE IV COMMITMENTS

None.

1.3 REGULATORY BACKGROUND

The original submission for the current 505(b)(2) application was reviewed previously by the Office of Clinical Pharmacology (NDA 201195/000; letter date: 12/21/09). Based on the original review, the submission was found to be acceptable from a clinical pharmacology perspective. **The original review did not contain labeling recommendations.** A Complete Response letter was issued on 10/22/10 due to nonclinical and product quality issues identified during the original review.

With the current submission, the applicant submitted a response to the previously issued Complete Response letter, as well as the proposed labeling for Docetaxel InjectionTM. The proposed labeling is based on the most recently approved label for the two-vial formulation of TaxotereTM (listed drug, NDA 20449), which was approved on 5/13/10.

The purpose of the current review is to summarize the relevant Clinical Pharmacology labeling recommendations for this 505(b)(2) application.

1.4 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Signatures:

Reviewer: Jeanne Fourie Zirkelbach, PhD
Division of Clinical Pharmacology 5

Team Leader: Qi Liu, PhD
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - K Robertson; MTL - P Cortazar; MO - K Snyder,
DCP- Reviewers - J Fourie Zirkelbach,
5: DDD - B Booth
PM TL -
PG TL -
DD - A Rahman

2 QUESTION BASED REVIEW

Note: Only relevant sections were completed.

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

2.1.3 What are the proposed dosage(s) and route(s) of administration?

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

2.2.4 Exposure-response

2.3 INTRINSIC FACTORS

- 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?**
- 2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**
 - 2.3.2.1 Pediatric patients**
 - 2.3.2.2 Renal impairment**
 - 2.3.2.3 Hepatic impairment**
 - 2.3.2.4 What pregnancy and lactation use information is there in the application?**

2.4 EXTRINSIC FACTORS

- 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?**
- 2.4.2 Drug-drug interactions**

2.5 GENERAL BIOPHARMACEUTICS

- 2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**
- 2.5.2 What is the composition of the to-be-marketed formulation?**
- 2.5.3 What moieties should be assessed in bioequivalence studies?**
- 2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**
- 2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?**

2.6 ANALYTICAL SECTION

- 2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?
- 2.6.2 Which metabolites have been selected for analysis and why?
- 2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?
- 2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, <http://www.fda.gov/cder/guidance/4252fnl.pdf>)
 - 2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?
 - 2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?
 - 2.6.4.3 What are the accuracy, precision, and selectivity at these limits?
 - 2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?
 - 2.6.4.5 What is the QC sample plan?

3 DETAILED LABELING RECOMMENDATIONS

The sponsor's proposed labeling included Section 8.5 *Pediatric Use* from the reference product label. The FDA reviewer deleted this section from the proposed labeling. All the other sections of the Clinical Pharmacology Sections of the label were acceptable and identical to the most recent approved language found in the reference product label.

Only relevant clinical pharmacology sections are shown in track change format below. The sponsor's proposed changes from the most recent Taxotere label are shown in **BLUE and are double underlined**. FDA proposed changes are single underlined.

(b) (4)

