CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218711Orig1s000

CLINICAL REVIEW(S)

Clinical Review	
NDA:	218711
Link to EDR:	\\CDSESUB1\evsprod\NDA218711\0000
Submission Date:	10/06/2023
PDUFA Goal Date:	11/06/2024 (with major amendment)
Review Clock:	Standard
Brand Name:	BEIZRAY
Generic Name:	BH009 (docetaxel)
Formulation:	Injection for intravenous use
Clinical Reviewer	Tatiana Prowell
Clinical Team Leader:	Sundeep Agrawal
Sponsor:	Zhuhai Beihai Biotech Co., Ltd.
Submission Type:	505(b)(2)
Dosing regimen:	Administer intravenously (IV) over 1 hour every 3 weeks. • BC locally advanced or metastatic: 60 mg/m^2 to 100 mg/m^2 single agent (2.1) • BC adjuvant: 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles (2.1) • NSCLC: after platinum therapy failure: 75 mg/m^2 single agent (2.2) • NSCLC: chemotherapy naive: 75 mg/m^2 followed by cisplatin 75 mg/m^2 (2.2) • CRPC: 75 mg/m^2 with 5 mg prednisone twice a day continuously (2.3) • GC: 75 mg/m^2 followed by cisplatin 75 mg/m^2 (both on day 1 only) followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion (2.4) • SCCHN: 75 mg/m^2 followed by cisplatin 75 mg/m^2 IV (day 1), followed
Indications:	BEIZRAY is a microtubule inhibitor indicated for: • 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
• 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
• Castration-Resistant Prostate Cancer (CRPC): with prednisone in metastatic castration-resistant prostate cancer
• Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction
• Squamous Cell Carcinoma of the Head and Neck (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN

I. Executive Summary:

Docetaxel (Taxotere®) is an intravenously-administered microtubule inhibitor initially approved by FDA in 1996. It is currently indicated for use in multiple solid tumors, including operable node-positive as well as locally advanced or metastatic breast cancer; locally advanced or metastatic non-small cell lung cancer (NSCLC); castration-resistant prostate cancer (CRPC); advanced gastric and gastroesophageal (GE) junction adenocarcinoma; and locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Docetaxel contains a high concentration of (b) (4) polysorbate 80, which is associated with many clinically significant AEs including hypersensitivity, nephrotoxicity, and neurotoxicity. It is also incompatible with common PVC sets used for intravenous administration. BH009 (Beizray) is a polysorbate 80-free formulation of docetaxel injection developed to achieve equivalent systemic exposure of docetaxel without the toxicity and incompatibility associated with polysorbate 80. BH009 (Beizray) is administered once every 3 weeks as an IV infusion over 1 hour and is being developed for the same indications as docetaxel, the listed drug, under the 505(b)(2) pathway.

The basis of the 505(b)(2) application is Study 20-VIN-0225, a multicenter, single-dose, open-label, two-way crossover bioequivalence (BE) study in 41 evaluable patients with advanced

solid tumors comparing BH009 [(BEIZRAY), docetaxel injection 80 mg/4mL (20 mg/mL)] to Winthrop (docetaxel) injection (20 mg/mL), an authorized generic of Taxotere® manufactured by Sanofi-Aventis Deutschland GmbH.

The results of the study demonstrated the bioequivalence of BH009 (Beizray) and the docetaxel reference product for unbound and total docetaxel, with a safety profile that was similar between the two treatment groups and consistent with the known safety profile of docetaxel reference product.

The clinical team recommends regular approval for BH009 for the same indications as docetaxel (Taxotere®). The clinical team disagrees with the Applicant's proposal to (b) (4) (b) (4) (b) (4). The clinical team also notes that the ethanol content of BH009 is approximately double that of the docetaxel reference product and concurs with the Applicant's proposal to include this information in Sections 5 and 17.

