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APPLICATION NUMBER:

211875Orig1s000

CLINICAL REVIEW(S)

NDA Clinical Review
505(b)2 Resubmission

NDA #	211875
Pathway submitted	505(b)(2) resubmission after Complete Response
Resubmission Date	02/07/2022
Product	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)
Therapeutic Class	Cytotoxic antineoplastic (taxane)
Cross-Referenced NDA(s)	NDA 021660 (Abraxane), NDA 020262 (Taxol)
Proposed Indications	1. Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. 2. Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. 3. Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine.
Sponsor	HBT Labs Inc.
CDTL	Christy Osgood
Division Director	Laleh Amiri-Kordestani

1 SUMMARY OF APPLICATION

HBT Labs Inc. (HBT) has submitted an amendment to NDA 211875 following the June 30, 2021, tentative approval letter. Approval of the NDA could not be granted at that time because the application is subject to expiration of a period of patent protection and/or exclusivity. Therefore, final approval of the application could not be granted before the period has expired. In this amendment, HBT requested final approval based on entrance into a license agreement with Abraxis, the patent/exclusivity holder, which provides to HBT the following:

(1) a non-exclusive, fully paid up, royalty-free license under the Licensed Patents to Manufacture the HBT NDA Product solely to be Marketed in the Territory;"

(2) "a non-exclusive, fully paid up, royalty-free license under the Licensed Patents to Market the HBT NDA Product solely in the Territory."

(3) The "Launch Date" is defined to be no later than September 27, 2022 and may be earlier under certain circumstances.

(4) Abraxis agreed to "a waiver of any regulatory exclusivities necessary to effectuate the foregoing license with respect to the HBT NDA Product."

This agreement was reviewed by the 505(b)2 committee which determined that all patent and exclusivity had been addressed and recommended full approval. Please see 505(b)2 assessment dated July 5, 2022 for details.

Additionally, the current amendment contains minor CMC changes, which has been reviewed by the product quality team and found acceptable. Please see full review IQA review for details.

The original NDA submission was a 505(b)(2) application for their product "Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)"

The original 505(b)(2) application referenced the findings, safety and effectiveness for Abraxane (NDA 021660) as well as referenced published literature for Taxol (NDA 020262) as the Abraxane application was approved via the 505(b)(2) pathway using Taxol as the reference drug (See Table 1). The applicant has submitted a bioequivalence (BE) study (HBT001-BE-01) to demonstrate that the proposed drug product is bioequivalent to Abraxane. Refer to the clinical review memo dated May 15, 2019 in DARRTs for the review of safety data from the BE study.

2 Clinical Label Changes

No clinical labeling changes made during this amendment.

Indications in label:

- Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
- Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
- Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine.

The sponsor label for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) was revised to align with the recent updated changes in the reference drug Abraxane label. All references to the drug in studies originally performed with Abraxane in clinical Sections 5, 6, 8.5, and 14 were revised to "protein bound paclitaxel' to avoid confusion with the sponsor's product name.

Recommendation: Overall, this 505(b)(2) NDA amendment included a licensing agreement with the patent owner and the owner provided a written statement that it did not object to FDA's full approval of the 505(b)(2) application. Therefore, from a clinical perspective the recommendation for this application is approval.

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/s/

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NDA Clinical Review
505(b)2 Resubmission

NDA #	211875
Pathway submitted	505(b)(2) resubmission after Complete Response
Resubmission Date	04/24/2020
Product	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)
Therapeutic Class	Cytotoxic antineoplastic (taxane)
Cross-Referenced NDA(s)	NDA 021660 (Abraxane), NDA 020262 (Taxol)
Proposed Indications	1. Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. 2. Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. 3. Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine.
Sponsor	HBT Labs Inc.
Primary Reviewer	Preeti Narayan
Clinical Team Leader	Christy Osgood
CDTL	Xiao Hong Chen

1 SUMMARY OF APPLICATION

HBT Labs Inc. (HBT) has submitted a resubmission to NDA 211875 addressing the deficiencies that were identified in the Complete Response (CR) letter dated June 14, 2019 to their original NDA submission. The original NDA submission was a 505(b)(2) application for their product "Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)" for the indication:

Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

In the resubmission, HBT submitted additional data regarding specific CMC deficiencies that were outlined in the CR letter (these are addressed in the CMC review and CDTL review dated June 14, 2019 in DARRTS). No new clinical data was included with this resubmission. The original 505(b)(2) application referenced the findings, safety and effectiveness for Abraxane (NDA 021660) as well as referenced published literature for Taxol (NDA 020262) as the Abraxane application was approved via the 505(b)(2) pathway using Taxol as the reference drug (See Table 1). The applicant has submitted a bioequivalence

(BE) study (HBT001-BE-01) to demonstrate that the proposed drug product is bioequivalent to Abraxane. Refer to the clinical review memo dated May 15, 2019 in DARRTs for the review of safety data from the BE study. In the original review, no new safety signals were noted.