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

4 APPENDICES

4.1 NDA FILING AND REVIEW FORM

| | | | | |
|--|----------------------------------|------------------------------------|---|---------------------------------|
| | | | | |
| General Information About the Submission | | | | |
| NDA Number | 201195 | Brand Name | Decetaxel Injection® | |
| DCP Division (I, II, III, IV, V) | V | Generic Name | Docetaxel | |
| Medical Division | Oncology | Drug Class | Microtubule Stabilizer | |
| OCP Reviewer | Jeanne Fourie Zirkelbach, PhD | Indication(s) | Breast Cancer (BC), non small cell lung cancer (NSCLC), hormone refractory prostate cancer (HRPC), Gastric adenocarcinoma (GC), squamous cell carcinoma of the head and neck (SCCNH). | |
| OCP Team Leader | Qi Liu, PhD | Dosage Form | 20 mg/0.5 mL and 80 mg/2 mL and diluent | |
| Date of Submission | 12/7/2010 | Dosing Regimen | IV over 1 hr every 3 weeks. Breast Cancer: 60 100 mg/m ² , Non small cell lung cancer: 75 mg/m ² , Prostate cancer: 75 mg/m ² , Gastric adenocarcinoma: 75 mg/m ² , Head and Neck Cancer: 75 mg/m ² . | |
| Due Date of OCP Review | 5/17/11 | Route of Administration | Intravenous infusion | |
| Standard PDUFA Due Date | 6/10/2011 | Sponsor | Accord | |
| Clinical Pharmacology Information | | | | |
| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | | | |
| Tabular Listing of All Human Studies | | | | |
| HPK Summary | | | | |
| Labeling | X | | | |
| Reference Bioanalytical and Analytical Methods | | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| Healthy Volunteers- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Dose proportionality - | | | | |
| fasting / non fasting single dose: | | | | |
| fasting / non fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |

| | | | | |
|---|-----------------------------------|-----------------|--|--|
| In vivo effects on primary drug: | | | | |
| In vivo effects of primary drug: | | | | |
| In vitro: | | | | |
| Subpopulation studies - | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| pediatrics: | | | | |
| PD: | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| PK/PD: | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| Population Analyses - | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability: | | | | |
| Relative bioavailability - | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies: | | | | |
| QTC studies: | | | | |
| In-Vitro Release BE | | | | |
| (IVIVC): | | | | |
| Bio-wavier request based on BCS | | | | |
| BCS class | | | | |
| III. Other CPB Studies | | | | |
| Biliary Elimination | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | | | |
| Filability and QBR comments | | | | |
| | "X" if yes | Comments | | |
| Application filable? | X | | | |
| Comments sent to firm? | | | | |
| QBR questions (key issues to be considered) | | | | |
| Other comments or information not included above | | | | |
| Primary reviewer Signature and Date | J Fourie Zirkelbach, Ph.D. | | | |
| Secondary reviewer Signature and Date | Q Liu, Ph.D. | | | |

CC: HFD-150 (CSO – **D Hanner**; MTL– P Cortazar; MO –**K Snyder**)

HFD-860 (Reviewer – J Fourie Zirkelbach; TL – Q Liu; DDD - B Booth; DD - A Rahman)

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

/s/

JEANNE FOURIE
04/08/2011

QI LIU
04/08/2011

Clinical Pharmacology Review

| | |
|------------------------|---|
| NDA | 201195/000 |
| Submission Date: | 21-Dec-2009 |
| Brand Name: | Docetaxel Injection |
| Generic Name: | Docetaxel |
| Formulation: | 20 mg/0.5 mL and 80 mg/2 mL and diluent |
| OCP Reviewer: | Young Jin Moon, Ph.D. |
| OCP Team Leader: | Julie Bullock, Pharm.D. |
| OCP Division: | Division of Clinical Pharmacology V |
| ORM Division: | Division of Drug Oncology Products |
| Sponsor: | Accord Healthcare, Inc. |
| Submission Type; Code: | 505 (b) (2) NDA |
| Indication: | Breast cancer, Non-small cell lung cancer, Prostate cancer, Gastric adenocarcinoma, Squamous cell carcinoma of the head and neck cancer |

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1 EXECUTIVE SUMMARY

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Accord submitted an original New Drug Application (NDA 201195) for Docetaxel Injection. The reference listed drug is Taxotere[®] for Injection (docetaxel; Sanofi-Aventis). The following proposed indications have been approved for Taxotere[®] for Injection[®] (NDA 20-449):

For the treatment of breast cancer; non-small cell lung cancer; hormone refractory prostate cancer; gastric adenocarcinoma; squamous cell carcinoma of the head and neck cancer.

The applicant was informed by the Division on 4 June 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 Taxotere[®] for Injection (NDA 20-449).

