CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-449/S-028

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	20-449/SE1-028
BRAND NAME:	Taxotere®
GENERIC NAME:	Docetaxel Hydrochloride
DOSAGE FORM/STRENGTH:	40 mg/ml Docetaxel (Anhydrous) in Single-Dose Vials For Intravenous Injection
INDICATION:	Metastatic Prostate Cancer
SUBMISSION DATE:	26-Jan-2004
SUBMISSION TYPE:	NDA-Supplement
APPLICANT:	Aventis Pharmaceuticals Bridgewater, NJ 08807
OND DIVISION:	Division of Oncology Drug Products (HFD-150)
OCPB DIVISION:	Division of Pharmaceutical Evaluation I (HFD-860)
OCPB REVIEWER:	Sophia Abraham, Ph.D.
OCPB TEAM LEADER:	Atiqur Rahman, Ph.D.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The Applicant seeks approval for the use of Taxotere® (docetaxel) in combination with prednisone in the treatment of patients with androgen-independent (hormone-refractory) metastatic prostate cancer. In support of this new indication, Aventis conducted a pivotal Phase 3 study (Study TAX327) and used this study for their sNDA registration. Study TAX327 was a prospective, multi-center, active-control, open-label, randomized (1:1:1), parallel-group, comparative, 3-arm Phase 3 study in 1006 patients. The primary objective of this study was to compare overall survival after Arm A (mitoxantrone plus prednisone) and Arm B (75 mg/m^2 Taxotere® every three weeks plus prednisone) combined with Arm C (weekly 30 mg/m^2 Taxotere® plus prednisone) in patients with metastatic hormone-refractory prostate cancer. The proposed dosing regimen is Taxotere® 75 mg/m^2 administered intravenously over one hour every three weeks in combination with prednisone 5 mg administered orally twice a day (BID).

The pharmacokinetics of docetaxel were assessed using a population (NONMEM) analysis of sparse plasma samples collected from a subset of patients (n=40) in Study

TAX 327. Docetaxel total body clearance was unaltered when administered in combination with prednisone.

OVERALL RECOMMENDATION

The supplemental NDA 20-449 submitted for the use of Taxotere® (docetaxel) in combination with prednisone in the treatment of patients with androgen-independent (hormone-refractory) metastatic prostate cancer is acceptable from clinical pharmacology and biopharmaceutics perspectives.

LABELING RECOMMENDATION

The proposed labeling statement, [

] that was added to the **CLINICAL PHARMACOLOGY/ HUMAN PHARMACOKINETICS** section of the current package insert for Taxotere® should read as follows:

"A population pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone."

Please forward the above Recommendations to the Applicant.

/S/

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

/S/

Reviewer: Sophia Abraham, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA: 20-449
HFD-150/Division file
HFD-150/Staten, Dagher, Ridenhour
HFD-860/Mehta, Rahman, Abraham
CDR/Biopharm

SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Aventis Pharmaceuticals developed an adjuvant therapy of Taxotere® (docetaxel) in combination with prednisone for a newly proposed indication (Viz., in the treatment of patients with androgen-independent, including hormone-refractory, metastatic prostate cancer). The proposed dose is docetaxel 75 mg/m^2 administered as a 1-hour infusion every three weeks and prednisone 5 mg administered orally twice a day (BID) for three weeks. In support of this new indication, Aventis conducted a pivotal Phase 3 study (Study TAX327) and used this study for their sNDA registration. Study TAX327 was a prospective, multi-center, active-control, open-label, randomized (1:1:1), parallel-group, comparative, 3-arm Phase 3 study in 1006 patients. The primary objective of this study was to compare overall survival after Arm A (mitoxantrone plus prednisone) and Arm B (75 mg/m^2 every three weeks Taxotere® plus prednisone) combined with Arm C (weekly 30 mg/m^2 Taxotere® plus prednisone) in patients with metastatic hormone-refractory prostate cancer.

The pharmacokinetics (PK) of docetaxel were assessed in a subset of patients in Study TAX 327 (total n=40 patients) on Day 1 (docetaxel alone treatment) and on Day 22 (docetaxel+prednisone combination treatment). Plasma concentration/time data were analyzed using the previously developed population PK (NONMEM) model (original NDA 20-449) to determine the effect of prednisone on docetaxel total body clearance. The results of the NONMEM analysis showed that although prednisone is an inducer of CYP3A4 and 3A5, the two enzymes involved in docetaxel metabolism, it does not have any effect on docetaxel total body clearance when both drugs were administered in combination. Taxotere® current package insert is updated to reflect this finding.

