APPLICATION NUMBER:
022234Orig1s000

PHARMACOLOGY REVIEW(S)
On *initial* overview of the NDA application for filing:

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?</td>
<td>N/A</td>
<td></td>
<td>Non-clinical study data were not submitted.</td>
</tr>
<tr>
<td>2 Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Is the pharmacology/toxicology section legible so that substantive review can begin?</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?</td>
<td>N/A</td>
<td></td>
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</tr>
<tr>
<td>5 If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?</td>
<td>N/A</td>
<td></td>
<td>No request for studies were made.</td>
</tr>
<tr>
<td>Content Parameter</td>
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<tr>
<td>-------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the applicant addressed any abuse potential issues in the submission?</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ** _Yes_  

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

None

G. Sachia Khasar, Ph.D. 10/27/2010  
Reviewing Pharmacologist  

S. Leigh Verbois, Ph.D. 10/28/2010  
Team Leader/Supervisor
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GABRIEL S KHASAR
10/29/2010

SANDI L VERBOIS
10/29/2010
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22,234
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: July 11, 2007
PRODUCT: Docetaxel Injection
INTENDED CLINICAL POPULATION: Breast, NSCLC, Prostate, Gastric, Head and Neck
SPONSOR: Hospira
DOCUMENTS REVIEWED: Module 1, Volume 1.1
Module 2, Volume 1.1
Module 4, Volumes 9-12
Module 8, Volume 8.1
REVIEW DIVISION: OODP/DDOP
PHARM/TOX REVIEWER: Margaret E. Brower, Ph.D.
PHARM/TOX SUPERVISOR: Haleh Saber, Ph.D.
DIVISION DIRECTOR: Robert Justice, M.D.
PROJECT MANAGER: Frank H. Cross, Jr.
EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approve as 505(b)(2).

B. Recommendation for nonclinical studies: None.

C. Recommendations on labeling: The content of the pharmacology/toxicology sections of the label is similar to that of the reference drug. Modifications to these sections were primarily made to comply with conversion to the PLR format.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
   The impurity specification limits of Hospira for Docetaxel Injection are comparable to the limits of the reference listed drug (RLD), Taxotere, and are acceptable. Docetaxel derived from Docetaxel Injection has a similar bioavailability as docetaxel derived from Taxotere. The formulations appear to be equivalent. Docetaxel Injection and Taxotere demonstrated a similar immunogenic potential, as measured by complement activation.

B. Pharmacologic activity
   No additional data.

C. Nonclinical safety issues relevant to clinical use
   Docetaxel Injection and Taxotere appear to be bioequivalent.
PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 22,234
Review number: 1
Sequence number/date/type of submission: July 11, 2007/(505(b)(2) NDA
Information to sponsor: Yes ( ) No ( X)
Sponsor and/or agent: Hospira, Inc. Lake Forest, IL
Manufacturer: Mayne Pharma Ltd., Mulgrave, Victoria, Australia

Reviewer name: Margaret Brower, Ph.D.
Division name: OODP/DDOP
Review completion date: April 29, 2008

Drug:
Trade name: Docetaxel injection (RLD: Taxotere)
Generic name: docetaxel
Code name: RP 56976
Chemical name: (2R,3S)-N-benzoyl-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β, 20-Epoxy-1,2α, 4, 7β, 10β, 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate
Molecular weight/molecular formula: C₄₃H₅₃NO₁₄
CAS No.: 114977-28-5
Structure:

Relevant INDs/NDAs: NDA 20,449 (RLD), IND 35,555 (RLD)

Pharmacologic class: Microtubule inhibitor

Intended clinical population:
Breast cancer in patients with locally advanced or metastatic cancer following failure of prior chemotherapy. In combination with doxorubicin and cyclophosphamide for adjuvant treatment of patients with node-positive breast cancer.
NSCLC, locally advanced or metastatic, following failure of platinum-based therapy, or in combination with cisplatin in patients who have not previously received chemotherapy.
Prostate cancer in combination with prednisolone for treatment of androgen independent (hormone refractory) metastatic cancer.
Clinical formulation: 10mg/mL

Comparison of qualitative and quantitative compositions of Hospira’s docetaxel and Taxotere

<table>
<thead>
<tr>
<th>Component</th>
<th>Taxotere (mg/mL)</th>
<th>Hospira’s docetaxel (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>docetaxel</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>(b)(4)</td>
<td>260</td>
</tr>
<tr>
<td>Dehydrated alcohol USP</td>
<td>(b)(4)</td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Water for injection USP</td>
<td>(b)(4)</td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Citric acid USP</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Polyethylene glycol 300 NF</td>
<td></td>
<td>q.s. (b)(4)</td>
</tr>
</tbody>
</table>

q.s. = quantity sufficient

Theoretical amount calculated using specific gravity of

Route of administration: iv

Disclaimer: Tabular and graphical information is from sponsor’s submission unless stated otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA # 22,234 are owned by Hospira or are data for which Hospira has obtained a written right of reference. Any information or data necessary for approval of NDA# 22,234 that Hospira does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug’s approved labeling. Any data or information described or referenced below from a previously approved application that Hospira does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA # 22,234.