1.1 RECOMMENDATIONS

This application is acceptable from a clinical pharmacology perspective.

Labeling Recommendations

None

Signatures:

Reviewer: Young Jin Moon, Ph.D.
Division of Clinical Pharmacology 5

Team Leader: Julie Bullock, Pharm.D.
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - D Hanner; MTL - E Maher; MO - Q Ryan
DCP-5: Reviewer - Y Moon; TL - J Bullock
DDD - B Booth
DD - A Rahman

1.2 CLINICAL PHARMACOLOGY SUMMARY

Taxotere® for Injection (docetaxel) is a product of Sanofi-Aventis and was 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 cancer.

Taxotere® for Injection is provided as two vials, one containing the active ingredient and the other the diluent, in a blister pack in one carton. The dosage form and two strengths of Taxotere® (docetaxel) Injection Concentrate are described in the approved labeling as follows:

- 20 mg/0.5 mL: 20 mg docetaxel in 0.5 mL polysorbate 80 (PS80) and Diluent for Taxotere® 20 mg (13% w/w) ethanol in water for injection
- 80 mg/2 mL: 80 mg docetaxel in 2 mL polysorbate 80 and Diluent for Taxotere® 80 mg (13% w/w) ethanol in water for injection.

Taxotere® is typically administered as a 1-hour infusion once every 3 weeks over a 10-cycle course. Doses range from 60 to 100 mg/m², alone or in combination with other chemotherapeutic agents. In the current application, Taxotere® for Injection is designated as the reference listed drug (RLD).

Accord submitted the current application to market a new drug product, Docetaxel Injection as an alternative to the RLD. The indications for which the applicant is seeking approval are:

- 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 cancer

These five indications are identical to the approved indications for the RLD. Accord's proposed product will contain the same concentration of the active ingredient as the reference listed drug. The proposed product will also be accompanied with a diluent vial. Similar to the RLD, both vials will be co-packed in one carton. The proposed product would require similar initial and final dilution prior to intravenous infusion. However, changes are proposed in the formulation whereby the proposed drug product will differ from the formulation of the RLD in terms of its qualitative and quantitative composition of the inactive ingredients. A comparative description of the proposed formulation and the RLD formulation is given in below tables.

Table 1. Comparative formulations of the reference product and proposed product - product vial

| Ingredient | | Proposed product: Docetaxel injection concentrate | Reference product: Taxotere | Proposed product: Docetaxel injection concentrate | Reference product Taxotere |
|----------------------|-------------------------|--|--------------------------------|--|-------------------------------|
| | | Per 0.5 mL | Per 0.5 mL | Per 2 mL | Per 2 mL |
| Active ingredient | Docetaxel (anhydrous) | 20 mg | 20 mg | 80 mg | 80 mg |
| Inactive ingredients | Citric acid (anhydrous) | q.s. to pH | -- | q.s. to pH | -- |
| | Dehydrated alcohol | 30 mg | -- | 120 mg | -- |
| | Polysorbate 80 | (b) (4) | 520 mg | (b) (4) | 2080 mg |
| Total volume | | 0.5 mL | 0.5 mL | 2 mL | 2 mL |

The applicant has used docetaxel anhydrous against docetaxel trihydrate used in RLD. Citric acid has been used in the applicant's formulation to keep pH in line with RLD. (b) (4)

Table 2. Comparative formulations of the reference product and proposed product - diluent vial

| Ingredient | For 20 mg/0.5 mL product | | For 80 mg/2 mL product | |
|---------------------|--|---|--|---|
| | Proposed product: Diluent for Docetaxel injection concentrate 20 mg | Reference product: Diluent for Taxotere 20 mg | Proposed product: Diluent for Docetaxel injection concentrate 80 mg | Reference product: Diluent for Taxotere 80 mg |
| Dehydrated alcohol | -- | 13% w/w | -- | 13% w/w |
| PEG 400 | 13% w/v | -- | 13% w/v | -- |
| Water for injection | q.s. to 1.5 mL | q.s. to 1.5 mL | q.s. to 6 mL | q.s. to 6 mL |

The applicant has used PEG 400 instead of dehydrated alcohol which is used in RLD. The purpose of PEG 400 in the applicant's diluent vial and ethanol in RLD's diluent vial is the same (b) (4)

The proposed product, docetaxel injection concentrate 40 mg/mL, once approved, will be supplied as given below, similar to the RLD.