BACKGROUND

Docetaxel is a semisynthetic antineoplastic agent that is very similar to paclitaxel in structure, mechanism of action, and spectrum of antitumor activity. Docetaxel differs structurally from paclitaxel at the C-10 position where docetaxel has a hydroxy group instead of an acetyl group and contains an -OC(CH_3)$_3$ moiety on the C-13 side chain as opposed to a benzamide phenyl group as in paclitaxel. Docetaxel is synthesized from 10-deacetyl baccatin III, a noncytotoxic substance extracted from the needles of the European yew tree (*Taxus baccata*). The mechanism of action is similar to that for paclitaxel. Docetaxel promotes the assembly of microtubules and stabilizes their formation by inhibiting depolymerization.

The FDA approved docetaxel for Injection Concentrate under the trade name, Taxotere®, on 15-May-1996 (original NDA 20-449) for the treatment of refractory, locally advanced or metastatic breast cancer. On 23-Dec-1999, the FDA approved Taxotere® for the treatment of advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy. The approved recommended dosing regimen is 60-100 mg/m^2 infused intravenously (IV) over one hour once every three weeks. Taxotere® is available as sterile, non-pyrogenic concentrates in single-dose vials containing either 20 mg/0.5 ml or 80 mg/2 ml docetaxel (i.e., 40 mg/ml). The Concentrate is to be diluted prior to use with 13% ethanol in water for Injection.

The pharmacokinetics of docetaxel were evaluated in cancer patients after administration of 20-115 mg/m^2 in Phase 1 studies. The area under the curve (AUC) is dose proportional following doses of 70-115 mg/m ^{2} with infusion times of 1 to 2 hours. Docetaxel plasma levels decline triexpoentially with half-lives of 4 minutes, 36 minutes and 11.1 hours for the alpha, beta and gamma elimination phases, respectively. Docetaxel is metabolized by cytochrome P450 (CYP) 3A4 and 3A5 enzymes to one major metabolite and three minor metabolites. All four metabolites are oxidation products of the tert-butyl group attached to the C13-side chain. The metabolites are markedly less cytotoxic and less myelotoxic than the parent drug. Mean total body clearance and steady state volume of distribution are 21 L/h/m^2 and 113 L, respectively. A [^{14}C] study in three cancer patients indicated that docetaxel is eliminated in both the urine and feces following oxidative metabolism of the *tert* -butyl ester group, but fecal excretion is being the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug. Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. A population pharmaco-kinetic analysis of plasma data from 535 patients treated with 100 mg/m^2 of docetaxel indicate that the pharmacokinetics of docetaxel are not influenced by age or gender and docetaxel total body clearance is not modified by pretreatment with dexamethasone (8 mg bid orally for 3 to 5 days starting one day prior to Taxotere® infusion). In patients with mild-to-moderate liver function impairment (SGOT and/or SGPT >1.5 times the upper limit of normal [ULN] concomitant with alkaline phosphatase >2.5 times ULN), total body clearance is lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). Patients with combined abnormalities of transaminase and alkaline phosphatase should, in general, not be treated with Taxotere®. The pharmaco-kinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

In vitro studies showed that docetaxel is about 94% protein bound, mainly to α_1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism can be inhibited by CYP3A4 inhibitors, such as ketoconazole, erythromycin, troleando-mycin, and nifedipine. Based on *in vitro* findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel plasma levels.

In human primary hepatocytes, dexamethasone is a significant induction of CYP3A4/5 and a slight induction of CYP2A6 and prednisone is a significant inducer of CYP3A4/5 and a slight inducer of CYP2A6.

Aventis Pharmaceuticals developed an adjuvant therapy of docetaxel in combination with prednisone for a newly proposed indication (Viz., in the treatment of patients with androgen-independent, including hormone-refractory, metastatic prostate cancer). The proposed dose is docetaxel 75 mg/ m^2 administered as a 1-hour infusion every three weeks and prednisone 5 mg administered orally twice a day (BID) for three weeks. In

support of this new indication, Aventis conducted a pivotal Phase 3 study (Study TAX327) and used this study for their sNDA registration. Based on the results of this study, the Applicant provided an updated version for Taxotere® package insert (see Appendix II).