II. Regulatory History

Docetaxel (BEIZRAY) is a microtubule inhibitor. The reference product (docetaxel/Taxotere®) was initially approved by FDA in 1996 and currently has multiple oncological indications, including:

- 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
- 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
- Castration-Resistant Prostate Cancer (CRPC): with prednisone in metastatic castration-resistant prostate cancer
- Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction
- Squamous Cell Carcinoma of the Head and Neck (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN

Key regulatory interactions pertaining to the clinical review and milestones are as follows:

07/23/2020: The Applicant submitted IND #146359.

10/05/2022: Type B pre-NDA written response only meeting. The Agency agreed that a single BE study could support regular approval, that no additional clinical studies would be needed, and the Applicant would rely upon safety findings for Taxotere® (NDA 20449) as the listed drug. The Agency stated that the BE study would not support labeling changes. The Applicant also

indicated their intention to request a waiver of pediatric studies of BH009 as the efficacy of Taxotere in pediatric patients has not been fully established; the overall safety of Taxotere in pediatric patients was consistent with the known safety in adults; the BSA-adjusted clearance of docetaxel was comparable to that of adults; BH009 has demonstrated bioequivalence to Taxotere in adults; and the high alcohol content of BH009 would pose a concern in pediatric patients. FDA agreed with the Applicant's plan.

05/09/2023: Applicant was notified by FDA that this 505(b)(2) does not trigger the Pediatric Research Equity Act (PREA).

10/06/2023: NDA received and granted standard review with PDUFA goal date of 08/06/2024.

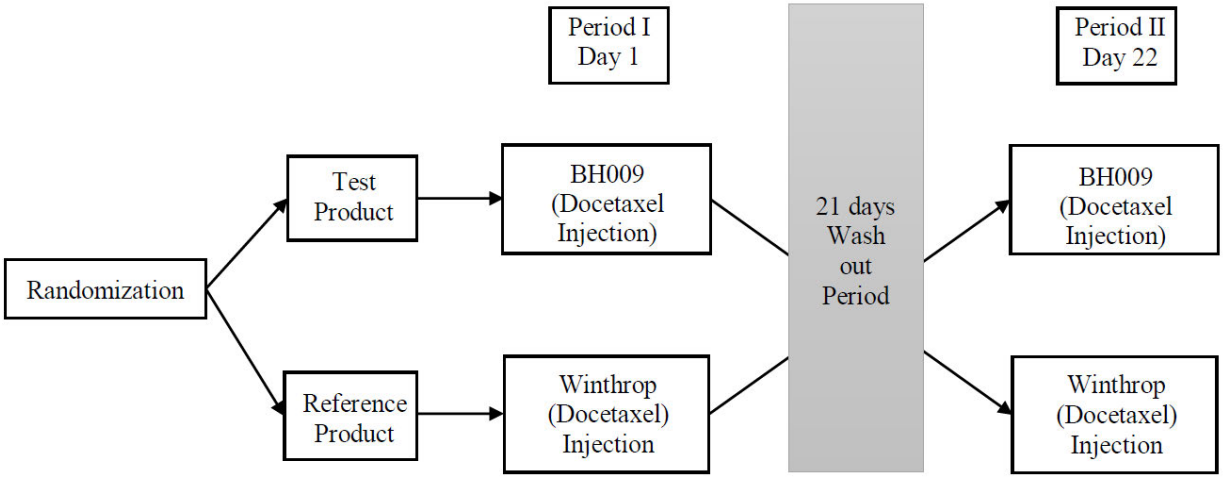
05/14/2024: CMC information request (IR) to the Applicant to provide sufficient evidence that the new albumin manufactured by Octapharma does not affect bioavailability (BA) and BE of the proposed product for which the in vivo BE study was conducted on the formulation mixed with albumin manufactured by (b) (4)

06/24/2024: CMC information submitted by the Applicant in response to the Agency IR was determined to constitute a major amendment, extending PDUFA goal date to 11/06/2024. See the CMC review memo for further discussion of the CMC review issues and resulting major amendment.

