# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022312Orig1s000**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# BIOPHARMACEUTICS REVIEW

## Office of New Drug Quality Assessment

| | | | |
|---|---|---|---|
| **Application No.:** | NDA 22-312 | **Reviewer:** Angelica Dorantes, Ph.D | |
| **Submission Date:** | November 12, 2010 | **Supervisor:** Patrick J. Marroum, Ph.D | |
| **Division:** | DDOP | **Date Assigned:** | March 3, 2011 |
| **Sponsor:** | Apotex, Inc | **Date of Review:** | April 22, 2011 |
| **Trade Name:** | Docetaxel Injection 40 mg/ml | **Type of Submission:** 505 (b)(2) NDA<br>**Re-Submission Class 2** | |
| **Generic Name:** | Docetaxel | | |
| **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 40 mg/ml (20 mg/0.5 ml and 80 mg/2 ml) | | |
| **Route of Administration** | Intravenous | | |
| **Type of Review:** | **BIOWAIVER REQUEST** | | |

## SUBMISSION:

Apotex, Inc. submitted the Original NDA 22-312 for Docetaxel Injection 40 mg/ml on March 27, 2008, under 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act. The Re-submission for this NDA is dated November 12, 2010, and it includes Apotex's response to the CR Letter dated September 22, 2010.

This NDA 505 (b)(2) application relies for its 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® for Injection, NDA 20-449 of Sanofi-Aventis U.S L.L.C. 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:** Apotex Inc. developed Docetaxel Injection at the same therapeutic concentration as Taxotere® in the infusion solution, but with a different qualitative and quantitative formulation compared to Taxotere®. The formulation for Apotex Inc.'s Docetaxel Injection, 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL) is pharmaceutically equivalent to that of Taxotere®, except that a different excipient in the drug product Concentrate is used in the Apotex product. In addition, the Apotex Inc. used Polysorbate 80 in the Diluent.

The next table presents a comparison of the formulations for the RLD product, Taxotere® and proposed Docetaxel for Injection product.

**Docetaxel Injection Concentrate:**

| Composition | RLD Taxotere (as per PDR) Qty. | Apotex Product Qty. |
|---|---|---|
| Docetaxel (Anhydrous) | 40.0 mg/mL * | 40.0 mg/mL |
| Polysorbate 80 | [redacted] | [redacted] |
| Polyethylene Glycol 300 (PEG-300) | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

**Docetaxel Diluent:**

| Composition | RLD Taxotere (as per PDR) Qty. | Apotex Product Qty. |
|---|---|---|
| Alcohol [redacted] Alcohol) | [redacted] | [redacted] |
| Polysobate 80 | [redacted] | [redacted] |
| Water for Injection | [redacted] | [redacted] |

* Used as Alcohol [redacted] USP [redacted] Alcohol)

It is indicated that [redacted] it was not possible to have exactly the same formulation for the diluent as the RLD. The sponsor selected to add Polysorbate 80 as part of the formulation. Polysorbate 80 is added [redacted] Alcohol [redacted] A stability study carried out at accelerated conditions (40ºC/75%RH) showed [redacted]

**BIOWAIVER:**

In the original submission, Apotex Inc. requested that the Agency's requirement for the submission of in vivo Bioavailability/Bioequivalence (BA/BE) data to support the approval of Docetaxel Injection 40 mg/ml (20 mg/0.5 ml and 80 mg/2 ml) 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.

***Biowaiver's Justification:*** Apotex Inc.'s Docetaxel formulation has the same concentration of the active ingredient as the Taxotere® formulation and is provided in the same format as a single dose vial as a sterile, pyrogen-free non-aqeous viscous solution with an accompanying sterile, non-pyrogenic diluent. However, there are qualitative and quantitative differences in the formulation compared to the RLD. A key difference in the Apotex formulation compared to the RLD is with respect to the inclusion of Polyethylene Glycol 300 NF which is not present in Taxotere® and reduced amounts of alcohol. The addition of Polyethylene Glycol 300 NF [redacted] and the use of reduced amounts of alcohol are not expected to have any impact on the efficacy and safety of the drug. Polyethylene Glycol 300 NF [redacted] has

been reported to have less toxicity as compared to alcohol [redacted] Polyethylene Glycol 300 NF can be used as an excipient at levels of up to 65% for an infusion injectable. The concentration of Polyethylene Glycol 300 NF in Apotex Inc.'s formulation ranged from [redacted] in the final infusion solution, which is [redacted] the IIG limit of 65%.