Table 1: Reference information provided by the applicant

Source of Information	Information Provided [specific sections of draft labeling text (1.14.1.3)]
NDA 021660 (Abraxane)	Previous finding of safety and effectiveness for metastatic breast cancer (labeling sections 1, 2, 4, 5, 6, 7, 8, 10, 12, 13, 14, 17)
NDA 020262 (Taxol)	Previous finding of safety with respect to: • Postmarketing experience (labeling section 6.2) • Accidental exposure (labeling section 6.3)
Published literature (Taxol)[1]	• Mechanism of Action (labeling section 12.1) • Metabolism (labeling section 12.3) • Carcinogenesis, Mutagenesis, Impairment of Fertility (labeling section 13.1)
Published literature (Abraxane)[2]	Pharmacokinetics in Hepatic Impairment, Renal Impairment and Population pharmacokinetic analyses (labeling section 12.3)

[1] Refer to 2.4.6 for a list of published literature and 4.3 for copies of published literature.
[2] Refer to 2.5.7 for a list of published literature and 5.4 for a copy of published literature.

2 Clinical Label Changes

The annotated label included in the resubmission by the sponsor now includes all the current indications for Abraxane. Previously the sponsor had only included the breast cancer indication and carved out the indications for non-small cell lung cancer and adenocarcinoma of the pancreas.

Indications in label:

- Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
- Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
- Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine.

The sponsor label for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) was revised to align with the recent updated changes in the reference drug Abraxane label. All references to the drug in studies originally performed with Abraxane in clinical Sections 5, 6, 8.5, and 14 were revised to “protein bound paclitaxel’ to avoid confusion with the sponsor’s product name.

Recommendation: Overall, this 505(b)(2) NDA resubmission references the findings, safety and effectiveness for Abraxane as well as referenced published literature for Taxol. The BE study did not reveal any new safety signals. The information provided by HBT describing Taxol was not necessary for approval from a clinical perspective and relied only on the information provided for Abraxane.

No new clinical data was included with the resubmission. Therefore, from a clinical perspective the recommendation for this application is approval.

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/s/

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06/29/2021 02:19:49 PM

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06/29/2021 02:22:06 PM

NDA #	211875
Pathway submitted	505(b)(2)
Submit Date	08/29/18
Product	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)
Therapeutic Class	Cytotoxic antineoplastic (taxane)
Cross-Referenced NDA(s)	NDA 021660 (Abraxane), NDA 020262 (Taxol)
Proposed Indication	Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
Sponsor	HBT Labs Inc.
Primary Reviewer	Preeti Narayan, M.D.
Secondary Reviewer	Jennifer Gao, M.D.

1 SUMMARY OF APPLICATION

HBT Labs Inc. has submitted a 505(b)(2) application for their product "Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)" for the indication:

> *Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.*

This 505 (b)(2) application references the findings, safety and effectiveness for Abraxane (NDA 021660) as well as referenced published literature for Taxol (NDA 020262) as the Abraxane application was approved via the 505(b)(2) pathway using Taxol as the reference drug (See Table 1).

Table 1: Reference information provided by the applicant

Source of Information	Information Provided [specific sections of draft labeling text (1.14.1.3)]
NDA 021660 (Abraxane)	Previous finding of safety and effectiveness for metastatic breast cancer (labeling sections 1, 2, 4, 5, 6, 7, 8, 10, 12, 13, 14, 17)
NDA 020262 (Taxol)	Previous finding of safety with respect to: • Postmarketing experience (labeling section 6.2) • Accidental exposure (labeling section 6.3)
Published literature (Taxol)[1]	• Mechanism of Action (labeling section 12.1) • Metabolism (labeling section 12.3) • Carcinogenesis, Mutagenesis, Impairment of Fertility (labeling section 13.1)
Published literature (Abraxane)[2]	Pharmacokinetics in Hepatic Impairment, Renal Impairment and Population pharmacokinetic analyses (labeling section 12.3)

[1] Refer to 2.4.6 for a list of published literature and 4.3 for copies of published literature.
[2] Refer to 2.5.7 for a list of published literature and 5.4 for a copy of published literature.

As per the applicant in their submission cover letter "HBT's proposed drug product and Abraxane are the same with respect to active ingredient, dosage form, route of administration, strength, and previously approved conditions of use." The applicant has submitted a bioequivalence (BE) study (HBT001-BE-01) to demonstrate that the proposed drug product is bioequivalent to Abraxane. The applicant notes that the proposed drug product formulation includes sodium hydroxide (NaOH) and hydrochloric acid (HCl) for pH adjustment which are not in the Abraxane labeling. No other clinical studies for this NDA were submitted.

The annotated label compared with the reference drug (Abraxane) provided by the applicant has no changes for metastatic breast cancer. The draft label has carved out the indications for non-small cell lung cancer (NSCLC) and metastatic adenocarcinoma of the pancreas when compared to the Abraxane label.