III. Study Overview

This NDA submitted under the 505(b)(2) pathway provides the results from Study 20-VIN-0225 entitled "A multicenter, open label, randomized, balanced, two treatment, two period, two sequence, crossover, single dose, bioequivalence study of BH009 against Winthrop (docetaxel) injection in patients with solid tumors requiring treatment with docetaxel monotherapy." The study design is shown in Figure 1 below, taken from the Applicant's protocol.

Figure 1: Schema, Study 20-VIN-0225



The study enrolled adults (N=46) of any sex/ ECOG 0-1, with histologically or cytologically confirmed advanced solid tumors scheduled to receive, or already receiving, single-agent docetaxel in the dose of 75 mg/m2 with a plan for at least 2 more cycles of the same. Participants were required to have a life expectancy of at least 3 months, adequate organ function and marrow reserve, and were required to have recovered to CTCAE grade 0-1 from adverse events related to prior anticancer therapy except alopecia and endocrinopathies controlled with hormone replacement therapy. Patients were excluded for severe cardiovascular disease within 6 months of study entry, active infection, severe pleural effusion or gross ascites, QT prolongation, grade ≥2 peripheral neuropathy, active Hepatitis B or C, HIV, brain metastases, major surgery within 4 weeks or minor surgery within 2 weeks, recent use of cytochrome P450 inducers, inhibitors, or substrates, or clinically significant alcohol or illicit substance use. Adequate washout from prior anti-cancer agents was required, participants could not be pregnant or breastfeeding, and adequate contraception was required. Participants were also notably excluded for a history of hypersensitivity or idiosyncratic reactions to docetaxel, its excipients, and/or related substances including polysorbate 80, paclitaxel, alcohol, dexamethasone, granisetron, or ondansetron.

All participants were admitted to the hospital and received premedication with dexamethasone 8 mg twice a day for 24 hours prior to both BH009 and docetaxel administration. All participants remained hospitalized for 72 hours in each period, 24 hours prior to investigational product administration and 48 hours post-dosing. BH009 and docetaxel were administered at no greater than 1 mg/minute for the first 10 minutes to minimize risk of infusion reactions, and if no reactions were observed, the infusion rate was increased to complete total administration over 1 hour (+/- 5 minutes). Any patients whose infusion extended beyond 1 hour (+/- 5 minutes) was to be withdrawn from study. Concomitant medications were to remain constant throughout both periods of the study. Safety was assessed throughout the hospitalization in each period with additional clinic visits, including laboratory assessments, on study days 7 and 29. Patients with TEAEs were to be followed until resolution/stabilization of the TEAE(s), up to a

maximum of 30 days.

In Study Period I (Day 1): Participants received 75 mg/m2 dose of docetaxel injection for infusion (either BH009 or reference product) on the first day of the chemotherapy cycle.
In Study Period II (Day 22): Participants were crossed over to the other treatment arm to receive 75 mg/m2 dose of docetaxel injection for infusion (either BH009 or reference product depending on crossover sequence).

Blood samples for PK assessment were collected prior to and after the start of IV infusion on Day 1 (Period I) and Day 22 (Period II). A total of 17 blood samples for PK assessment were to be collected during each period. These included a pre-infusion blood sample within 5 minutes prior to start of infusion, followed by samples at 30 and 50 minutes during the infusion, at the end of the infusion, and then at 5, 10, 20, and 30 minutes and 1, 2, 3, 6, 8, 12, 24, and 48 hours after the end of the infusion. If infusion duration extended beyond 1 hour (± 5 minutes), participants were to be withdrawn from the study. Plasma concentration of unbound docetaxel and total docetaxel were quantified.

Safety monitoring during the study in addition to AE assessment as noted above included ECG, hematology, and chemistry laboratories on the day prior to dosing in Periods I and II, and at end of study, as well as pregnancy tests and breath tests for alcohol consumption and urine toxicology screen on the day prior to dosing in Periods I and II.