- 0.5 mL product vial & 1.5 mL diluent vial
- 2.0 mL product vial & 6.0 mL diluent vial

Reviewer's analysis

Ratio of PS80:docetaxel in 505(b)(2)s to date have been within ranges of (b) (4) (that of the RLD:2-vial and 1-vial formulations), but the ratio of PS80:docetaxel of Accord's product is (b) (4). Since docetaxel binds to human serum albumin, AAG and lipoproteins, and PS80 can increase free docetaxel concentration by binding to AAG and replacing docetaxel from AAG, the reviewer examined whether the ratio of PS80:docetaxel in Accord's formulation would affect PK profile of docetaxel.

Based on *in vitro* binding results from Loos et. al. (1), at a PS80 concentration of 1.0 µL/mL the unbound fraction will increase from 6.95 to 7.84% compared to a formulation where no PS80 is present ("none" in Table 3). Values in Table 3 are presented in Figure 1.

Table 3. Extent of binding of docetaxel to human plasma, as function of polysorbate 80 (Ref. 1)

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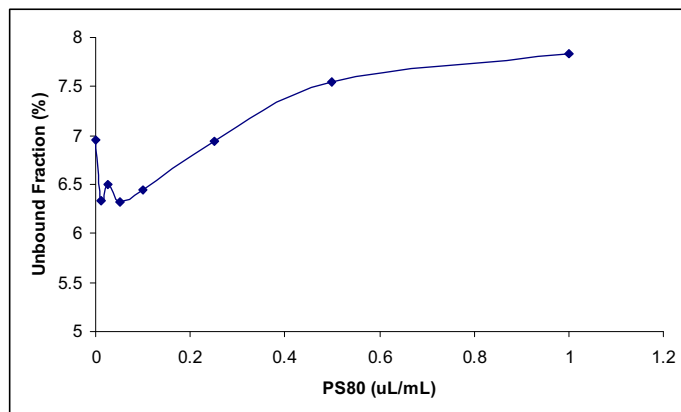


Figure 1. Table 3 values presented graphically.

The amount of PS80 in plasma will depend on dose, body surface area (BSA), and plasma volume. Following a standard 75 mg/m² dose of docetaxel using Accord's formulation (b) (4) the PS80 concentration in plasma could range between approximately 0.954 μL/mL – 1.06 μL/mL (Table 4).

Table 4. PS80 concentration in plasma

| PS80 concentration in plasma (μL/mL) | | | |
|--------------------------------------|----------------------|---------|---------|
| Plasma Volume | Ratio PS80:Docetaxel | | |
| | (b) (4) | (b) (4) | (b) (4) |
| 3000 mL | 0.954 ^a | 1.04 | 1.08 |
| 2700 mL | 1.06 | 1.16 | 1.20 |

(b) (4)

Although unbound fractions at 1.06 μL/mL are not shown in Table 3, as shown in Figure 1 it should not be much different because the % fraction unbound seems to reach a plateau at > 0.5 μL/mL PS80. Furthermore, the unbound fraction of docetaxel varied widely among patients with a median (range) of (b) (4). Thus, the minor change in unbound fraction caused by formulation differences in PS80 is not likely to have a significant impact on the PK of docetaxel.

References

1. Loos WJ, *et al.* (2003) Clin. Pharmacol. & Ther 74(4):364-371
2. Minami, H, *et al.* (2006) Cancer Sci 97(3):235-241

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

Refer to the RLD original NDA 20-449 (Approval Date: 5/14/96) for the issues listed in Section 2.1.2 to Section 2.4.