The results of the comparative physiochemical testing done on the final infusion solution demonstrate that Docetaxel Injection [redacted] and Taxotere® have similar osmolarity. The pH of the final infusion solution of the Apotex product in both the 5% dextrose solution [redacted] and in the 0.9% NaCl solution [redacted] was slightly higher than that reported for the Taxotere® formulation [redacted] in 5% dextrose solution and [redacted] in 0.9% NaCl). The difference in the pHs is not expected to have any significant impact as the pH of Apotex Inc.'s Docetaxel final infusion solution is close to biological pH and the product is administered as an intravenous infusion (bioavailability 100%), and consequently the difference in pH will not impact the amount of drug delivered to the site of injection and subsequently to the site of action. In addition, Apotex Inc.'s Docetaxel Injection [redacted] has a similar stability pattern as Taxotere®.

Additionally, please note that in a PreNDA meeting held on September 7, 2007, FDA agreed with Apotex Inc.'s assessment that a clinical study in support of the 505(b)(2) application for Docetaxel Injection was not required.

## RECOMMENDATION:

The Biopharmaceutics group at the Office of New Drug Quality Assessment (ONDQA) has reviewed the information included in NDA 22-312 for Docetaxel Injection 40 mg/ml. Based on the Agency's CFR 320.22(b)(1) regulations and the information showing that **1)** Apotex Inc.'s Docetaxel formulation has the same concentration of the active ingredient as the Taxotere® formulation and is provided in the same format as a single dose vial as a sterile, pyrogen-free non-aqeous viscous solution with an accompanying sterile, non-pyrogenic diluent 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 Apotex's Docetaxel Injection is self-evident. Therefore, the sponsor's request for a biowaiver for their Docetaxel Injection 40 mg/ml (20 mg/0.5 ml and 80 mg/2 ml) product is acceptable and the biowaiver is granted.

**Angelica Dorantes, Ph. D.**
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

**Patrick J. Marroum, Ph. D.**
Biopharmaceutics Supervisor
Office of New Drug Quality Assessment

cc: NDA 22-312, Debbie Mesmer

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/s/

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ANGELICA DORANTES
04/26/2011

PATRICK J MARROUM
04/26/2011

# Clinical Pharmacology Review

| | |
|---|---|
| **NDA** | 22-312 |
| **Submission Date:** | 27 March 2008 |
| **Brand Name:** | Docetaxel Injection® |
| **Generic Name:** | Docetaxel Anhydrous |
| **Formulation:** | 25 mg/mL concentrate for injection |
| **OCP Reviewer:** | Jeanne Fourie, PhD |
| **OCP Team Leader:** | Brian Booth, PhD |
| **OCP Division:** | Division of Clinical Pharmacology V |
| **ORM Division:** | Division of Drug Oncology Products |
| **Sponsor:** | Apotex Inc. |
| **Submission Type; Code:** | Original NDA; S-000 |
| **Dosing regimen:** | 60-100 mg/m$^2$ IV infusion over 1 hr once every 3 weeks |
| **Indication:** | Treatment of Breast Cancer, Non-Small Cell Lung Cancer, Hormone Refractory Prostate Cancer, Gastric Adenocarcinoma and Squamous Cell Carcinoma of the head and Neck |

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# 1 EXECUTIVE SUMMARY

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Apotex Inc. submitted an original New Drug Application (NDA 22-312/S-000) for Docetaxel Injection®.

Based on the comparison to the reference listed drug (Taxotere® for Injection; Sanofi-Aventis), Apotex was granted a waiver of the bioequivalence requirements for Docetaxel Injection® in accordance with 21 CFR 320.22 (b)1. Since the Apotex drug product is pharmaceutically equivalent to the reference listed drug, the current 505(b)2 application did 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

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-312. This application is acceptable from a clinical pharmacology perspective.

**Phase IV commitments**
None.

**Labeling Recommendations**

The Clinical Pharmacology sections of the labeling for Docetaxel Injection® (Apotex Inc.) have been reproduced within the Detailed Labeling Recommendations Section below.

**Signatures:**

| | |
|---|---|
| Reviewer: Jeanne Fourie, Ph.D.<br>Division of Clinical Pharmacology 5 | Deputy Director & Team Leader: Brian Booth, Ph.D.<br>Division of Clinical Pharmacology 5 |

Cc: DDOP: CSO - C Cottrell; MTL - E Maher; MO - Q Ryan,
DCP-5: Reviewers - J Fourie,
DDD - B Booth
DD - A Rahman

