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APPLICATION NUMBER:

211875Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	211875
Supporting document/s:	17
Applicant's letter date:	April 23, 2020
CDER stamp date:	April 24, 2020
Product:	Paclitaxel Protein-Bound Particles for Injectable Suspension
Indication:	Metastatic breast cancer
Applicant:	HBT Labs, Inc.
Review Division:	Division of Hematology Oncology Toxicology (for Division of Oncology 1)
Reviewer:	Wei Chen, PhD
Supervisor/Team Leader:	Tiffany Ricks, PhD
Division Director:	John Leighton, PhD, DABT (Laleh Amiri Kordestani, MD)
Project Manager:	Jessica Kim

Comments and recommendations

NDA 211875 was originally submitted on August 29, 2018. The applicant provided this resubmission to address the deficiencies listed in the Complete Response Letter (CRL) to the original submission, dated 06/14/2019. No nonclinical deficiencies were identified in the original NDA submission, and the applicant did not submit additional nonclinical study reports. The applicant stated that the NDA relies on FDA's previous findings of safety and publicly available information on nonclinical properties of Taxol and Abraxane to support this NDA. The reliance on Taxol was not necessary for approval. Labeling changes in the nonclinical sections were made to comply with the content and formatting of the Pregnancy and Lactation Labeling Rule (PLLR) and to be consistent with the label for Abraxane. For final agreed upon changes to the Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) label, refer to the approved package insert.

This application is recommended for approval by the Pharmacology/Toxicology discipline.

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/s/

WEI CHEN
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 211875
Supporting document/s:	0001
Sponsor's letter date:	August 29, 2018
CDER stamp date:	August 29, 2018
Product:	Paclitaxel Protein-Bound Particles for Injectable suspension
Indication:	Metastatic breast cancer
Applicant:	HBT LABS INC
Review Division:	Division of Hematology Oncology Toxicology (for Division of Hematology Products)
Reviewer:	Wei Chen, PhD
Supervisor/Team Leader:	Tiffany Ricks, PhD
Division Director:	John Leighton, PhD, DABT (Julia Beaver, MD)
Project Manager:	Mitchell Chan, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 211875 are owned by HBT LABS INC or are data for HBT LABS INC has obtained a written right of reference. Any information or data necessary for approval of NDA 211875 that HBT 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 reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 211875.

Introduction

This NDA was submitted under the 505(b)(2) regulatory pathway for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), supplied as a lyophilized powder of 100 mg paclitaxel formulated as albumin-bound particles in a single-dose vial for reconstitution. The proposed drug product and Abraxane are the same with respect to the active ingredient, dosage form, route of administration, strength and use indications. The only difference is that the proposed drug product formulation includes sodium hydroxide and hydrochloric acid for pH adjustment. Abraxane was approved via the 505(b)(2) regulatory pathway using Taxol as the listed drug. This application also uses Taxol (NDA 20262) as the listed drug. The applicant is relying on FDA's previous findings of safety and publically available information on nonclinical properties of Taxol and Abraxane to support this NDA. No additional nonclinical pharmacology/toxicology data on paclitaxel were submitted with this application or warranted to support the approval of the application.

The CMC review team requested a Pharmacology/Toxicology consult on the acceptability of the toxicological evaluation and risk assessment on extractables/leachables submitted with this application.

Study submitted and reviewed:

1) Evaluation of three extractables-paclitaxel injectable suspension drug product
2) Evaluation of two extractables (b) (4) - paclitaxel injectable suspension drug product

Integrated Summary and Safety Evaluation:

Three extractables were detected above the analytical evaluation threshold (AET) of (b) (4) µg/mL in the conducted extractable studies for several components used in (b) (4) delivery of the paclitaxel suspension (b) (4). Two leachables were detected above the AET of (b) (4) µg/mL in the bag. The names and estimated concentrations of these extractables/leachables detected above AET were provided in the tables below (copied from the Applicant's submission)

Summary of Organic Extractables Detected Above the AET ((b) (4) µg/mL)

Chemical	CAS Registry Number	Estimated Concentration (µg/mL)
(b) (4)		

Summary of Organic Extractables Detected Above the AET ((b) (4) µg/mL)

Chemical	CAS Registry Number	Estimated Concentration (µg/mL)
(b) (4)		

The default AETs of (b) (4) µg/mL and (b) (4) µg/mL were calculated based on 120 µg/day outlined in ICH M7 for a single mutagenic impurity with dosing duration of one month or less. The proposed drug product is indicated for advanced cancer, and paclitaxel, the active ingredient of the proposed drug product, is genotoxic; therefore, ICH M7 guidance does not apply to the proposed drug product, and the daily exposures to impurities in the proposed drug product are not required to be controlled under 120 µg/day. The toxicological evaluation and risk assessment on these extractables detected above the AET was prepared (b) (4), and mainly based on the information in toxicology databases from FDA, USEPA, Joint FAO/ WHO/ JECFA, International Agency for Research on Cancer (IARC), OECD, and the European and the European Chemicals Agency (ECHA). The published toxicology data indicated that Safety Concern Threshold (SCT) (b) (4) µg/day, SCTs of (b) (4) µg/day, and the permitted daily exposures (PDEs) (b) (4) µg/day. The Applicant concluded that the SCTs and the PDEs based on the published nonclinical data provide sufficient safety margins for the detectable extractables at the estimated concentrations shown in the tables above. The cited SCTs and PDEs used for qualifying these extractables/leachables were verified by the review; the provided risk assessment conclusion is considered appropriate based on the available nonclinical data.

Overall, given the published toxicologic data on the listed 5 extractables, the genotoxic feature and proposed indication of the proposed drug product, there are no safety concerns for these 5 extractables at the estimated concentrations from the Pharmacology/toxicology perspective. The nonclinical recommendation for this application is approval.

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/s/

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