SUMMARY OF STUDY TAX327

Title: ***A Multi-center Phase 3 Randomized Trial Comparing Taxotere® Administered Either Weekly or Every Three Weeks in Combination with Prednisone Versus Mitoxantrone in Combination with Prednisone for Metastatic Hormone-Refractory Prostate Cancer***

Study TAX327 was a prospective, multi-center, active-control, open-label, randomized (1:1:1), parallel-group, comparative, 3-arm Phase 3 study in 1006 patients. The primary objective of this study was to compare overall survival after mitoxantrone and prednisone (Arm A), and Taxotere® and prednisone (Arm B: Taxotere® every three weeks combined with Arm C: weekly Taxotere®) in patients with metastatic hormone-refractory prostate cancer. As secondary objectives, pain progression-free survival, prostate-specific antigen (PSA) progression-free survival, tumor progression-free survival, disease progression-free survival, incidence and duration of pain improvement, incidence and duration PSA response, quality of life, response rate, safety, and pharmacokinetics of docetaxel in combination with prednisone were also compared. Patients were randomized (1:1:1) to receive either:

- **Arm A:** Mitoxantrone 12 mg/m² intravenously every three weeks, plus prednisone 5 mg orally BID, for 10 cycles.

- **Arm B:** Taxotere® 75 mg/m² intravenously (day 1) every three weeks, plus prednisone 5 mg orally BID, for 10 cycles.

- **Arm C:** Taxotere® 30 mg/m² intravenously weekly for 5 of 6 weeks (on days 1, 8, 15, 22, 29), plus prednisone 5 mg orally BID, for 5 cycles

Patients treated with Taxotere® were pre-medicated with dexamethasone in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Three comparisons of interest were made: Arm B versus Arm A, and Arm C versus Arm A, and (Arm B+Arm C) versus Arm A. The primary efficacy analysis compared overall survival in the intent-to-treat population between the two docetaxel arms (Arm B+Arm C) and the control mitoxantrone+prednisone arm (Arm A).

The pharmacokinetics (PK) of docetaxel were assessed in a subset of patients in Study TAX 327 (total n=40 patients). The 40 patients ranged in age, weight, and body surface area from 49-85 years, 70-148 kg, 1.62-2.58 m^2, respectively. A 6-sample optimal sampling strategy was used (this included predose, 15 minutes before the end of docetaxel infusion, and 15 minutes, 45 minutes, 2 hours, and 5 hours after the end of docetaxel infusion). A total of 25 patients in Arm B, who were administered Taxotere® 75 mg/m^2 every 3 weeks (q3w) IV over 1 hour, had blood samples collected during the first cycle (Day 1, docetaxel PK without concomitant prednisone) and the second cycle

(Day 22, docetaxel PK with concomitant prednisone). A total of 15 patients in Arm C, who were administered Taxotere® 30 mg/ m^2 IV every week (qw) over 30 minutes, had blood samples collected on Day 1 and Day 22. The start of prednisone during the first cycle was delayed by one day in order to accommodate pharmacokinetic assessment for these patients.

Plasma docetaxel concentrations were measured using a validated LC/MS/MS method. Calibration curves were linear over the concentration range of 1.0-500 ng/ml with a lower limit of quantitation at — ng/ml. The calibration range was extended up to 8000 ng/ml with 20-fold dilution to accommodate plasma samples with concentrations higher than 500 mg/ml. The coefficient of determination (r^2) for the calibration curves ranged from — The within and between run precision (%CV) of quality control samples ranged from — The within and between run accuracy of quality control samples were within — %. The average recovery for docetaxel at 1.5 ng/ml and 400 ng/ml was 99% and 83%, respectively and for the internal standard was 77%.

Plasma concentration/time data were analyzed using the previously developed population PK (NONMEM) model (original NDA 20-449) to determine the effect of prednisone on the pharmacokinetics of docetaxel. A three-compartment structural model with first-order elimination and an exponential error statistical model were found to best describe the plasma concentration/time data. A Bayesian approach (POSTHOC analysis) was used to calculate the individual clearance and area under plasma curve (AUC) values for docetaxel (see Appendix 1).

