CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205934Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	12/22/2015
From	Geoffrey Kim
Subject	Division Director Summary Review
NDA # **Supplement #**	205934
Applicant	Teikoku Pharma USA Inc
Date of Submission	2/26/2015
PDUFA Goal Date	12/26/2015
Proprietary Name / **Non-Proprietary Name**	Docetaxel Injection (b)(4)
Dosage Form(s) **Strength(s)**	Solution, Injection 20mg/ml, 80 mg/4ml, 160mg/8ml
Applicant Proposed Indication(s)/Population(s)	Docetaxel Injection (b)(4) is a microtubule inhibitor indicated for: **1.Breast Cancer (BC)**: single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC 2.**Non-Small Cell Lung Cancer (NSCLC)**: single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC 3.**Hormone Refractory Prostate Cancer (HRPC)**: with prednisone in androgen independent (hormone refractory) metastatic prostate cancer 4.**Gastric Adenocarcinoma (GC)**: with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction 5. **Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN)**: with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Genevieve Schechter
Pharmacology Toxicology Review	Wimolnut Manheng

OPQ Review – Drug Product	Rajiv Agarwal
OPQ Review – Drug Substance	Haripada Sarker
OPQ Review – Drug Product Process	Vidya Pai
OPQ Review - Facilities	Wayne Seifert
OPQ Review - Biopharmaceutics	Jing Li
Microbiology Review	Nandini Bhattacharya
Clinical Pharmacology Review	Runyan Jin
OPDP	Nicholas Senior
CDTL Review	Xiao Hong Chen
OSE/DMEPA	Davis Mathew
Patient Labeling	Nathan Caulk

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Introduction

On February 26, 2015, Teikoku Pharma, submitted NDA 205934 for Docetaxel Injection, (Non-Alcohol Formula). The application was reviewed under the 505(b)(2) approval pathway. The listed drug (LD) for this 505(b)(2) application is One-Vial Taxotere® (docetaxel) Injection, 20 mg/mL and 80 mg/4mL by Sanofi-Aventis U.S. LLC, which is approved by the FDA under NDA 20449.

Docetaxel Injection, (Non-Alcohol Formula) contains the same active ingredient, proposed route of administration, and proposed indications as the listed drug, Taxotere, but differs in inactive excipients from the LD. The proposed indications are as follows:

1.Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC
2.**Non-Small Cell Lung Cancer (NSCLC)**: single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC
3.**Hormone Refractory Prostate Cancer (HRPC)**: with prednisone in androgen independent (hormone refractory) metastatic prostate cancer
4.**Gastric Adenocarcinoma (GC)**: with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction
5. **Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN)**: with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN

The most notable difference between Docetaxel Injection, (Non-Alcohol Formula) and Taxotere is the lack of alcohol as an excipient. Thus, the applicant proposed to omit the warning and precaution regarding alcohol content from the package insert.

2. Background

Docetaxel is a microtubule inhibitor that was approved by the US FDA 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. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cell.

All currently marketed docetaxel formulations contain alcohol, with a content ranging from 2.0 to 6.4 g in a 200 mg dose. FDA issued a safety warning on June 20, 2014 to health care professionals and patients that the intravenous chemotherapy drug docetaxel contains ethanol, also known as alcohol, which may affect the central nervous system and may impair the

patient's ability to drive or use machines immediately after infusion. Alcohol content is included in the warnings and precaution section of all docetaxel formulations.

The applicant has included in this NDA a request for a waiver of in vivo bioequivalence (BE) (eCTD 1.12.15) for docetaxel injection. The biowaiver request was discussed in a pre-NDA meeting (August 19, 2013), in which the Agency indicated that such a waiver may be granted if TPU submitted a side-by-side comparison of CMC and biopharmaceutical characteristics of the LD and TPU's product in the final infusion solution to be administered to patients.

3. CMC/Device

Per the CDTL Review:
"The Applicant requested a waiver of *in vivo* bioavailability/bioequivalence (BA/BE) requirements for Taxotere (docetaxel) Injection (b)(4) largely based on 21 CFR § 320.22 (b)(1) and the solubility property of parenteral solutions. In comparison to the LD drug product, the proposed formulation does not contain alcohol, but contains soybean oil, PEG 300 and citric acid as new inactive ingredients. PEG 300 and citric acid have been used in approved Docetaxel Injection products. The amount of Polysorbate 80 was slightly higher than the amount used in the LD and the IIG limit. The applicant has justified that the differences of pH and osmolality between the LD and the proposed formulation will not impact the drug distribution and elimination. (b)(4) between the proposed drug product and Taxotere. The additional studies on protein binding and complement activation did not show significant difference between the proposed product and Taxotere"

"Complete information regarding the characterization, manufacturing and controls for docetaxel trihydrate drug substance is provided in DMF No. (b)(4). DMF was reviewed and found to be adequate."