## 1.2 CLINICAL PHARMACOLOGY SUMMARY

Taxotere® for Injection (docetaxel), a product of Sanofi-Aventis, US, received approval on 14-May-1996 for use as a single agent in the treatment of refractory, locally advanced or metastatic breast cancer under NDA 20-449. Additional indications for the use of docetaxel were subsequently approved, including its use for the treatment of advanced or metastatic non-

small cell lung cancer after failure of platinum containing chemotherapy (December 1999), the treatment of metastatic, hormone-refractory prostate cancer in combination with prednisone (May 2004), the treatment of advanced gastric cancer in combination with cisplatin and 5-fluorouracil (March 2006), and the treatment of locally advanced, squamous cell head and neck cancer in combination with cisplatin and 5-fluorouracil (October 2006). Taxotere® Injection Concentrate is available in single-dose vials containing a sterile, pyrogen-free, non-aqueous viscous solution at a strength of 20 mg/0.5 mL or 80 mg/2 mL of docetaxel (anhydrous) with an accompanying sterile, non-pyrogenic diluent vial. The approved dosage is 60-100 mg/$m^2$ administered intravenously as a one-hour infusion every 3 weeks. In the current application, Taxotere® for Injection is designated as the reference listed drug (RLD) by the applicant.

Apotex Inc. plans to market a new drug product, Docetaxel Injection®, (40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL)) as an alternative to the RLD. The indications for which the applicant is seeking approval include the treatment of breast cancer, non-small cell lung cancer and hormone refractory prostate cancer. These indications are identical to the approved indications for the RLD. The applicant is not seeking approval for the gastric adenocarcinoma and squamous cell carcinoma indications of the RLD, as these are currently under patent protection. The Apotex drug product consists of an Injection (b) (4) vial containing the active ingredient (docetaxel anhydrous) and a Diluent vial. The active ingredient and route of administration for Apotex's Docetaxel Injection® are identical to the RLD. The Infusion Solution for the Apotex drug product was also developed for use at the same therapeutic concentration as the RLD.

The Apotex Inc. drug product has a different qualitative and quantitative formulation compared to Taxotere® for both the Injection Concentrate and the Diluent. In particular, the formulation of the Apotex drug product is pharmaceutically equivalent to that of Taxotere®, except that the Apotex formulation contains reduced amounts of alcohol and has a different excipient (polyethylene Glycol 300 NF) added to the Docetaxel Injection (b) (4). The added polyethylene glycol (b) (4) for the drug substance, and the level of this exipient is below the limit defined within the Inactive Ingredient Guide. In addition, the Apotex formulation uses Polysorbate 80 in the Diluent, whereas the RLD used Polysorbate 80 in the Injection concentrate.

The qualitative and quantitative composition of the Docetaxel Injection® (Apotex) and Taxotere® formulations are summarized in Table 1. A comparison of the Docetaxel Injection® (Apotex) and Taxotere® final dilution for infusion is shown in Table 2. Based on the comparison to the RLD, the Office of New Drug Quality Assessment (ONDQA) granted Apotex Inc. a waiver of the bioequivalence requirements for Docetaxel Injection® in accordance with 21 CFR 320.22 (b)1.

**Table 1** Qualitative and Quantitative composition of the Docetaxel Injection® (Apotex) and Taxotere® Formulations.

**Docetaxel Injection Concentrate:**

| Composition | RLD Taxotere (as per PDR) Qty. | Apotex Product Qty. |
|---|---|---|
| Docetaxel (Anhydrous) | 40.0 mg/mL * | 40.0 mg/mL |
| Polysorbate 80 | [redacted] (b) (4) | |
| Polyethylene Glycol 300 (PEG-300) | | |

*As Docetaxel Trihydrate in the RLD.

**Docetaxel Diluent:**

| Composition | RLD Taxotere (as per PDR) Qty. | Apotex Product Qty. |
|---|---|---|
| Alcohol (b) (4) Alcohol) | [redacted] (b) (4) | |
| Polysobate 80 | | |
| Water for Injection | | |

* Used as Alcoh (b) (4) USP (b) (4) Alcohol)

**Table 2** Comparison of the Docetaxel Injection® (Apotex) and Taxotere® Final Dilution for Infusion

**Comparison in Final Dilution for Infusion:**

| Composition Raw Material | Apotex | | RLD Taxotere® | |
|---|---|---|---|---|
| | Final Dilution for Infusion Concentration | | | |
| | Minimum 0.3 mg/mL | Maximum 0.74 mg/mL | Minimum 0.3 mg/mL | Maximum 0.74 mg/mL |
| Docetaxel (Anhydrous) | 0.3 mg/mL | 0.74 mg/mL | 0.3 mg/mL | 0.74 mg/mL |
| Polyethylene Glycol 300 | [redacted] (b) (4) | | | |
| Polysorbate-80 | | | | |
| Alcohol (b) (4) Alcohol) | | | | |

| Composition Raw Material | Apotex | | RLD Taxotere® | |
|---|---|---|---|---|
| | Final Dilution for Infusion Concentration | | | |
| | Minimum 0.3 mg/mL | Maximum 0.74 mg/mL | Minimum 0.3 mg/mL | Maximum 0.74 mg/mL |
| Water for Injection | Present | Present | Present | Present |
| 0.9% Sodium Chloride or 5% Dextrose Solution | [redacted] (b) (4) | | | |

# 2 QUESTION BASED REVIEW

## 2.1 GENERAL ATTRIBUTES

Refer to the 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 and Section 4 are not applicable to this application.

