CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205934Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 22, 2015
From	Xiao Hong Chen, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	205934
Applicant	Teikoku Pharma USA, Inc.
Date of Submission	February 26, 2015
PDUFA Goal Date	December 26, 2015
Proprietary Name / Established (USAN) names	Docetaxel
Dosage forms / Strength	20 mg/mL; 80 mg/4mL; 160 mg/8 mL
Proposed Indication(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
Recommended:	**Approval**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Product Quality; in Panorama, dated 16-Oct-2015 and 22-Dec-2015 (addendum)
  - Haripada Sarker, Ph.D. for drug substance
  - Rajiv Agarwal, Ph.D.for drug product
  - Vidya Pai, Ph.D.for drug product process
  - Wayne Seifert, Ph.D. for facility
  - Nandini Bhattacharya , Ph.D. for microbiology
  - Jing Li, Ph.D. for biopharmaceutics
- Clinical Pharmacology (Runyan Jin, Ph.D.); in DARRTS, dated 16-Oct-2015
- Pharmacology/Toxicology (Wimolnut Manheng, Ph.D.); in DARRTS, dated 22-Oct-2015
- Labeling (Nicholas J Senior, Pharm.D.); in DARRTS, dated 16-Oct-2015
- Patient Labeling (Nathan P. Caulk, Pharm.D.); in DARRTS, dated 15-Oct-2015

Background

This review is an addendum for a final overall recommendation for pre-approval inspection of this NDA. In the CDTL memo dated 16-Oct-2015, the overall recommendation for the NDA was pending due to the "Withhold" recommendation made by the District office after pre-approval and GMP inspection of the drug product manufacturing and testing facility, AMRI Burlington, Inc. (EFI: 3002951540) conducted between 8/10/2015 and 19/2015 with OAI. A compliance decision of approve has now been rendered for the AMRI Burlington Inc. site. 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. Refer to Wayne Seifert's review dated December 21, 2015 in panorama. There are no outstanding deficiencies from all review disciplines. Refer to the CDTL memo dated October 16, 2015.

Recommendation

The NDA is recommended for Approval.

Xiaohong Chen -A

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Cross-Discipline Team Leader Review

Date	October 30, 2015
From	Xiao Hong Chen, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	205934
Applicant	Teikoku Pharma USA, Inc.
Date of Submission	February 26, 2015
PDUFA Goal Date	December 26, 2015
Proprietary Name / Established (USAN) names	Docetaxel
Dosage forms / Strength	20 mg/mL; 80 mg/4mL; 160 mg/8 mL
Proposed Indication(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
Recommended:	Pending (pending an overall recommendation for facilities)

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Product Quality; in Panorama, dated 16-Oct-2015 Final recommendation pending
  - Haripada Sarker, Ph.D. for drug substance
  - Rajiv Agarwal, Ph.D.for drug product
  - Vidya Pai, Ph.D.for drug product process
  - Wayne Seifert, Ph.D. for facility Recommendation Pending
  - Nandini Bhattacharya , Ph.D. for microbiology
  - Jing Li, Ph.D. for biopharmaceutics
- Clinical Pharmacology (Runyan Jin, Ph.D.); in DARRTS, dated 16-Oct-2015
- Pharmacology/Toxicology (Wimolnut Manheng, Ph.D.); in DARRTS, dated 22-Oct-2015
- Labeling (Nicholas J Senior, Pharm.D.); in DARRTS, dated 16-Oct-2015
- Patient Labeling (Nathan P. Caulk, Pharm.D.); in DARRTS, dated 15-Oct-2015

1. Introduction

The NDA was filed as a 505(b)(2) application, using Taxotere (NDA 020449) as the listed drug (LD). The listed drug, Taxotere, was initially approved on May 14, 1996, as a 2-vial drug product with one vial for Docetaxel Injection and the other for the Diluent. The 1-vial formulation of Taxotere, which is referenced by the current application, was approved on August 2, 2010. There have been 7 approved 505 b(2) drug products that referenced Taxotere (either 1 or 2-vial formulations). None of the NDAs contains exactly the same inactive ingredients as the formulation of Taxotere, except for NDA 022534, which used the same excipients but in lower quantities.

