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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2) (Resubmission)
Application Number(s)	202356
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Division / Office	DOP1 / OHOP
Clinical Reviewer	William Pierce, PharmD
Clinical Team Leader	V. Ellen Maher, MD
Review Completion Date	February 26, 2014
Established Name	docetaxel
(Proposed) Trade Name	Docetaxel Injection Concentrate
Therapeutic Class	Microtubule inhibitor
Applicant	Pfizer, Inc.
Formulation(s)	IV
Dosing Regimen	Multiple (see product information, 2.1)
Indication(s)	Multiple (see product information, 2.1)
Intended Population(s)	Multiple (see product information, 2.1)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA for docetaxel injection, in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, was submitted to request approval of therapeutic equivalence of the proposed product to Taxotere, as defined in the FDA Orange Book. The sponsor of NDA 20-449 for Taxotere is Sanofi-Aventis. The exclusivity of the indications below has expired.

Breast Cancer
- Docetaxel Injection is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.
- Docetaxel Injection in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

Non-Small Cell Lung Cancer
- Docetaxel Injection as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.
- Docetaxel Injection in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

Prostate Cancer
- Docetaxel Injection in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

Gastric Adenocarcinoma
- Docetaxel injection in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

Head and Neck Cancer
- Docetaxel injection in combination with cisplatin and fluorouracil is indicated for induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

No new clinical data were submitted for this NDA. The Taxotere NDA 20-449 has been previously reviewed for efficacy and safety. Based on the additional clinical information received from the Applicant in this NDA resubmission, and the labeling revisions to the Pfizer docetaxel prescribing (USPI) and patient package insert (PPI) annotated in

Section 8 of this review, the DOP1 Clinical Review Team recommends that this 505(b)(2) NDA resubmission be approved.

The Clinical Review Team also recommends the other approved docetaxel product USPIs and PPIs be updated to adequately disseminate the risks of ethanol-related toxicities for each docetaxel drug product.

1.2 Risk Benefit Assessment

Please refer to NDA 20-449.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: docetaxel

Proprietary Name: Docetaxel Injection Concentrate

Applicant: Pfizer, Inc.
235 East 42nd Street
New York, NY 10017
Tel: (212) 733-2061
Fax: (212) 833-5567

Drug Class: Microtubule inhibitor

Proposed Indications

- 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.
- Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic 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 Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN.

Reviewer Comment: The Applicant has applied for all of the currently listed indications in the Taxotere USPI.

Proposed Dosage and Administration

Administered IV over 1 hour every 3 weeks (1 cycle) for the following cancers:

- BC, locally advanced or metastatic: 60-100 mg/m^2 single agent
- BC adjuvant: 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 for 6 cycles
- NSCLC, after platinum failure: 75 mg/m^2 single agent
- NSCLC, chemotherapy-naive: 75 mg/ m^2 followed by cisplatin 75 mg/ m^2
- HRPC: 75 mg/ m^2 with 5 mg prednisone twice a day continuously
- 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
- Induction chemotherapy of inoperable SCCHN followed by radiotherapy: 75 mg/ m^2 followed by cisplatin 75 mg/ m^2 IV (day 1), followed by fluorouracil 750 mg/ m^2 per day as a continuous 24-hr IV infusion (days 1-5) for 4 cycles.
- Induction chemotherapy followed by chemoradiotherapy of locally advanced SCCHN: 75 mg/ m^2 followed by cisplatin 100 mg/ m^2 IV (day 1), followed by fluorouracil 1000 mg/ m^2 per day as a continuous 24-hr IV infusion (days 1-4) for 3 cycles.

Premedication Regimen

- Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice a day) for 3 days starting 1 day before administration
- HRPC: oral dexamethasone 8 mg at 12 hours, 3 hours, and 1 hour before treatment

For dosage adjustments during treatment see Full Prescribing Information.