"Specification for Docetaxel Injection is consistent with the USP Monograph for Docetaxel Injection, and is in accordance with the ICH Q3B(R) guidance. The registration batches of Docetaxel Injection were manufactured and released by AMRI Burlington, Inc. in accordance with their release specification.
Stability data demonstrated that Docetaxel Injection is stable when stored at long term 25°C/60% RH for 18 months and intermediate (30°C/65%RH) storage conditions for 12 months. Based on stability data and ICH QIE guidelines, an *expiry of 24 months* was granted for Docetaxel Injection stored at Store at controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30 °C (59° to 86°F)."

"The manufacturing process for Docetaxel Injection consists of the following key manufacturing (b)(4)

"The applicant has provided sufficient data to demonstrate that the risks for non-sterility and excessive endotoxin have been mitigated. These data include the validation studies and controls for the [redacted](b)(4), the container closure integrity studies, and the controls for endotoxins and bioburden in the raw materials, container closure components, and finished product. The product quality microbiology review completed by Nandini Bhattacharya, Ph.D. found the microbiological information acceptable and recommended approval of the NDA from a quality microbiology standpoint."

"The status of the AMRI Burlington, Inc. site with respect to this application has been changed from OAI to VAI for PAI. All listed facilities are now currently in a state of compliance and the application is recommended for approval from a facilities assessment standpoint."

I concur with the conclusions reached by the drug product, drug product process, drug substance, microbiology, biopharmaceutics, and facilities reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months was granted for Docetaxel Injection stored at 20-25°C, with excursions permitted between 15-30°C. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

From the pharmacology/toxicology review:
"A GLP-compliant pharmacokinetic study comparing docetaxel injection and Taxotere in male Beagle dogs following an IV infusion dose of 0.75 mg/kg was conducted. Based on pharmacokinetic parameters in this study, docetaxel injection and Taxotere were determined to be comparable within a 95% confidence interval.
An in vitro, non-GLP, pharmacokinetic study comparing docetaxel protein binding to dog and human plasma between docetaxel injection and Taxotere was also submitted. Protein binding decreased in a concentration-dependent manner with both formulations (docetaxel injection vs Taxotere) over the concentration ranges evaluated (0.10-100 µg/mL). The protein binding values were similar for the two formulations in dog and human plasma.
A special toxicology study designed to assess complement activating (C3a and SC5b-9) potential of docetaxel injection compared to Taxotere in human serum at concentrations of 1 µg/mL to 100 µg/mL after 30 and 90 minute exposure times was conducted. There was no biologically significant difference in C3a mean concentrations across all time courses between docetaxel injection and Taxotere. However, mean concentrations of SC5b-9 observed with docetaxel injection were lower than Taxotere. The Applicant claims that docetaxel injection had less complement activation potential in SC5b-9 when compared to Taxotere."

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology studies were submitted. The applicant is relying on the findings of safety and effectiveness for the approved drug One-Vial Taxotere® (docetaxel) Injection, to support the approval of their product. The Office of Clinical Pharmacology/Division of

Clinical Pharmacology V has reviewed the information contained in the NDA and find it acceptable from a clinical pharmacology perspective.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

The sterilization method for Docetaxel Injection uses [redacted] (b)(4) [redacted] (b)(4) I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

No clinical information is included in this NDA application. There are no clinical issues.

8. Safety

No clinical information is included in this NDA application. There are no clinical issues.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

Refer to the final package insert. The applicant initially proposed the drug product established name as Docetaxel Injection [redacted] (b)(4) [redacted]

(b)(4). The Docetaxel Injection in this NDA is a single vial formulation, no prior dilution with a diluent and is ready to add to the infusion solution, consisting of 0.9% Sodium Chloride solution or 5% Dextrose solution to product a final concentration of 0.3 mg/mL to 0.74 mg/mL. Therefore, the word (b)(4) has been deleted from the drug product established name.

DMEPA's review of the information contained in the proposed PI find it to be identical to the LD with the exception of the unit of measurement that was missing following numerical temperature values. Review of the proposed container labels and carton labeling identified improvements which can be implemented to provide clarity from a safety perspective. The statement "Non-Alcohol Formula" competes in prominence with the established name on the container label and carton labeling, and was recommended to decrease the prominence of the statement. The statement "Cytotoxic Agent" lacks prominence, and was recommended revising the font color of this statement to red.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval.

- Risk Benefit Assessment

This NDA relies on FDA's findings of safety and efficacy for the listed drug, One-Vial Taxotere® (docetaxel) Injection. The data contained in this application was limited to Chemistry, Manufacturing, and Controls information as well as non-clinical studies. The review teams have no outstanding deficiencies and recommend approval. Based on the information provided in this application, I concur with the review team that there is a favorable benefit-risk assessment for Docetaxel Injection, (Non-Alcohol Formula).

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies: none.

- Recommendation for other Postmarketing Requirements and Commitments: none

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/s/

GEOFFREY S KIM
12/22/2015