The drug product in the current NDA is a parenteral solution for IV administration and has the same active ingredient, route of administration, dosage form, and indications as the LD, but contains different inactive ingredients. The drug product is a non-alcohol formulation of Docetaxel Injection. The applicant, Teikoku Pharma USA, Inc., has requested a waiver of the in vivo bioequivalence study, which was deemed to be acceptable.

2. Background

Docetaxel injection is proposed to be marketed in a single use vial at the following three strengths, 20 mg/mL; 80 mg/4mL; 160 mg/8 mL. The drug product does not need prior dilution before it is added to the infusion solution (either 0.9% Sodium Chloride solution or 5% Dextrose solution). The drug product is indicated for the following treatment:

Breast Cancer: single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC;
Non-Small Cell Lung Cancer: single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC;
Hormone Refractory Prostate Cancer: with prednisone in androgen independent (hormone refractory) metastatic prostate cancer;
Gastric Adenocarcinoma: with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction;
Squamous Cell Carcinoma of the Head and Neck Cancer: with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN. The appropriate amount of docetaxel may be between 0.10 mg/ml and 0.26 mg/ml administered after dilution with the infusion diluent.

This application relies on the Agency's determination of safety and efficacy for Taxotere (docetaxel injection), which was approved for marketing under NDA 020449 on 14-May-1996.

3. Chemistry, Manufacturing and Controls (CMC)

Drug Substance

Docetaxel trihydrate USP, manufactured by [redacted] is the active ingredient in Docetaxel Injection, Non-Alcohol Formula. It is a microtubule inhibitor, belonging to the taxoid family and is indicated for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, and head and neck cancer. It is manufactured by [redacted] he specification for docetaxel trihydrate complies with the USP monograph. Batch analysis data for the three exhibit batches were provided in the NDA, which conform to the specification. Three consecutive exhibit batches of docetaxel trihydrate USP manufactured at the production scale of approximately [redacted] have been placed on stability study; and sufficient stability data were submitted to support the [redacted] months retest date, which was deemed to be acceptable. Stress testing data demonstrate that the drug substance is stable under the conditions of [redacted] Complete information regarding the characterization, manufacturing and controls for docetaxel trihydrate drug substance is provided in DMF [redacted] DMF was reviewed and found to be adequate.

Drug Product

Docetaxel Injection, manufactured by Teikoku Pharma USA, is a non-alcohol formulation for IV administration. Docetaxel Injection is available in 20 mg/mL (single-dose), 80 mg/4 mL and 160 mg/8 mL multi-use vials. Each mL contains 20 mg docetaxel. The preparation and administration of Docetaxel Injection, Non-Alcohol Formula is the same as the listed drug, Taxotere®. Docetaxel Injection does not require prior dilution, it is directly diluted by injecting the drug product into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL docetaxel solution. Docetaxel diluted solution at the above concentration range is physically and chemically stable when stored at room temperature for 24 hours. The drug product (80 mg/4 mL and 160 mg/8 mL configurations) is designated for multi-use; a puncture study was performed to provide data in support of the stability and integrity of the multi-use container to prevent microbial contamination.

The container closure system consists of Type 1 clear glass vials capped with [redacted] rubber stoppers and aluminum flip-off seals. The vials are packed in the cartons as secondary packaging system, to protect from the exposure of light as docetaxel is slightly light sensitive. Due to the viscous nature of the product caused by the two major [redacted] applicant targets presentations with excess fill volumes as recommended per USP<1151> for viscous liquids. For the three strength of Docetaxel Injection, 20 mg/mL, 80 mg/mL, and 160 mg/mL that are contained in vials with three different sizes, 2 mL, 8 mL, and 19 mL, the fill volumes are [redacted] mL, [redacted] mL and [redacted] mL, respectively.