Dosage Forms and Strengths

- 20 mg/2 mL single-dose vial
- 80 mg/8 mL single-dose vial
- 130 mg/13 mL single-dose vial
- 200 mg/20 mL single-dose vial

Contraindications

- Hypersensitivity to docetaxel injection or polysorbate 80
- Neutrophil counts of <1500 cells/mm^3

Warnings and Precautions

- Hepatic impairment
- Hematologic effects
- Hypersensitivity reactions
- Fluid retention
- Secondary acute myeloid leukemia (when administered with anthracycline and/or cyclophosphamide)
- Cutaneous reactions (erythema, desquamation)
- Neurologic reactions (paresthesia, dysesthesias, pain)

- Eye disorders
- Asthenia
- Use in pregnancy
- ***Alcohol content***

Reviewer Comment: New alcohol-related safety information, including a new Warning and Precaution subsection (5.12), have been proposed by Pfizer due to an increase in the ethanol content and the addition of propylene glycol in the Pfizer docetaxel product compared to the referenced product, Taxotere. *See Section 7 and 8 of this review for more information.*

Adverse Reactions
The most common adverse reactions are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

2.2 Availability of Proposed Active Ingredient in the United States

Taxotere (docetaxel) is marketed in the US. Multiple other drug products containing the docetaxel active ingredient are marketed in the US.

Other approved docetaxel formulations include:

- NDA 022234 Docetaxel Injection, Hospira, Inc., 3/8/2011
- NDA 022534 Docefrez Injection, Sun Pharma Global, 5/3/2011
- NDA 201195 Docetaxel Injection, Accord Healthcare, Inc., 6/8/2011
- NDA 201525 Docetaxel, Sandoz, 6/29/2011
- NDA 022312 Docetaxel Injection, Apotex, Inc., 1/11/2012
- NDA 203551 Docetaxel Injection Concentrate, Actavis Inc., 4/12/2013

2.3 Summary of Pre-submission Regulatory Activity

On November 1, 2010, a pre-NDA (IND 109,463) meeting was held to discuss a proposal for a 505(b)(2) submission. On April 29, 2011, the original NDA 202356 was submitted under the 505(b)(2) pathway by Pfizer, Inc. On February 29, 2012, FDA issued a Complete Response (CR) to the Applicant due to the numerous nonclinical and product quality deficiencies as conveyed in the CR letter. Due to these deficiencies, a review of the proposed prescribing information for this docetaxel product was not conducted during the original NDA review. On June 7, 2012, a Type A meeting was held between the FDA and the Applicant to discuss NDA resubmission. On August 14, 2012, the Applicant submitted a Class 2 NDA resubmission in accordance with 21 CFR 314.110. On October 9, 2012, an FDA clinical information request (IR) was sent to the Applicant requesting information to characterize potential alcohol- and propylene glycol-

related toxicities related to Pfizer docetaxel and to provide a rationale for the unique Warnings and Precautions subsection for alcohol content proposed for Pfizer docetaxel. On October 24, 2012, Pfizer submitted a response (STN #14; eCTD 0013) to the FDA Clinical IR. On February 14, 2013, FDA issued a Complete Response (CR) to the Applicant due to product quality issues and incomplete characterization of ethanol- and propylene glycol -related toxicities for Pfizer docetaxel. The Clinical deficiencies identified in the last CR letter issued are as follows:

- *The combination of ethanol and propylene glycol in this proposed docetaxel formulation may result in an increase in the toxicity of your docetaxel product compared to that of the referenced drug (Taxotere). The magnitude of the potential increase in toxicity and the potential difference in toxicity profiles between your docetaxel product and the referenced drug remains uncertain without additional clinical information. Please provide additional information to better characterize potential alcohol-related toxicities. This information could include one of the following:*
    a. *Published references that enable adequate estimation of the toxicity expected from:*
        i. *The amount of ethanol used in your product;*
        ii. *The extent to which propylene glycol adds to ethanol intoxication; and*
        iii. *The potential interaction between these two agents (e.g., competition for alcohol dehydrogenase).*
    b. *Results from a clinical trial to assess the safety of your docetaxel product. A trial to assess the toxicity of ethanol and propylene glycol in combination, at amounts similar to those in your product may be acceptable if combined with adequate safety monitoring and assessment strategies for alcohol-related toxicities. The design of such a study should account for variability in expression of toxicity in patients in response to a given blood alcohol level. Should you choose to proceed with such a trial, we advise that you submit a protocol for our review*
    c. *A reformulation of your docetaxel product to deliver ethanol and propylene glycol at amounts (individually or in combination) that are not higher than other docetaxel products.*

2.4 Pediatric Waiver

The original pediatric exclusivity of Taxotere ended on November 14, 2010. The pediatric use information for the referenced drug product is based on data submitted in response to a pediatric Written Request under the Best Pharmaceuticals for Children Act (BPCA); this exclusivity expired on May 13, 2013.

