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RESEARCH**

APPLICATION NUMBER:

218711Orig1s000

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 ASSESSMENT AND EVALUATION

Application Number*: 218711 (IND-146359)

Supporting Document Number/s: 1

CDER Receipt Date: October 6, 2023

Sponsor: Zhuhai Beihai Biotech Co., Ltd.
Bldg. 2, No. 6366, Zhuhai Ave.
Jinwan, Zhuhai, 519090, PRC

Product: Beizray [Docetaxel Injection (Albumin solubilized), 80 mg/4 mL]

Pharmacologic Class: Microtubule inhibitor

Indication: Locally advanced or metastatic breast cancer, non-small cell lung cancer, castration-resistant prostate cancer, gastric cancer, and squamous cell carcinoma of head and neck

Therapeutic area: Oncology

Clinical Review Division: Division of Oncology I (DO I)

Pharm/Tox Division: Division of Hematology Oncology
Toxicology (DHOT)

Reviewer: C.J. George Chang, DVM, MS, PhD, DABT

Supervisor/Team Leader: Tiffany Ricks, PhD

Project Manager: Christal W. Lee, RPM

Reviewer Completion Date: September 12, 2024

Background

Zhuhai Beihai Biotech Co., Ltd. (Zhuhai, the applicant) submitted on October 6, 2023, NDA-218711 through the 505(b)(2) regulatory pathway for Beizray [BH009, Docetaxel Injection (Albumin solubilized), 80 mg/4 mL] for the treatment of patients with locally advanced or metastatic breast cancer, non-small cell lung cancer, castration-resistant prostate cancer, gastric cancer, and squamous cell carcinoma of head and neck. Beizray is an injection solution drug product (DP) of docetaxel where the DP solution contains 97.466% dehydrated alcohol (absolute ethanol). Each Beizray kit contains 2 single-dose vials of 80 mg/4 mL docetaxel and one vial of a solubilizer (50 mL, 25% human albumin solution). The recommended dosing regimen for Beizray is up to 100 mg/m² administered intravenously (IV) once every 3 weeks. The applicant selected the listed drug, Taxotere, for reliance on FDA's previous findings of safety and efficacy. Beizray differs from Taxotere in that the drug product does not contain polysorbate 80, has a higher amount of ethanol, and uses human albumin as a solubilizer (Tables 1 and 2).

Table 1 Formulation Comparison between Beizray (BH009) and Taxotere

Component	BH009 DP (80 mg/4 mL)	Taxotere® (80 mg/4 mL)
Docetaxel	80 mg	80 mg
Polysorbate 80	N/A	2160 mg
Dehydrated Alcohol	(b) (4) mg	1580 mg
Citric Acid Anhydrous	As needed	As needed

(Excerpted from the applicant's submission)

Table 2 Clinical Infusion Solution Composition Comparison between Beizray (BH009) and Taxotere

Component	BH009	Taxotere®
Docetaxel Concentration	0.14-0.31 mg/mL	0.3 - 0.74 mg/mL
Ethanol Concentration (v/v)	0.7%-1.6%	0.75% - 1.85%
Albumin Concentration (w/v)	1.1%-2.3%	N/A
Polysorbate 80 Concentration	N/A	8.1 - 20 mg/mL

Note: N/A = Not Applicable.

(Excerpted from the applicant's submission)

Pharmacology/Toxicology Review

Nonclinical Comparative Pharmacokinetic (PK) Study in Rats

In a non-GLP single-dose comparative PK study in Sprague-Dawley rats, no early mortalities and clinical signs of toxicity were noted after male and female rats were administered BH009 or Taxotere at 5 mg/kg through IV drip (in 10 min). The sex-combined ratio for docetaxel C_{max} between BH009 and Taxotere dose groups was 86.3%, after a single IV dose. The sex combined ratios for docetaxel AUC_{0-last} and AUC_{0-inf} between BH009 and Taxotere dose groups were 80.2% and 80.6%, respectively. (Table 3 and Figure 1)

Table 3 Pharmacokinetic Parameters of Systemic Exposure to Docetaxel in Rats Administered a Single IV Dose of 5 mg/kg BH009 or Taxotere