The primary objective of Study 20-VIN-0225 was:

- To evaluate pharmacokinetics and establish the bioequivalence of BH009 (Docetaxel Injection 80 mg/4 mL) relative to that of Winthrop (docetaxel) injection 20 mg/mL (an authorized generic drug of Taxotere®), in patients with solid tumors requiring treatment with docetaxel monotherapy at a dose of 75 mg/m2

The secondary objective was:

- To monitor the safety and tolerability profile of the study formulations

Using the estimated concentration time profiles of unbound and total docetaxel, the following variables were calculated:

- Primary variables: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$
- Secondary variable: T_{max}, $t_{1/2}$, K_{el}, V_d, CL and $AUC_{\_\%Extrap\_obs}$ + safety

For unbound and total docetaxel, the acceptance range for bioequivalence was 80% to 125% for 90% confidence intervals of the geometric least square means ratio (T/R) for Cmax, AUC0-t and AUC0-∞.

IV. Study Results:

A total of 52 patients were screened, of whom 46 were randomized. The safety population,

which included all patients who received one dose of study drug (N=46), was 63% female with a median age of 51 years (range: 32-83). The study was enrolled from five study sites in India, and all patients were Asian. The median BSA was 1.53 (range: 1.25, 1.88).

A total of 46 patients were treated in Period I, and 41 were treated in Period II. In total, 43 patients received one dose of BH009, and 44 received one dose of docetaxel reference product. A total of five patients withdrew after being treated in Period I but before being treated in Period II. One patient (b) (6) discontinued the study citing personal reasons after completion of the dose of BH009 in Period I. Three other patients (b) (6) withdrew consent with no further information provided at the Day 7 visit after receiving docetaxel reference product in Period I. One additional participant (b) (6) was discontinued by the Investigator after receiving BH009 in Period 1 due to disease progression that required a change in treatment. None of the five patients who withdrew from the study had an AE worse than grade 1 or 2. Participant disposition is shown in Table 1 below:

Table 1: Participant Disposition, Study 20-VIN-0225

	Docetaxel -> BH009 (N=22) n (%)	BH009 -> Docetaxel (N=24) n (%)	Overall (N=46) n (%)
Randomized	22 (100)	24 (100)	46 (100)
Treated	22 (100)	24 (100)	46 (100)
Completed	19 (86)	22 (92)	41 (89)
Discontinued after Period I dose	3 (14)	2 (8)	5 (11)
Withdrew consent	3 (14)	0 (0)	3 (7)
Investigator discretion	0 (0)	1 (4)	1 (2)
Personal reason	0 (0)	1 (4)	1 (2)

There were 59 protocol deviations on study, two of which were judged to be major. This patient ((b) (6)) had two delayed collections of PK samples during the docetaxel test product period due to cannula blockage, which did not impact patient safety but may have impacted PK results. The remaining were minor protocol deviations related to either laboratories or scheduled visits, the majority of which were slight deviations from expected days of visits due to logistics, which would not be expected to impact either patient safety or PK results. Overall, the protocol deviations do not impact the conclusions of the clinical review.

Bioequivalence was demonstrated for Cmax, AUC0-t, and AUC0-∞. The results for the primary BE outcomes are shown in Table 2 below. See the Clinical Pharmacology review memo for further details regarding the analysis of pharmacokinetic (PK) data and determination of

bioequivalence.

Table 2: Bioequivalence Results, Study 20-VIN-2205

PK Parameters (Units)	Acceptance Range of 90% CI	90% CI for Total Docetaxel	90% CI for Free Docetaxel
C_{max} (ng/mL)	80.00% - 125.00%	92.18% - 108.00%	85.22% - 101.70%
AUC_{0-t} (hr*ng/mL)	80.00% - 125.00%	91.89% - 107.18%	89.98% - 103.15%
$AUC_{0-\infty}$ (hr*ng/mL)	80.00% - 125.00%	91.10% - 106.04%	90.24% - 102.75%
Other	See FDA Clinical Pharmacology Review Memo		

The safety population consisted of 46 patients. Overall, 45 (98%) of participants reported at least one treatment-emergent adverse event (TEAE). A total of 198 treatment-emergent adverse events (TEAEs) occurred on study, 94 (47%) after administration of BH009 and 104 (53%) after administration of the docetaxel reference product.

