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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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/s/

SOPHIA ABRAHAM
02/09/2011

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-234/S-000
BRAND NAME: Docetaxel for Injection
GENERIC NAME: Docetaxel for Injection
DOSAGE FORM/ 10 mg/ml Vials
INDICATIONS: Breast Cancer, Non-Small Cell Lung Cancer, Prostate Cancer, (b) (4)

SUBMISSION DATE: 15-Nov-2007
SUBMISSION TYPE: NDA-Amendment
APPLICANT: Hospira, Inc.
DDOP: Division of Drug Oncology Products
OCP DIVISION: Division of Clinical Pharmacology 5
OCP REVIEWER: Sophia Abraham, Ph.D.
OCP TEAM LEADER: Brian Booth, Ph.D.

TABLE OF CONTENTS:

1. Executive Summary…… 1
   1.1 Recommendation…… 2
   1.2 Phase 4 Commitments…… 2
   1.3 Summary of Clinical Pharmacology Findings…… 2

2. Question Based Review

   2.1 General Attributes…… 2

   2.2 General Clinical Pharmacology…… 2

   2.3 Intrinsic Factors (sex, race, age, renal and hepatic impairment)…… 3

   2.4 Extrinsic Factors (drug interactions)…… 4

   2.5 General Biopharmaceutics…… 4

   2.6. Analytical Section…… 5

3. Clinical Pharmacology Labeling Recommendations…… 5

Appendices
   1. Applicant's Proposed Package Insert …… 8

1. EXECUTIVE SUMMARY

This is an amendment to the original NDA 22-234/S-000 for Docetaxel for Injection. The original NDA 22-234/S-000 was submitted on 09-Jul-2007 to support a new formulation for docetaxel (Viz., Docetaxel for Injection, 10 mg/mL) in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

At the time of the original NDA submission, the Applicant submitted the current package insert for Taxotere to support the new formulation of docetaxel in old labeling format. Upon the Agency's request via a teleconference on 19-Oct-2007 and through an e-mail on 22-Oct-2007, the Applicant updated Taxotere labeling and resubmitted it in the PLR format (see

Appendix 1). We have made some changes in the Clinical Pharmacology/Pharmacokinetics section (Section 12.3) of the PLR labeling (see Clinical Pharmacology Labeling Recommendations, section 3 of this review, pp. 5).

1.1 RECOMMENDATION

The Applicant should incorporate the clinical pharmacology labeling recommendations as outlined under Section 3 of this review (pp. 5).

1.2 PHASE 4 COMMITMENTS

[None]

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

See original review for NDA 22-234 (dated: 09-Jul-2007).

2 QUESTION BASED REVIEW

Refer to the original NDA 20-449 (Submission Date: 27-July-1994) for the following issues

2.1 General Attributes of the Drug

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 mechanism(s) of action and therapeutic indication(s)?

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 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

2.2.4.1 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 What are the PK characteristics of the drug and its major metabolite?
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 nonlinearity 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 (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?
2.3.2.1 Elderly
2.3.2.2 Pediatric patients
2.3.2.3 Gender
2.3.2.4 Race
2.3.2.5 Renal impairment
2.3.2.6 Hepatic impairment
2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?
2.3.2.7 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 (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?
2.4.2.7 What other co-medications are likely to be administered to the target patient population?
2.4.2.8 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?
2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?
2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

2.5 General Biopharmaceutics [NOT APPLICABLE]

2.5.1 Based on the biopharmaceutics classification system (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 relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?
2.5.2.1.1 What data support or do not support a waiver of in vivo BE data?
2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?
2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?
2.5.3 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?
2.5.4 When would a fed BE study be appropriate and was one conducted?

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?
2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?
2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?
2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?
2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma 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?
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)?
2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

3. *Clinical Pharmacology Labeling Recommendations*

12.3 Human Pharmacokinetics

Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m^2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70-115 mg/m^2 with intravenous infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, ß, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m^2.

Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. *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.

Metabolism: *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, troleandomycin, and nifedipine. Based on *in vitro* findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood concentrations. No clinical studies have been performed to evaluate this finding ***[see Drug Interactions (7)]***.

Elimination: A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was 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.

Effect of Age: A population pharmacokinetic analysis was carried out after Docetaxel Injection treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age.

Effect of Gender: The population pharmacokinetic analysis also indicated that gender did not influence the pharmacokinetics of docetaxel.

Effect of Hepatic Impairment: The population pharmacokinetic analysis indicated that in patients with clinical chemistry data suggestive of mild (AST and/or ALT > the upper limit of normal [ULN]) and moderate liver function impairment (AST and/or ALT >1.5 times the upper limit of normal [ULN] concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should, in general, not be treated with Docetaxel Injection ***[see Use in Special Populations (8.6)]***. Patients with severe hepatic impairment has not been studied.

Effect of Race: Mean total body clearance for 23 Japanese patients dosed at the range of 10-90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

Pharmacokinetics of docetaxel in Combination Therapies:

Dexamethasone: Docetaxel total body clearance was not modified by pretreatment with dexamethasone.

Cisplatin: The cClearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile

of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

Cisplatin and Fluorouracil: The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.