Docetaxel Injection contains the following compendial excipients, soybean oil, polysorbate 80, polyethylene glycol (PEG) 300, citric acid, [redacted]. All excipients used in the drug product formulation comply with the USP/NF compendial monographs. Note that all other 7 approved docetaxel injection drug products including the LD contain alcohol. Soybean oil serves as a [redacted] in this non-alcohol formulation. It [redacted] docetaxel [redacted] when diluted in 0.9% Sodium Chloride solution and 5% Dextrose solution for IV administration. Polysorbate 80 was chosen due to its use in all marketed docetaxel injection products. Polysorbate 80 serves as a [redacted] itric acid is used to [redacted] of the formulation.

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).

Drug Product Process

The sterilization method for Docetaxel Injection uses [redacted] due to [redacted] of docetaxel trihydrate. The manufacturing process for Docetaxel Injection consists of the following key manufacturing steps: [redacted] The manufacturing process has been appropriately validated.

4. Microbiology

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], 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.

5. Facilities Review and Inspection

An Establishment Evaluation Request (EER) was submitted to the Office of Compliance, and an overall recommendation is still pending, primarily due to "withhold" recommendation made by the District office after pre-approval and GMP inspection of the drug product manufacturing and testing facility, AMRI Burlington, Inc. (EFI: 3002951540) conducted 8/10 – 19/2015 with OAI.

6. Biopharmaceutics

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.

7. Nonclinical Pharmacology/Toxicology

TPU relied upon the FDA's previous findings of safety and effectiveness for Taxotere as reflected in the drug's approved labeling. The Applicant was not required to perform any animal toxicology studies in support of the NDA submission for docetaxel injection. However, the Applicant included reports a GLP-compliant single-dose pharmacokinetic (PK) study comparing docetaxel injection and Taxotere in male Beagle dogs. Based on pharmacokinetic parameters in this study, docetaxel injection and Taxotere were determined to be comparable within a 95% confidence interval. The applicant also submitted reports from a non-GLP PK study comparing docetaxel protein binding in dogs and human plasma suing both docetaxel and LE. The results showed that the protein binding values were similar for the two formulations in dog and human plasma. In addition, a GLP in vitro complement activation study in human serum, comparing their product to Taxotere has been performed. No biologically significant difference was observed in C3a mean concentrations across all time courses between docetaxel injection and Taxotere although results of this in vitro assay suggest docetaxel injection may result in less complement activation compared to Taxotere. From the Pharmacology/Toxicology perspective, docetaxel injection was recommended for approval.

8. Clinical Pharmacology

No clinical study or clinical pharmacology study are included in this application. 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. Based on the information provided in NDA 205934/SDN 5, the Office of Clinical Pharmacology/Division of Clinical Pharmacology V has found the NDA is acceptable from a clinical pharmacology perspective.

9. Clinical/Statistical- Efficacy

This application is submitted as a 505(b)(2) NDA relying on previous determination of efficacy and safety of LD, Taxotere, for its labeled indications. No clinical information has been included in the NDA. No clinical Review was done for this NDA.

10. Safety

11. Not applicable.

12. Advisory Committee Meeting

13. Not applicable.

14. Pediatrics

15. Not applicable.

16. Other Relevant Regulatory Issues

Not applicable.

17. Labeling

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.

18. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

A final recommendation for the NDA cannot be made at this time due to the pending overall recommendation for the pre-approval and GMP inspection of the manufacturing facilities involved in this application.

- **Risk Benefit Assessment**

The review of this NDA is based primarily on chemistry, manufacturing and controls and clinical pharmacology/biopharmaceutics data. All reviews recommended "approval" except CMC review that is still pending a final recommendation due to the pending recommendation from the review of the drug product manufacturing and testing facility AMRI.

- **Recommendation for Postmarketing Risk Management Activities**

Not applicable.

- **Recommendation for other Postmarketing Study Commitments**

None

- **Recommended Comments to Applicant**

None

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