INTRODUCTION/DRUG HISTORY/IMPURITY CONCERN:
Taxotere (Docetaxel for Injection Concentrate), NDA 20,449, was approved on May 15, 1996 for the treatment of refractory, locally advanced or metastatic breast cancer. On December 23, 1999, Taxotere was approved as a single agent for the treatment of advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy at the recommended dose of 60-100mg/m² administered iv once every three weeks. As an adjuvant therapy, Taxotere was approved on May 19, 2004 in combination with prednisone for the treatment of androgen independent (hormone refractory) metastatic prostate cancer at a recommended dose of 75mg/m² administered once every 3 weeks in combination with 5mg oral prednisone BID. In 2005, Taxotere was approved in combination with cisplatin and 5-FU for the treatment of gastric adenocarcinoma.

In 1997/1999, Taxotere was formulated as a 40mg/ml docetaxel solution in polysorbate 80. Different batches of polysorbate 80 were found to show small variations in residual alkalinity or acidity. However, docetaxel was found to exhibit a different degradation pathway and impurity profile in the new formulation as a result of the vehicle. The formulation change resulted in elevated specification limits of
specific degradants from a 1.5-fold to a 4-fold difference. Single-dose/lethality studies, and 2 multiple-dose studies in CD2F1 mice with elevated levels of these degradants resulted in increased mortality and/or neurotoxicity (see NDA 20,449 reviews 13 and 14). As a result, the shelf-life specifications of 2 problematic impurities of the new formulation were limited to [Redacted] respectively. Following CMC reanalysis using HPLC/UV/MS (CMC supplement S-002), an additional problematic impurity was reconsidered as “unspecified” with a specification limit of [Redacted]. All unspecified impurities were limited to [Redacted]. The sponsor agreed to these lower specifications.

The 2006 impurity specification limits for Taxotere (NDA 20,449, Sanofi Aventis) noted in the following table include batch testing limits following release, and following 6 months storage at 25°C/60% humidity (shelf-life specifications). These data were taken from CMC supplement SCS-037, dated March 17, 2006.

<table>
<thead>
<tr>
<th>Sanofi-aventis</th>
<th>Hospira</th>
<th>Release Specification</th>
<th>Shelf Life Specification</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>Identification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n/a – not applicable</td>
<td></td>
<td></td>
<td></td>
<td>(b)(4)</td>
</tr>
</tbody>
</table>

The Hospira acceptance criteria for [Redacted], below the current shelf-life specification of this impurity in the RLD. In addition, [Redacted] are not listed, and, if present, would be considered as unidentified individual impurities with an acceptance criteria of (b)(4). CMC has accepted this unidentified specification limit. Therefore, the impurity specification limits of Hospira for Docetaxel Injection appear to be acceptable at this time.

**Justification for 505(b)(2) Hospira docetaxel injection:**
Docetaxel Injection was developed as an analog to Taxotere, only requiring a single dilution into infusion solutions prior to administration, compared to Taxotere with a 2-step dilution process (diluted to a premix prior to dilution into infusion solutions). As seen on the previous page comparing the two formulations, Hospira’s docetaxel contains citric acid, polyethylene glycol, and a higher concentration of dehydrated alcohol USP. Hospira is also proposing dosing solutions of 80mg/8mL and 160mg/16mL; the 160mg/16mL dosing solution is in addition to the 80mg solution available for the reference drug. Docetaxel Injection will have the same dosage form, final concentration, route of administration, and intended indications as Taxotere.

**PHARMACOLOGY –** None
Safety pharmacology - None

PHARMACOKINETICS/TOXICOKINETICS

Comparative non-clinical pharmacokinetics were conducted to demonstrate that the change in formulation had no effect on drug delivery, or resulting protein binding and pharmacokinetics. Results indicated the following:

1. **In vitro** docetaxel release from micelles (free docetaxel) in 0.9% NaCl was comparable for both formulations.
2. **In vitro** docetaxel protein binding in dog and human plasma was comparable following 4, 6 and 24h.
3. Systemic pharmacokinetics of docetaxel in Beagle dogs administered 0.96 to 0.99 mg/kg Docetaxel Injection, and 0.86 to 0.88 mg/kg Taxotere were comparable (Study 1203-006, Pharmacokinetics crossover study with docetaxel in dogs).
4. Docetaxel derived from Docetaxel Injection has a similar bioavailability as docetaxel derived from Taxotere. The formulations appear to be equivalent.

TOXICOLOGY

Immunogenicity

Docetaxel Injection and Taxotere demonstrated a similar immunogenic potential, as measured by complement activation (increased concentrations of SC5b-9).

There were no additional toxicology studies submitted.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:
The impurity specification limits of Hospira for Docetaxel Injection are comparable to the limits of the reference listed drug, Taxotere, and are acceptable. Docetaxel derived from Docetaxel Injection has a similar bioavailability as docetaxel derived from Taxotere. The formulations appear to be equivalent. Docetaxel Injection and Taxotere demonstrated a similar immunogenic potential, as measured by complement activation.

Recommendations:
There are no pharmacology/toxicology issues which preclude approval of Docetaxel Injection as a 505(b)(2).
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
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Margaret Brower
6/9/2008 11:15:09 AM
PHARMACOLOGIST

Haleh Saber
6/9/2008 01:36:32 PM
PHARMACOLOGIST