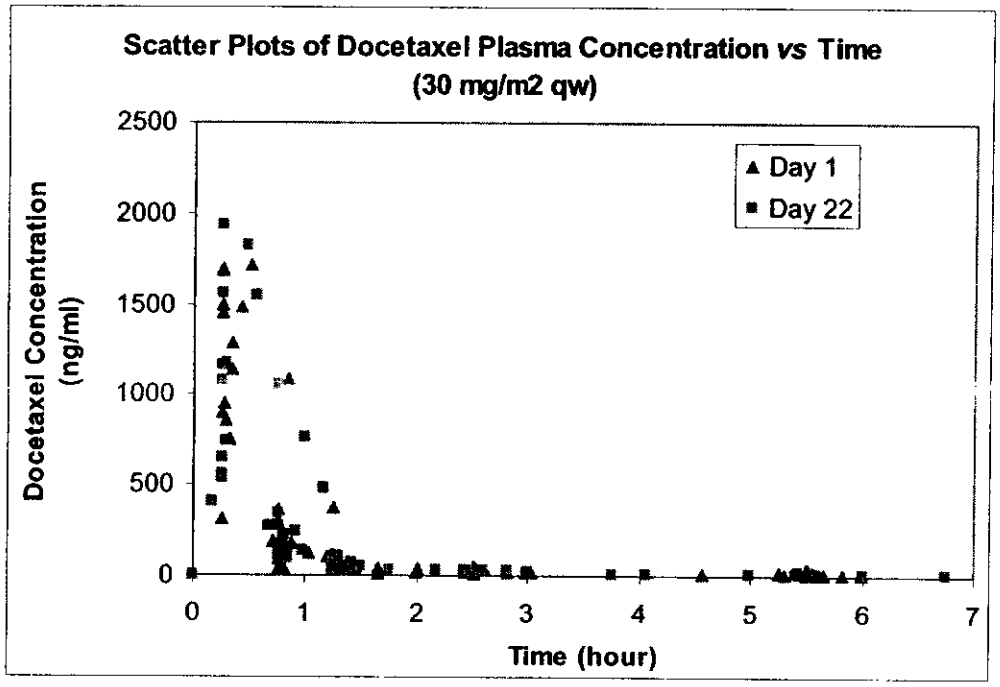
Results:

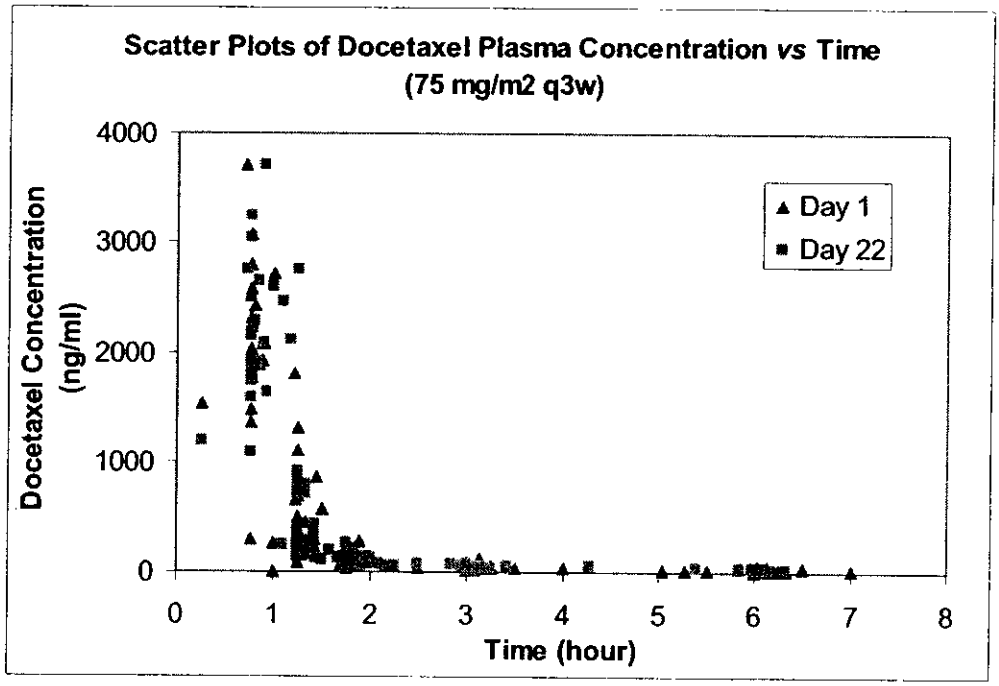
Mean ± SD (CV%) Bayesian Clearance and AUC Estimates for Docetaxel

		Day 1 (without Prednisone)		Day 22 (with Prednisone)
Docetaxel 30 mg/m^2 qw	**N**		**n**	
CL (L/hr)	15	50.7±11.2 (22%)	15	54.7±13.4 (25%)
CL (L/hr/m^2)	15	25.3± 5.2 (21%)	15	27.4± 7.3 (27%)
AUC (µg*hr/ml)	15	1.2± 0.28 (23%)	15	1.15± 0.33 (28%)
Docetaxel 75 mg/m2 q3w	**n**		**n**	
CL (L/hr)	25	50.2±9.9 (19%)	21	48.3±11.7 (24%)
CL (L/hr/m^2)	25	25.8± 5.0 (19%)	21	25.0± 6.7 (27%)
AUC (µg*hr/ml)	25	3.0± 0.60 (20%)	21	3.2± 0.99 (31%)