In the original NDA submission, Pfizer requested to be exempt from providing pediatric use data because the disease/condition is not likely to be used in a substantial number of pediatric patients and necessary studies are impossible or highly impracticable.

Reviewer Comment: The pediatric use information for the Pfizer Docetaxel Concentrate labeling was carved out of the original NDA submission due to BPCA exclusivity. Due to the expiration of the BPCA pediatric exclusivity for the referenced product, this information was added to the Pfizer Docetaxel prescribing information (USPI) during this review cycle. The Applicant's pediatric waiver request for Pfizer Docetaxel Concentrate remains acceptable.

2.5 Other Relevant Background Information

Refer to NDA 20-449. There are no unexpired patents or unexpired exclusivity for the referenced product in the Orange Book Database (Accessed 12/4/2013).

3 Ethics and Good Clinical Practices

Not applicable.

4 Significant Safety Issues Related to Other Review Disciplines

Clinical Pharmacology

The FDA's Division of Clinical Pharmacology V (DCP5) completed a detailed review of the clinical pharmacology information and related labeling in this NDA resubmission to address potential safety concerns regarding ethanol (ETOH) and propylene glycol (PG) present in the proposed Pfizer docetaxel formulation. During the Clinical Pharmacology review, the FDA Office of Clinical Pharmacology (OCP) Predictive Safety Team (PST) was consulted. The Clinical Pharmacology Review Team recommended approval of this NDA resubmission for Pfizer docetaxel. Key findings from the Clinical Pharmacology review include the following:

- The predicted end-of-infusion blood ETOH concentration (15 mg/dL) may produce mild symptoms of intoxication and is below the legal blood alcohol concentration limit for driving.
- The 7.5 g total dose of PG following a single 200 mg dose of Pfizer docetaxel appears to be below the threshold of clinical concern.
- Pharmacokinetic drug interactions resulting in further elevations in blood ETOH or PG concentrations are unlikely.
- The labeling language proposed by the Applicant adequately addresses potential safety risks of alcohol-associated CNS effects.

See the Clinical Pharmacology review filed on January 28, 2014 for more information.

Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilence (DPV-II)

The DOP1 Clinical Review Team requested a consult from the FDA's Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilence II (DPV-II) to review and assess AERS safety reports for alcohol intoxication possibly related to docetaxel and to provide advice regarding the content of applicable labeling for docetaxel products and alcohol content. The OSE DPV-II Review Team concluded that postmarketing cases of alcohol intoxication associated with docetaxel and literature support the proposed Warning and Precautions for Pfizer docetaxel and for other currently marketed docetaxel products. *See the OSE DPV-II Review filed on February 14, 2014 for more information.*

Reviewer Comment: Key information from the Clinical Pharmacology and OSE DPV-II review is incorporated into the safety review for each clinical deficiency in Section 7 of this review.

Chemistry, Manufacturing, and Control (CMC)

Adequate data has been provided to ensure the quality of the drug substance and drug product in this submission. The required CMC revisions to the prescribing information have been incorporated during the labeling negotiations for this NDA. The CMC Review Team recommends approval of this NDA. *See the CMC review filed on January 17, 2014 for more information.*

5 Sources of Clinical Data

No new clinical trial data was submitted for this NDA. The Taxotere NDA (20-449) was reviewed for efficacy and safety for multiple therapeutic indications. In addition to the approval of Taxotere, other drug products containing the docetaxel active ingredient have been approved and were deemed therapeutically equivalent to Taxotere.

In this NDA resubmission, the Applicant submitted the following new information for review:

- *Response to 14-February-2013 FDA Complete Response Letter, NDA 202356*
- *Projected Blood Concentrations of Ethanol and Propylene Glycol following Infusion of Docetaxel* (report)
- Docetaxel Injection Concentrate USPI and PPI (updated)
- Annotated Comparison with Listed Drug (labeling)

6 Review of Efficacy

See NDA 20-449.

7 Review of Safety

Refer to NDA 20-449 for the overall safety findings related to docetaxel. Product-specific safety issues related to the ethanol (ETOH) and propylene glycol (PG) content in the proposed Pfizer docetaxel formulation are reviewed in this submission.

Background/Clinical Review History

The Applicant has created a new formulation of docetaxel that delivers a two- or three-fold increase in the amount of ETOH administered per dose compared to the ETOH that is delivered with each dose of the referenced drug (Taxotere). The magnitude of this alcohol exposure exceeds the alcohol exposure of all of the previously approved docetaxel products currently marketed in the United States (US).