The overall AE profile was similar across the two treatment periods, noting that the limited sample size in this BE study results in wide confidence intervals around the point estimates of incidence of each TEAE. Myelosuppression TEAEs were somewhat more common in the BH009 period, and GI toxicities were somewhat more common in the docetaxel reference product period. The most commonly reported AEs for the BH009 versus docetaxel reference product were: asthenia (50.0% vs 54.5%), alopecia (41.7% vs 36.4%), leukopenia (33.3% vs 13.6%), diarrhea (29.2% vs 40.9%), nausea (29.2% vs 27.3%), neutropenia (29.2% vs 22.7%), arthralgia (16.7% vs 22.7%), vomiting (12.5% vs 22.7%), pain (12.5% vs 13.6%), headache (12.5% vs 9.1%), anemia (12.5% vs 4.5%), pyrexia (8.3% vs 27.3%), fatigue (8.3% vs 9.1%), abdominal pain upper (8.3% vs 4.5%), and rash (8.3% vs 4.5%). Most TEAEs (96%) were CTCAE grade 1 and 2. At the time of the data cutoff, 85% of TEAEs had resolved, 14% had not resolved, and <1% were unknown.

At the pre-NDA meeting, the Applicant had noted that each administration of BH009 at 100 mg/m2 delivers 4 m/m2 of ethanol, which is double that of the docetaxel reference product, and that the informed consent had been updated to warn participants of this in 08/2020. The predicted end-of-infusion blood ethanol concentration following a maximal dose of BH009 of 200 mg would be 19 mg/dL, which is much lower than the 100 mg/dL level generally agreed to result in impairment. This is included in Sections 5.13 and 17 of the Applicant's proposed labeling. The safety review included an assessment of AEs for any indication of alcohol intoxication. The only potentially relevant AEs noted were grade 1 hiccups, which occurred in 3 participants, two receiving docetaxel reference product and one receiving BH009, and thus did

not appear to be increased.

Of the reported TEAEs on study, six (3%) were grade 3, two (1%) were grade 4, and none (0%) were fatal. The grade 3/4 TEAEs were all laboratory abnormalities that have been reviewed in further detail. In the BH009 group, there was one patient with grade 3 anemia, grade 4 leukopenia, and grade 4 neutropenia (b) (6) In the docetaxel group, there was one patient (Patient ID: (b) (6) with grade 3 leukopenia, one patient (Patient ID: (b) (6) (b) (6) with grade 3 leukopenia and grade 3 neutropenia, and one patient (Patient ID: (b) (6) (b) (6) with grade 3 anemia. These grade ≥ 3 AEs were without complications, resolved in < 30 days, and were judged by the Investigator, Applicant, and FDA to be non-serious.

The only unexpected TEAE was hemoptysis, which was grade 1, occurred in a 66-year-old man with advanced NSCLC while receiving the docetaxel reference product, and resolved.

No serious adverse events (SAEs), adverse events leading to discontinuation, or deaths were reported on study.

V. Clinical Conclusions:

This multicenter, single-dose, two-way crossover study demonstrated bioequivalence for BH009 compared to the reference product of docetaxel (Taxotere®) per FDA's Clinical Pharmacology Review Team (see Clinical Pharmacology review memo). The safety profiles of BH009 and the docetaxel reference product on study were consistent with the current docetaxel USPI, with asthenia, alopecia, myelosuppression, gastrointestinal toxicity, and rash being the most common TEAEs reported on study. No new safety signals were identified. Grade 3/4 TEAEs were uncommon in this single-dose crossover study and were all uncomplicated laboratory abnormalities of myelosuppression. There were no SAEs, discontinuations due to TEAE, or deaths reported on study. There were 5 patients who discontinued the study after receiving the first of two planned doses, but these were balanced (2 after BH009 and three after docetaxel reference product) and did not appear to be related to toxicity, as none of these participants had a reported AE worse than grade 1 or 2. Despite an increased ethanol content of BH009, there were no AEs suggestive of alcohol intoxication. Nonetheless, as a precaution, information about the alcohol content of BH009 has been added to the warnings and precautions of the agreed-upon USPI, as well as to patient labeling.