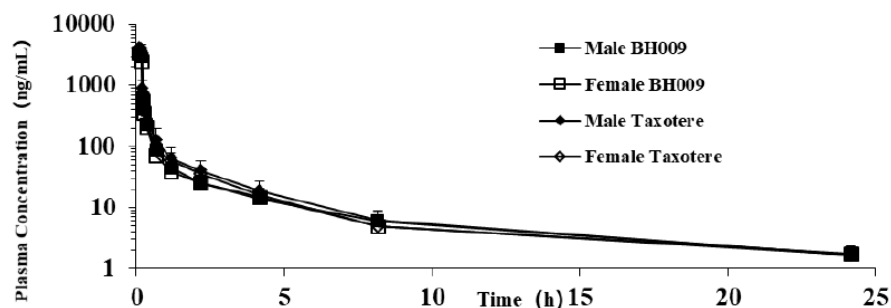
Group	1		2	
Dosing Test Article	BH009		Taxotere	
Route	Slow IV Injection		Slow IV Injection	
Dose (mg/kg)	5.00		5.00	
PK Parameter	Mean	SD	Mean	SD
C _{max} (ng/mL)	3450	537	4000	668
T _{max} (h)	0.0903	0.0242	0.111	0.0412
T _{1/2} (h)	6.10	1.01	5.15	1.45
V _{d,ss} (L/kg)	15.8	3.35	10.2	3.11
CL(mL/min/kg)	115	16.0	94.6	18.5
AUC _{0-last} (h•ng/mL)	723	129	902	200
AUC _{0-inf} (h•ng/mL)	738	132	916	199
AUC _{0-last} /Dose (h.kg.ng/mL/mg)	145	25.8	180	40.0
AUC _{0-inf} /Dose (h.kg.ng/mL/mg)	148	26.4	183	39.8
Bioavailability (%) ^a	80.6	--	--	--

--: Not applicable due to less than 3 quantifiable values

a: Bioavailability (%) was calculated with mean AUC_{0-inf} and nominal administered dose of docetaxel.

(Excerpted from the applicant's submission)

Figure 1 Plasma Concentration-Time Profiles of Docetaxel in Rats Administered a Single IV Dose of 5 mg/kg BH009 or Taxotere



(Excerpted from the applicant's submission)

Ethanol Content in Beizray (BH009)

The amount of ethanol present in BH009 is twice the amount in Taxotere.

Following administration of a maximum dose of 200 mg BH009, the predicted end-of-infusion blood ethanol concentration in humans is about 19 mg/dL and less than 100 mg/dL, which is known to result in impairment of motor function, including altered perception, ataxia, impaired judgment, lack of coordination, mood, personality, behavioral changes, nystagmus, prolonged reaction time, and slurred speech. For existing docetaxel products with alcohol, including Taxotere, product labeling includes a warning and precaution that the alcohol content within the drug products may affect the CNS and impact on the ability to drive or use machines

immediately after the therapy. The Beizray label includes the same information in the warnings and precautions section.

Extractable and Leachable Studies

– Sequential System Compatibility and Safety Assessments

The applicant conducted extractable and full-scan leachable studies on the following components:

- Manufacturing (b) (4)
- Administration devices (infusion bag, syringe, and infusion set)
- Container closure systems (CCS; transparent tubing (b) (4) glass vial (b) (4) rubber stopper/combined aluminum-plastic cap)

Summary of the General Extractable and Full-Scan Leachable Processes:

1. Conducted the extractable study of each of the empty systems (b) (4) administration device, and CCS) with various types of harsh extraction solvents;
2. Analyzed and quantified extracted solutions for the concentrations of individual elements, organic compounds, and special organic compounds with analytical instrumentations following USP compendial methods;
3. Compared the concentration of each identified element or compound with its associated analytical evaluation threshold (AET);
4. If above the specific AET, estimated the permissible daily exposure (PDE) using available toxicology or surrogate data for that element or organic compound, determined the limit value, and assessed the margin of safety (MOS) for each element or organic compound.
(If MOS <1.0, selected into leachable study; if MOS >1.0, did not run a leachable study.)
5. Identify and measure in the extraction studies of special-interest, highly carcinogenic chemicals including (b) (4)
(b) (4)
(b) (4) – As none of those organic compounds was detected, no further toxicology assessment for those compounds is needed.
6. Conducted a full-scan leachable study using 2-3 stability-validation batches of Beizray to assess the leachability of identified element (e.g. (b) (4) or organic compounds at release (0 month), simulated Beizray sample in accelerated conditions (equivalent to 6 months of storage), and long-term stability samples at 6 months, 12 months, and 24 months of storage.