**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 and route 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 or biomarkers 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**

**2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?**

**2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?**

**2.2.4.3 Does this drug prolong the QT or QTc interval?**

**2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

**2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites**

**2.2.5.1 What are the single dose and multiple dose PK parameters?**

**2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?**

**2.2.5.3 What are the characteristics of drug absorption?**

**2.2.5.4 What are the characteristics of drug distribution?**

**2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

**2.2.5.6 What are the characteristics of drug metabolism?**

**2.2.5.7 What are the characteristics of drug excretion?**

**2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?**

**2.2.5.9 How do the PK parameters change with time following chronic dosing?**

**2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?**

## 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**

**2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?**

**2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?**

**2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?**

**2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?**

**2.4.2.5 Are there other metabolic/transporter pathways that may be important?**

**2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?**

**2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

## *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?**

See General Clinical Pharmacology Section 1.2, Table 1 and Table 2 for the quantitative and qualitative comparisons between the Apotex to-be-marketed formulation and the RLD.

**2.5.3 What moieties should be assessed in bioequivalence studies?**

Based on the comparison to the RLD, ONDQA granted Apotex a waiver of the bioequivalence requirements for Docetaxel Injection® in accordance with 21 CFR 320.22 (b)1. Since the Apotex drug product is pharmaceutically equivalent to the RLD, the current 505(b)2 application did not include clinical studies and relies on the FDA's findings of safety and effectiveness for Taxotere® for Injection (NDA 20-449).

**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 *[NOT APPLICABLE]*

**2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?**

**2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?**

# 3 DETAILED LABELING RECOMMENDATIONS

Only relevant Clinical Pharmacology sections of Apotex's Docetaxel Injection® label are included below.

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

# 4 APPENDICES

None.

## 4.1 INDIVIDUAL STUDY REVIEWS

Not applicable.

## 4.2 QT REVIEW

Not applicable.

## 4.3 ANALYTICAL

Not applicable.

### 4.3.1 Office of Clinical Pharmacology

## 5 *NEW DRUG APPLICATION FILING AND REVIEW FORM*

### 5.1.1.1.1 General Information About the Submission

| | | | |
|---|---|---|---|
| **NDA Number** | 22-312 | **Brand Name** | Docetaxel Injection® |
| **DCP Division (I, II, III, IV, V)** | V | **Generic Name** | Docetaxel Anhydrous |
| **Medical Division** | Oncology | **Drug Class** | Microtubule Stabilizer |
| **OCP Reviewer** | Jeanne Fourie, Ph.D. | **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 (SCCHN) |
| **OCP Team Leader** | Brian Booth, Ph.D. | **Dosage Form** | 20 mg/0.5 mL and 80 mg/2mL Injection (b) (4) with an accompanying diluent |
| **Date of Submission** | March 27, 2008 | **Dosing Regimen** | IV over 1hr every 3 weeks<br>BC: 60-100 mg/m$^2$<br>NSCLC: 75 mg/ m$^2$<br>HRPC: 75 mg/ m$^2$<br>GC: 75 mg/ m$^2$<br>SCCHN: 75 mg/ m$^2$ |
| **Due Date of OCP Review** | March, 2009 | **Route of Administration** | IV Infusion |
| **5.1.1.2 Standard PDUFA Due Date** | April 28, 2009 | **Sponsor** | Apotex Inc. |

### *5.1.1.2.1.1.1.1 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) -** | | | | |
| ***5.2 HEALTHY VOLUNTEERS-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| 5.2.1 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** | | | | |

5.2.1.1.1.1 Filability and QBR comments

| **5.2.1.2** | **"X" if yes** | **5.2.1.2.1.1.1.1.1 Comments** |
|---|---|---|
| **5.2.1.3 Application filable?** | **X** | |
| **5.2.1.4 Comments sent to firm?** | | |
| **QBR questions (key issues to be considered)** | | |
| **Other comments or information not included above** | | |
| **Primary reviewer Signature and Date** | **Jeanne Fourie, Ph.D.** | |
| **Secondary reviewer Signature and Date** | **Brian Booth, Ph.D.** | |

CC: HFD-150 (CSO) – C Cottrell ; MTL – E Maher; MO – Q Ryan)
HFD-860 (Reviewer - J Fourie; DDD Acting TL - B Booth; DD - A Rahman)

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/s/
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Jeanne Fourie
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PHARMACOLOGIST

Brian Booth
2/12/2009 03:18:21 PM
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Atiqur Rahman
2/12/2009 04:20:17 PM
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