There were no hypersensitivity reactions reported on Study 20-VIN-0225; however, the study notably excluded patients with a history of hypersensitivity or idiosyncratic reactions to docetaxel or its excipients, paclitaxel, and polysorbate 80, and pre-treated all patients in both periods with dexamethasone. (b) (4) (4) (b) (4)

The clinical team therefore recommends regular approval but disagrees with the Applicant's proposed labeling changes (b) (4)

(b) (4)

VI. Inspections

All but one of the sites were approved based on previous history. A single site (FEI: 3008467694; Fujian South Pharmaceutical Co., Ltd. No.98 Dongxin Road, Xuefeng Town, Mingxi County, Fujian Province 365200, China, Sanming, Fujian, China, 365200) was inspected and approved based on PAI in 10/2024.

See ORA review memo and IQA review memo for further details.

VII. Advisory Committee Meetings

Not applicable.

VIII. Postmarketing Requirements/Commitments

None.

IX. Recommended Regulatory Action:

The clinical team recommends regular approval for BH009 for the same indications as docetaxel (Taxotere®).

(b) (4) the review team recommends the following language in the BH009 (Beizray) USPI consistent with the original docetaxel (Taxotere®) USPI:

HIGHLIGHTS:

Severe hypersensitivity, including fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of BEIZRAY and administration of appropriate therapy (5.5)

BOXED WARNING:

Do not administer BEIZRAY to patients who have a history of severe hypersensitivity reactions to docetaxel *[see Contraindications (4)]*. Severe hypersensitivity reactions have been reported in patients despite dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the BEIZRAY infusion and administration of appropriate therapy *[see Warnings and Precautions (5.5)]*.

2 DOSAGE AND ADMINISTRATION

2.6 Corticosteroid Premedication Regimen

All patients should be premedicated with oral corticosteroids (see below for prostate

cancer) such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day prior to BEIZRAY administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions *[see Boxed Warning, Warnings and Precautions (5.5)].*
For metastatic castration-resistant prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg at 12 hours, 3 hours, and 1 hour before the BEIZRAY infusion *[see Warnings and Precautions (5.5)].*

4 CONTRAINDICATIONS
BEIZRAY is contraindicated in patients with:
• a history of severe hypersensitivity reactions to docetaxel. Severe reactions, including anaphylaxis, have occurred *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS
5.5 Hypersensitivity Reactions
Severe hypersensitivity, including fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of BEIZRAY and administration of appropriate therapy (5.5)

Due to the increased alcohol content of BEIZRAY compared to the docetaxel reference product, the following information has also been added to Sections 5 and 17:

5 WARNINGS AND PRECAUTIONS
5.13 Alcohol Content
Cases of intoxication have been reported with some formulations of docetaxel due to the alcohol content. The alcohol content in a dose of BEIZRAY Injection may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in BEIZRAY Injection on the ability to drive or use machines immediately after the infusion. Each administration of BEIZRAY Injection at 100 mg/m2 delivers 4.0 g/m2 of ethanol. For a patient with a BSA of 2.0 m2, this would deliver 8.0 grams of ethanol [see Description (11)]. Other docetaxel products may have a different amount of alcohol.

17 PATIENT COUNSELING
Alcohol Content in BEIZRAY
Explain to patients the possible effects of the alcohol content in BEIZRAY, including possible effects on the central nervous system [*see Warnings and Precautions (5.13)*].
Ability to Drive or Operate Machines
Explain to patients that BEIZRAY may impair their ability to drive or operate machines due to its side effects [*see Adverse Reactions (6)]* or due to the alcohol content of BEIZRAY [*see Warnings and Precautions (5.13)*]. Advise them not to drive or use machines if they experience these side effects during treatment.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TANYA M PROWELL
10/21/2024 11:55:15 AM

SUNDEEP AGRAWAL
10/21/2024 01:10:12 PM

CHRISTY L OSGOOD
10/21/2024 08:03:28 PM