Determination of Analytical Evaluation Thresholds (AETs):

1. For elements extracted from all systems evaluated:

$$(b) (4) \% \text{ Limit } (\mu\text{g/vial}) = \text{PDE } (\mu\text{g/day}) \div \text{MDI } (\text{vial/day}) \times (1-50\% \text{ uncertainty})$$

2. For organic compounds extracted from the manufacturing (b) (4)

(b) (4)

$$\text{Component AET } (\mu\text{g/mL}) = \frac{\text{SCT} \times \text{Minimum batch} \times \text{Extraction Area}}{\text{Maximum daily volume} \times \text{Total Contact Area} \times \text{Extraction Solvent Volume}} \times 50\%$$

3. For organic compounds extracted from the administration device:

(b) (4)

4. For organic compounds extracted from the container closure system:

$$\text{AET } (\mu\text{g/vial}) = \frac{\text{SCT } (\mu\text{g/day})}{\text{MDI } (\text{vial/day})} \times 50\% = \frac{(b) (4) \mu\text{g/day}}{\text{vial/day}} \times 50\% = (b) (4) \mu\text{g/vial}$$

SCT: Safety Concern Threshold (use 1.5 $\mu\text{g/day}$ recommended by the Product Quality Research Institute (PQRI); to calculate Analytical Evaluation Threshold (AET)

MDI: Maximum Daily Intake = (b) (4)

Limit value ($\mu\text{g/vial}$) = PDE ($\mu\text{g/day}$) / MDI (vial/day)

PDE is chemical species-specific

MOS= Limit value ($\mu\text{g/vial}$) / maximum measured concentration of chemical species ($\mu\text{g/vial}$)

A) Manufacturing (b) (4)

The identified leachable organic components above the AET from the (b) (4)

(b) (4)

(b) (4). The applicant conducted a toxicology risk assessment for those identified organic extractables above the AET; all calculated MOS values were >1 (Tables 4, 5, 6 and 9).

No elements, including (b) (4) exceeded the acceptable criteria for (b) (4) and no further toxicological assessment was required in terms of element extraction results.

The extraction study used pH 2.5 buffer and pH 10 buffer as extraction solvents for element extraction. [Note: (b) (4) was assessed and noted above its AET in a full-scan leachable study testing Beizray drug product and batches of stability validation batches of Beizray (all containing 97.466% dehydrated alcohol) for (b) (4) and a toxicology assessment was conducted for (b) (4)]

(b) (4) and special interest organic compounds including (b) (4) were not detected in the extractable study, so a leachable study for them was not conducted.

Table 4 MOS Values for Organic Compounds with Extractable Concentrations above the AET in Beizray (b) (4)

Name	CAS	Maximum Extraction Result (µg/cm ²)	PDE (µg/day)	Limit (µg/cm ²)	MOS	Whether as a Target
(b) (4)						NO
(b) (4)						NO
(b) (4)						NO

(Excerpted from the applicant's submission)

Table 5 Extractable Results and Related Toxicological Assessment Results for (b) (4) **(as a Semi-volatile Organic Compound) in Beizray** (b) (4)

Substance Name	* PDE (µg/day)	(b) (4) % PDE (µg/day)	Maximum Extracted Concentration (µg/mL)	Maximum Daily Intake (µg/day)	Below (b) (4) % PDE
(b) (4)					YES

Maximal daily intake of (b) (4) is (b) (4) µg/day and from (b) (4) is (b) (4) µg/day; (b) (4) µg/day is used to assess the toxicology assessment for (b) (4)

(Excerpted from the applicant's submission)

Table 6 Extractable Results and Related Toxicological Assessment Results for (b) (4) **(as a Volatile Organic Compound) in Beizray** (b) (4)

Extractable Name	CAS Number	* PDE (µg/Day)	(b) (4) % PDE (µg/day)	Daily Maximum Intake (µg/Day)	Below (b) (4) % PDE
(b) (4)					YES

(Excerpted from the applicant's submission)

A full-scan leachable study using Beizray drug product solution and Beizray stability validation batches (all containing 97.466% of dehydrated alcohol) showed element (b) (4) in (b) (4) (b) (4) (up to (b) (4) µg/mL) and (b) (4) (up to (b) (4) µg/mL) was the only element above its AET (b) (4) µg/mL for (b) (4) and (b) (4) µg/mL for (b) (4), and toxicology assessment showed (b) (4) is below the acceptable criteria (b) (4) % PDE (Table 7 and 9).