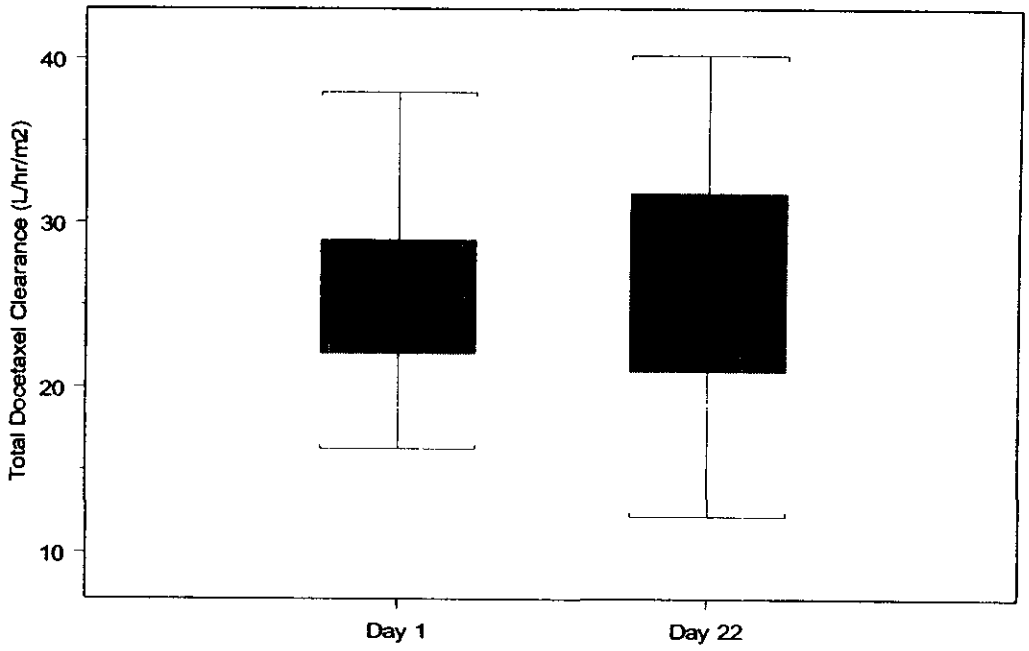
No significant differences are observed between mean docetaxel clearance values when docetaxel was administered alone (Day 1) or with prednisone (Day 22) at each dosing level (30 mg/m^2 qw or 75 mg/m^2 q3w) (90% confidence interval: 92-108%, p=0.981).

Scatter plots of docetaxel plasma concentration versus time following both dosing regimens are shown in the Figures below.





A comparison of combined clearance values after the two dosing regimens (30 mg/m^2 qw and 75 mg/m^2 q3w) on Day 1 (no prednisone, n=40) versus Day 22 (plus prednisone, n=36) is shown in the Figure below:



Mean±SD (range) docetaxel clearance is 25.6±5.03 (16.3-37.9) L/hr/m^2 on day 1 (n=40) and 26.0±6.9 (12.2-40.2) L/hr/m^2 on Day 22 (n=36).

In conclusion, although prednisone is an inducer of CYP3A4 and 3A5, the two enzymes involved in docetaxel metabolism, it does not have any effect on docetaxel clearance when both drugs were administered in combination.

Withheld
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page(s) of trade secret and/or confidential commercial information

(b4)

29 pages redacted from this section of the approval package consisted of draft labeling

APPENDIX III

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20-449**	**Brand Name**	**Taxotere®**
OCPB Division (I, II, III)	**DPE-I**	**Generic Name**	**Docetaxel**
Medical Division	**HFD-150**	**Drug Class**	**Taxenes**
OCPB Reviewer	**Abraham**	**Indication(s)**	**Metastatic prostate cancer**
OCPB Team Leader	**Rahman**	**Dosage Form**	**40 mg/ml intravenous injection**
		Dosing Regimen	**75 mg/m2 over 1-hour Q3W**
Date of Submission	26-Jan-2004	**Route of Administration**	**IV**
Estimated Due Date of OCPB Review	**15-Mar-2003**	**Applicant**	Aventis Pharmaceuticals
PDUFA Due Date	**27-Jul-2003**	**Priority Classification**	**S**
Division Due Date			

Clin. Pharm. and Biopharm. 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	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
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:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
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:		1	1	
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:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1	1	
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	**Sophia Abraham,**	
Secondary reviewer Signature and Date	**Atik Rahman**	

CC: NDA 21-326, HFD-850(Electronic Entry or Lee), HFD-150 (Staten), HFD-860 (Mehta, Rahman, Booth, Abraham)

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/s/

Sophia Abraham
5/10/04 02:43:29 PM
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Atiqur Rahman
5/10/04 02:51:52 PM
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