Section 2.6 is not applicable to this application.

2.5.2 What is the composition of the to-be-marketed formulation?

See General Clinical Pharmacology Section 1.2, for the quantitative and qualitative comparisons between Docetaxel Injection and the RLD.

2.5.3 What moieties should be assessed in bioequivalence studies?

The applicant was informed by the Division on 4 June 2008 that a bioequivalence study with the RLD is not needed. This submission did not include clinical studies and relies on the FDA's findings of safety and effectiveness for Taxotere[®] for Injection (NDA 20-449).

3 DETAILED LABELING RECOMMENDATIONS

None

Office of Clinical Pharmacology

4 NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information about the Submission

| | | | |
|---|-------------------------|--------------------------------|--|
| NDA Number | 201195/000 | Brand Name | Docetaxel Injection |
| DCP Division (I, II, III, IV, V) | V | Generic Name | Docetaxel |
| Medical Division | Oncology | Drug Class | Antineoplastic agent that acts by disrupting the microtubular network |
| OCP Reviewer | Young Jin Moon, Ph.D. | Indication(s) | Breast cancer Non small cell lung cancer Prostate cancer Gastric adenocarcinoma Squamous cell carcinoma of the head and neck cancer |
| OCP Team Leader | Julie Bullock, Pharm.D. | Dosage Form | IV injection |
| Date of Submission | December 21, 2009 | Dosing Regimen | Varies depending on indications. Doses ranging from 60 to 100 mg/m ² given as a 1 hour infusion every 3 weeks, alone or in combination with other chemotherapeutic agent |
| Due Date of OCP Review | September 17, 2010 | Route of Administration | IV infusion |
| Standard PDUFA Due Date | October 21, 2010 | Sponsor | Accord |

Clinical Pharmacology Information

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|--|---------------------------|-----------------------------|----------------------------|--------------------------|
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | | | |
| Tabular Listing of All Human Studies | | | | |
| HPK Summary | | | | |
| Labeling | X | | | |
| Reference Bioanalytical and Analytical Methods | | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| Healthy Volunteers | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Dose proportionality - | | | | |
| fasting / non fasting single dose: | | | | |
| fasting / non fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In vivo effects on primary drug: | | | | |
| In vivo effects of primary drug: | | | | |

| | | | | |
|--|---|--|--|--|
| In vitro: | | | | |
| Subpopulation studies - | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| pediatrics: | | | | |
| PD: | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| PK/PD: | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| Population Analyses - | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability: | | | | |
| Relative bioavailability - | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies: | | | | |
| QTC studies: | | | | |
| In-Vitro Release BE | | | | |
| (IVIVC): | | | | |
| Bio-wavier request based on BCS | X | | | |
| BCS class | | | | |
| III. Other CPB Studies | | | | |
| Biliary Elimination | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|------------|-----------|------------|--|
| Criteria for Refusal to File (RTF) | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | X | | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | X | | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | | | X | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | | X | | |
| 5 | Has a rationale for dose selection been submitted? | | | X | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | X | | | Information of Reference Listed Drug (RLD) |
| 7 | Is the clinical pharmacology and biopharmaceutics section | X | | | Information of |

| | | | | | |
|---|--|---|--|---|--------------------|
| | of the NDA legible so that a substantive review can begin? | | | | RLD |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | X | | | Information of RLD |
| Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) | | | | | |
| Data | | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | | | X | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | X | |
| Studies and Analyses | | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | | | X | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | X | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | | X | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | X | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | | | X | |
| General | | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | | | X | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | X | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Young Jin Moon