Table 7 Toxicological Assessment Results for Elements (b) (4) **in Full-Scan Leachable Study Using Beizray Stability Batches**

Element	PDE (µg/day)	Acceptable Criteria: (b) (4) % PDE (µg/day)	Maximum Daily Intake (µg/day)	Below (b) (4) % PDE
(b) (4)				YES

Maximal daily intake of (b) (4) from (b) (4) is (b) (4) µg/day and from (b) (4) is (b) (4) µg/day; (b) (4) µg/day is used to assess the toxicology assessment for (b) (4)

(Excerpted from the applicant's submission)

B) Administration Device

The components of the drug administration device for Beizray include Infusion bag, Syringe, and Infusion set.

The toxicology risk assessment for identified extractables above the analytical evaluation threshold (AET) was conducted. Identified extractable components above the AET included

(b) (4) from the administration device. See Table 8 and 9 below for the MOS and PDE values for those organic compounds.

The extractables are acceptable from the pharmacology/toxicology perspective based on the PDE determination and MOS calculation.

Table 8 MOS of Organic Compounds with Concentrations above AET (b) (4) µg/set) in Beizray Administration Device

Compound	CAS	Maximum Extraction Result (µg/set)	PDE/TTC (µg/day)	Limit (µg/set)	MOS
(b) (4)					

(Excerpted from the applicant's submission)

Table 9 Data Sources for Organic Compounds of Interest in Establishing PDE for the Administration Device of Beizray DP

Compound (CAS No.)	PDE/TTC (µg/day)	Nonclinical Study data	Data Source
(b) (4)			
		A 90-day oral daily dosing toxicology study in rats (NOAEL of (b) (4) mg/kg/day)	(b) (4)
		A 2-year oral daily dosing toxicology study in rats	
		(NOAEL: (b) (4))	

	mg/kg/day	
(b) (4)	A long-term oral daily dosing study in humans (PNEC ≥ (b) (4) mg/kg food)	(b) (4)
	Oral toxicity in rats NOAEL: (b) (4) mg/kg/day	
	Permissible exposure limits (PEL): (b) (4) µg/m ³	
	A 2-year oral daily dosing toxicology study in rats (NOAEL: (b) (4) mg/kg/day)	
	Toxtree search results	
	Toxtree search results	

TTC: Threshold of toxicology concern

C) Container Closure System (CCS)

Three components of the container closure system of Beizray are transparent tubing (b) (4) glass vial (b) (4) 10 mL size), (b) (4) rubber stopper, and combined aluminum-plastic cap.

No elements or special concern organic compounds (including (b) (4)) were noted with concentrations above the AET in the full-scan leachable study for Beizray CCS. The applicant identified 22 organic compounds with maximal concentrations above the AET

(b) (4) $\mu\text{g}/\text{vial}$ based on $1.5 \mu\text{g}/\text{day}$ SCT) from the full-scan leachable study for the CCS on 3 Beizray stability-validation batches and provided a toxicological assessment for those 22 organic compounds. The summary table (Table 10) below includes the PDEs, the toxicology data source supporting each estimated PDE, maximum measured results, and the calculated MOS values.

Table 10 Calculated PDE Values, Maximum Measured Results, Calculated MOS Values, and Related Toxicology Data Sources for Leachable Organic Compounds from Beizray Container Closure System

Compound	PDE ($\mu\text{g}/\text{day}$)	Maximum Measured Result ($\mu\text{g}/\text{vial}$)	MOS	Toxicology Data Source
(b) (4)				

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Notes:

(b) (4)

(Excerpted from the applicant's submission)

Overall Summary of Extractable/Leachable Results and Related Safety Assessment

- No elements or special concern organic compounds (including (b) (4)) were noted above the AET in extractable and/or full-scan leachable studies and no toxicological assessment was required, except for (b) (4) which was noted above AET in a leachable study but was found of no toxicology concern through a toxicological assessment conducted.
- All organic compounds above AET in the extraction/full-scan leachable studies had MOS values over 1.0. Therefore, all organic compounds identified had no safety risk to patients at the recommended dose for Beizray.

The applicant provided adequate justification for PDEs and safety margins for extractables or leachables from the (b) (4), the administration device, and the container closure system of Beizray. In addition, considering the advanced cancer indications, intermittent dosing for Beizray, and toxic and genotoxic nature of docetaxel, there are no safety concerns regarding the extractable or leachable impurities from the (b) (4) manufacturing equipment, administration device, and the container closure systems of Beizray.

Conclusion

The nonclinical data submitted by the applicant are adequate for approval of Beizray for the proposed indications under the 505(b)(2) regulatory pathway.

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