Prednisone: 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.

Cyclophosphamide and Doxorubicin: A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 22-234/S-000
BRAND NAME: Docetaxel for Injection
GENERIC NAME: Docetaxel for Injection
DOSAGE FORM/ 10 mg/ml Vials
INDICATIONS: Breast Cancer, Non-Small Cell Lung Cancer, Prostate Cancer, (b) (4)

SUBMISSION DATE: 09-Jul-2007
SUBMISSION TYPE: NDA-New
APPLICANT: Hospira, Inc.
DDOP: Division of Drug Oncology Products
OCP DIVISION: Division of Clinical Pharmacology 5
OCP REVIEWER: Sophia Abraham, Ph.D.
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   2.2 General Clinical Pharmacology…… 3

   2.3 Intrinsic Factors (sex, race, age, renal and hepatic impairment)…… 5

   2.4 Extrinsic Factors (drug interactions)…… 5

   2.5 General Biopharmaceutics…… 6

   2.6. Analytical Section…… 7

3. Clinical Pharmacology Labeling Recommendations…… 7

Appendices
   1. Proposed Package Insert (Major Changes)…… 8

1. EXECUTIVE SUMMARY

Hospira submits a New Drug Application (NDA 22-234/S-000) in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act in support of a new formulation for docetaxel, Docetaxel for Injection (10 mg/mL).

The new formulation for docetaxel will be available in both single-dose vials containing 20 mg/2 mL and multi-dose vials containing either 80 mg/8 mL or 160 mg/16 mL of docetaxel (anhydrous). Docetaxel for Injection is essentially similar to the initially diluted Taxotere Concentrate with 13% ethanol in water for injection. Docetaxel for Injection is to be infused directly without prior dilution.

A Waiver from conducting in vivo studies for the new drug product is granted based on the fact that the 10 mg/mL Hospira's Docetaxel for Injection has the same concentration as for the initially diluted Taxotere solution for Injection. Intravenous infusion of the two products will result in an identical amount of drug delivered directly to the systemic circulation.

The current labeling for Taxotere was updated with respect to the proposed changes made in the new drug product (see Appendix 1).

1.1 RECOMMENDATION

NDA 22-234/S-000 submitted in support of a new formulation for Docetaxel for Injection is acceptable to the Office of Clinical Pharmacology.

1.2 PHASE 4 COMMITMENTS

[None]

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Taxotere (docetaxel), a product of Sanofi-Aventis, US, received approval on 14-May-1996 as a single agent for the treatment of refractory, locally advanced or metastatic breast cancer under NDA 20-449. Additional indications for the use of docetaxel were approved including 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).The approved drug product (Taxotere for Injection) is available only in single-dose vials containing 20 mg/0.5 mL or 80 mg/2 mL of docetaxel (anhydrous). The approved dosage is 60-100 mg/m^2 administered intravenously as a one-hour infusion every 3 weeks.

Hospira (another Applicant) plans to market a new drug product for docetaxel (Docetaxel for Injection). The active ingredient, indications, and route of administration for Docetaxel for Injection are the same as those of the previously approved drug product (Taxotere for Injection). The differences between the new and previously drug products are as follows:

- The strength of the new drug product is 10 mg/mL while the strength of the previously drug product is 40 mg/mL. However, the new product has the same strength (10 mg/mL) as for the initially diluted solution of Taxotere for injection.

- A multi-dose application of 80 mg/8 mL and 160 mg/16 mL dosage forms were added to the new formulation while the innovative dosage form is supplied as single-dose vials.

- The qualitative/quantitative composition of the new formulation is different from the previous formulation. A comparison between the two formulations is shown Table 1.

Table 1. Comparison of Qualitative and Quantitative Compositions of Hospira's Docetaxel Injection and Initial Diluted Taxotere Solution

Component	Initial Diluted Taxotere Solution (mg/mL)	Hospira's Docetaxel Injection (mg/mL)
Docetaxel	10	10
Polysorbate 80 NF	(b) (4)	260
Dehydrated Alcohol USP	(b) (4)	(b) (4)
Water for Injection USP	(b) (4)	--
Citric Acid (b) (4) USP	--	4
Polyethylene Glycol 300 NF	--	q.s. (b) (4)
q.s. = quantity sufficient		

*Theoretical amount calculated using specific gravity of (b) (4).

2 QUESTION BASED REVIEW

Refer to the original NDA 20-449 (Submission Date: 27-July-1994) for the following issues

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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?

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2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity 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 (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?
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2.3.2.5 Renal impairment
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2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

2.3.2.7 What pregnancy and lactation use information is there in the application?

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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?

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2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions**?**

2.5 General Biopharmaceutics [NOT APPLICABLE]

2.5.1 Based on the biopharmaceutics classification system (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 relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

2.5.2.1.1 What data support or do not support a waiver of in vivo BE data?
2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

2.5.3 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?
2.5.4 When would a fed BE study be appropriate and was one conducted?
2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma 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?

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)?

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

3. OCPB Labeling Recommendations

[None]

4. Appendices

4.1 **Proposed Package Insert (Major Changes)**

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