Reviewing Clinical Pharmacologist

Date

Julie Bullock

Team Leader

Date

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

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/s/

YOUNG J MOON
09/08/2010

JULIE M BULLOCK
09/10/2010

BIOPHARMACEUTICS REVIEW
Office of New Drugs Quality Assessment

| | | |
|-------------------------|---|---------------------------------------|
| Application No.: | NDA 201-195 | Reviewer: Angelica Dorantes, Ph.D |
| Submission Date: | December 21, 2009 | Supervisor: Patrick J. Marroum, Ph.D |
| Division: | DDOP | Date Assigned: February 4, 2010 |
| Sponsor: | Accord Healthcare, Inc. | Date of Review: July 15, 2010 |
| Trade Name: | Docetaxel Injection 20mg/0.5 ml and 80 mg/2 ml | Type of Submission: 505 (b)(2) NDA |
| Generic Name: | Docetaxel Injection | |
| Indication: | Docetaxel is used for the treatment of various types of cancers like breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer. | |
| Formulation/strengths | Injectable Solution 20 mg and 80 mg | |
| Route of Administration | Intravenous | |
| Type of Review: | BIOWAIVER REQUEST | |

SUBMISSION:

Accord Healthcare submitted NDA 201-195 for Docetaxel Injection 20 mg and 80 mg under 505 (b) (2) of the Federal Food, Drug, and Cosmetic Act. This 505 (b) (2) application relies for approval on the FDA's findings of safety and effectiveness for the Reference Listed Drug. This product has the same dosage form (i.e., injectable solution) as the Reference Listed Drug Taxotere® of Sanofi-Aventis U.S L.L.C. RLD product. This product is intended for the same indications, dosage regimen and route of administration as Taxotere®. The proposed indication for Docetaxel injection is the treatment of various types of cancers like breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer.

BIOPHARMACEUTICS:

Formulation: The formulation consists of two vials; the Drug product vial and the Diluent vial for drug product. Each mL of Docetaxel Injection Concentrate contains Docetaxel 40 mg. The product has to be reconstituted with Diluent for Docetaxel injection concentrate and the reconstituted solution should be diluted with 5% Dextrose injection or 0.9% Sodium Chloride Injection before administration. The quantitative composition and function of each component in the Drug product vial and Diluent vial is listed in the following tables.

| Composition of Accord's Docetaxel injection concentrate | | | |
|---|----------------------|-------------------|-----------------|
| Name of ingredients | Compendial reference | Function | Qty. / mL in mg |
| Docetaxel (anhydrous) | In house | Active | 40.00 |
| Citric acid (anhydrous) | USP | For pH adjustment | q.s. to pH |
| Dehydrated alcohol | USP | (b) (4) | 60.0 |
| Polysorbate 80 | USNF | | (b) (4) |

(u) (4)

| Composition of Accord's diluent for Docetaxel injection concentrate | | | |
|---|----------------------|----------|-----------------|
| Name of ingredients | Compendial reference | Function | Qty. / mL in mg |
| Polyethylene glycol 400 | USNF | (b) (4) | 130.00 |
| Water for injection | USP | | (b) (4) |
| (u) (4) | | | |

A comparative description of the proposed formulation and the RLD formulation is given below.

| Comparative formulations of the reference product and proposed product - product vial | | | | | |
|---|--------------------------|---|---------------------------------------|---|---------------------------------------|
| Ingredient | | Proposed product: Docetaxel inj concentrate | Reference product: Taxotere | Proposed product: Docetaxel inj concentrate | Reference product: Taxotere |
| | | Per 0.5 mL | Per 0.5 mL | Per 2 mL | Per 2 mL |
| Active ingredient | Docetaxel* (anhydrous) | 20 mg | | 80 mg | |
| Inactive ingredients | Docetaxel** (trihydrate) | | 20 mg | | 80 mg |
| | Citric acid (anhydrous) | q.s. to pH | | q.s. to pH | |
| | Dehydrated alcohol | 30 mg | | 120 mg | |
| | Polysorbate 80 | (b) (4) | 520 mg | (b) (4) | 2080 mg |
| Total volume | | 0.5 mL | 0.5 mL | 2 mL | 2 mL |

Note: Citric acid has been used in applicant's formulation to keep pH in line with RLD. (b) (4)

*Docetaxel, Trihydrate is a white to almost white crystalline powder with an empirical formula of $C_{43}H_{53}NO_{14} \cdot 3H_2O$, and a molecular weight of 861.9.