2 CLINICAL REVIEW OF SAFETY IN BIOEQUIVALENCE STUDY

Bioequivalence (BE) study HBT001-BE-01 was a phase 1, multicenter, randomized, open-label, 2-period, 2-sequence, crossover, 2-stage group sequential design study assessing the BE of a single dose of HBT001 versus Abraxane in patients with breast cancer. Study treatments were administered as a single 260 mg/m2 intravenous (IV) dose in approximately 3-week cycles. Period 1 in Cycle 1 (Period 1 and washout period) and Period 2 in Cycle 2 (Period 2 and follow-up period) evaluated the PK of paclitaxel following dosing with HBT001 or Abraxane. There was a minimum of 3- and up to 5-week washout interval between doses in each period. Following the successful completion of Periods 1 and 2, patients could have been eligible for up to 4 additional cycles of treatment with Abraxane in the extension phase of the study (up to a total of 6 chemotherapy cycles). The safety population in HBT001-BE-01 included all patients who received at least 1 dose (full or partial) of study drug (Cycles 1 or 2 only). The data cutoff was at the end of Cycle 2 (Cycle 2 Day 28).

The clinical study report (CSR) prepared by the applicant was reviewed. Twenty-two patients received a single IV infusion of Abraxane, and 21 of these patients also received a single IV infusion of HBT001.

No deaths occurred during the study. No severe adverse events (SAEs) were reported. Two treatment-emergent adverse events (TEAEs) leading to study drug discontinuation were reported during the study.

- Patient (b) (6) experienced Grade 3 fatigue (related) 17 days after receiving Cycle 1 (Abraxane) and was withdrawn from the study before cycle 2.
- Patient (b) (6) experienced Grade 3 blood alkaline phosphatase increased (not related) beginning on Day (b) (6) (27 days after receiving Abraxane in Cycle 5) and was withdrawn from the study.

Both fatigue and elevated blood alkaline phosphatase are known AEs of Abraxane. Table 2 lists the TEAEs from the safety population in the BE Study.

Table 2: TEAEs (Safety Population)

Body System / Adverse Event	Reported Incidence by Treatment Groups Study No. HBT001-BE-01 HBT001 (N = 21) n (%)	 ABRAXANE (N = 22) n (%)
Musculoskeletal and connective tissue disorders	21 (100.0)	19 (86.4)
Bone pain	9 (42.9)	7 (31.8)
Back pain	7 (33.3)	7 (31.8)
Myalgia	4 (19.0)	5 (22.7)
Musculoskeletal chest pain	1 (4.8)	0
Musculoskeletal pain	1 (4.8)	0
Investigations	14 (66.7)	14 (63.6)
Neutrophil count decreased	12 (57.1)	11 (50.0)
White blood cell count decreased	12 (57.1)	11 (50.0)
Alanine aminotransferase increased	6 (28.6)	3 (13.6)
Aspartate aminotransferase increased	4 (19.0)	1 (4.5)
Gamma-glutamyltransferase increased	1 (4.8)	2 (9.1)
Blood bilirubin increased	1 (4.8)	1 (4.5)
Blood creatine phosphokinase increased	1 (4.8)	0
Lymphocyte count decreased	1 (4.8)	0
Platelet count decreased	1 (4.8)	1 (4.5)
Urobilinogen urine increased	1 (4.8)	0
Blood and lymphatic system disorders	10 (47.6)	11 (50.0)
Neutropenia	9 (42.9)	10 (45.5)
Anaemia	2 (9.5)	4 (18.2)
Leukopenia	1 (4.8)	1 (4.5)
Febrile neutropenia	0	1 (4.5)
Hypercoagulation	0	1 (4.5)
Skin and subcutaneous tissue disorders	5 (23.8)	6 (27.3)
Alopecia	5 (23.8)	6 (27.3)

Body System / Adverse Event	Reported Incidence by Treatment Groups Study No. HBT001-BE-01 HBT001 (N = 21) n (%)	 ABRAXANE (N = 22) n (%)
Gastrointestinal disorders	4 (19.0)	4 (18.2)
Diarrhoea	1 (4.8)	2 (9.1)
Nausea	3 (14.3)	2 (9.1)
Gastritis	1 (4.8)	0
Stomatitis	0	1 (4.5)
General disorders and administration site conditions	0	1 (4.5)
Fatigue	0	1 (4.5)
Infections and infestations	0	1 (4.5)
Cystitis	0	1 (4.5)
Nervous system disorders	1 (4.8)	0
Peripheral sensory neuropathy	1 (4.8)	0
Total	21 (100.0)	22 (100.0)

Abbreviations: n, number of subjects; TEAE, treatment-emergent adverse event.
Note: Subjects may have had more than 1 TEAE per body system and preferred term. At each level of subject summarization, a subject was counted once if the subject reported 1 or more events. TEAEs were summarized by treatment at onset of the event. Adverse events were coded using MedDRA Version 19.1. Percentages were based on the number of subjects in the safety population within each treatment.
Source: CSR, End-of-Text Table 14.3.1.2.

Recommendation: Overall, this 505(b)(2) NDA application references the findings, safety and effectiveness for Abraxane as well as referenced published literature for Taxol, and the BE study did not reveal any new safety signals. Therefore, from a clinical perspective the recommendation for this application is approval.

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