**Docetaxel, Anhydrous is a white to almost white microcrystalline powder with an empirical formula of $C_{43}H_{53}NO_{14}$, and a molecular weight of 807.9.

| Comparative formulations of the reference product and proposed product - diluent vial | | | | |
|---|---|---|---|---|
| Ingredient | For 20 mg/0.5 mL product | | For 80 mg/2 mL product | |
| | Proposed product: Diluent for Docetaxel inj concentrate 20 mg | Reference product: Diluent for Taxotere 20 mg | Proposed product: Diluent for Docetaxel inj concentrate 80 mg | Reference product: Diluent for Taxotere 80 mg |
| Dehydrated alcohol | | 13% w/w | | 13% w/w |
| PEG 400 | 13% w/v | | 13% w/v | |
| Water for injection | q.s. to 1.5 mL | q.s. to 1.5 mL | q.s. to 6 mL | q.s. to 6 mL |

Note: Applicant has used PEG 400 (b) (4) instead of dehydrated alcohol which is used in RLD (b) (4). The purpose of PEG 400 in applicant's diluent vial and ethanol in RLD's diluent vial is the same (b) (4)

The proposed Docetaxel Injection product contains two additional inactive ingredients, citric acid (in the product vial) and polyethylene glycol (in the diluent vial). Citric acid, a pH modifying agent is present in the product vial and polyethylene glycol (b) (4) is present in the diluent vial. Dehydrated alcohol is present in the product vial in Accord's proposed product, while it is a component of the diluent vial in the RLD product.

The two additional ingredients, citric acid and polyethylene glycol as well as dehydrated alcohol are listed in the FDA's Inactive Ingredient (IIG) Database. These inactive ingredients have previously been approved for use in products with the same route of administration, at levels above those reflected in Accord's proposed formulation.

BIOWAIVER:

In this submission, 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.

According to CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

In this submission, Accord Healthcare provided information showing that their proposed formulation, route of administration, dosage form and indications of their product, Docetaxel Injection 20 mg and 80 mg are similar to those of the Referenced Listed Drug (RLD) product, Taxotere[®] (docetaxel) Injection of Sanofi-Aventis.

Reviewer Comments:

1. *The proposed Docetaxel Injection product contains two additional inactive ingredients, citric acid (in the product vial) and polyethylene glycol (in the diluent vial). The two additional ingredients, citric acid and polyethylene glycol as well as dehydrated alcohol are listed in the FDA's Inactive Ingredient (IIG) Database. Although, the proposed formulation includes two different ingredients when compared to the RLS product, these inactive ingredients have previously been approved for use in products with the same route of administration, at levels above those proposed in the formulation.*
2. *Docetaxel Injection is a dosage form intended solely for IV administration and is a true solution.*

RECOMMENDATION:

The ONDQA-Biopharmaceutics has reviewed the information included in NDA 20-195 for Docetaxel Injection 20 mg and 80 mg. Based on the Agency's CFR 320.22(b)(1) regulations and the information showing that 1) their product contains the same active ingredient as the reference listed drug product and all the inactive ingredients are within IIG limits, 2) the route of administration, dosage form and indications of their product are the same as the RLD product, ONDQA-Biopharmaceutics considers that the in vivo BA/BE of Accord Healthcare's Docetaxel Injection is self-evident. Therefore, the sponsor's request for a biowaiver for Docetaxel Injection 20 mg/0.5 ml and 80 mg/2 ml is acceptable and the biowaiver is granted.

Please convey the Recommendation as appropriate to the sponsor.

Angelica Dorantes, Ph. D.

Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.

Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 201-195, Debbie Mesmer

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

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/s/

ANGELICA DORANTES
07/21/2010

PATRICK J MARROUM
07/22/2010