In the previous NDA submission for Pfizer docetaxel, the Clinical Reviewer identified that the ETOH and PG in the proposed Pfizer docetaxel formulation may result in a difference in the safety profile of this product and the referenced drug (Taxotere) being relied upon for this 505(b)(2) NDA. Pfizer proposed a new Warnings and Precautions subsection for Alcohol Content (5.12) and (b) (4) that is not found in the Taxotere prescribing information (USPI), or in the prescribing information for any of the other docetaxel drug products currently approved and marketed in the United States (US). The information provided by the Applicant in previous NDA submissions and in response to FDA Clinical Information Requests did not adequately address these concerns. *See the Clinical Review filed under this NDA on January 13, 2013 for more information.*

In this submission, the Applicant (Pfizer) has provided a detailed literature review, pharmacokinetic predictions and simulations, and comparison to other approved and marketed docetaxel products to address the clinical deficiencies identified in the previous Complete Response letter (annotated below in the Updated Clinical Safety Review).

Updated Clinical Safety Review

1. ***….Please provide additional information to better characterize potential alcohol-related toxicities….***
    a. ***Published references that enable adequate estimation of the toxicity expected from:***
        i. ***The amount of ethanol used in your product***

Ethanol (ETOH) Exposure from Docetaxel Products

The total ETOH dose and estimated end-of infusion blood ETOH concentration (Cmax) were higher for Pfizer docetaxel than the referenced listed drug (Taxotere, two-vial formulation) or the currently marketed Taxotere one-vial formulation. The total ETOH dose of the Pfizer docetaxel is also higher than the ETOH dose for all of the currently marketed docetaxel drug product formulations. The total ETOH dose and predicted

end-of-infusion blood ETOH concentration following a maximum 200 mg dose of Pfizer docetaxel to a patient with a BSA of 2.0 m^2 were 6.4 Grams (g) and 15 mg/dL, respectively.

Table 1 lists the doses of ETOH and PG for the proposed Pfizer docetaxel product and all of the other currently marketed docetaxel products. The predicted end-of-infusion blood concentration of ETOH for the maximum dose (100 mg/m^2) of Pfizer docetaxel and Taxotere are also listed to help assess the clinical significance of the total dose (gram) exposures for each product.

Table 1: Ethanol and Propylene Glycol Dose (grams) and Blood Ethanol Concentrations (mg/dL)

	Dose of Ethanol (grams)*	Dose of Propylene Glycol (grams)*	Predicted Blood Ethanol Concentration** (mg/dL)
Docetaxel (Pfizer)	6.4	7.5	15
Taxotere (1-vial) *(Currently marketed)*	4.0	0	-
Taxotere (2-vial) *(Original NDA approval)*	2.0	0	5
Docetaxel (Sandoz)	5.5	0	-
Docetaxel (Accord)	4.0	0	-
Docetaxel (Actavis)	4.0	0	-
Docetaxel (Hospira)	3.7	0	-
Docetaxel (Sun)	2.9	0	-

** Assumes maximum dose of 100 mg/m^2 docetaxel, BSA= 2.0 m^2; 200 mg dose administered*
*** Calculated at the end of the IV Infusion (Cmax)*

The Applicant assessed the potential impact of interpatient variability and factors that may impact ETOH clearance by adjusting the half-life ($t_{1/2}$) for elimination of ETOH to durations of two-fold shorter (i.e., $t_{1/2}$ = 1 hour) and two-fold longer (i.e., $t_{1/2}$ = 4 hours) than the median estimated $t_{1/2}$ of two hours. The estimated resultant end-of-infusion ETOH concentrations for Pfizer docetaxel were 12 mg/dL and 16 mg/dL based on these corrections and did not result in significant differences in the overall ETOH exposure.

Reviewer Comment: Eckardt et. al. [Alcohol Clin Exp Res 1998 Aug (22)(5):998-1040] concludes there is general agreement that between-individual variation in elimination rates are as large as 2 - 4 fold when subjects are given the same alcohol dose. Therefore the Applicant's use of $\pm$ 2-fold half-life adjustment to assess interpatient exposure variability appears reasonable.

Patients may be ready to operate equipment and drive home at approximately 30 minutes following the 1-hour IV infusion of Pfizer docetaxel. Therefore, the FDA Clinical Pharmacology Reviewer predicted the blood concentration of ETOH at 30 minutes after completion of the IV infusion. The estimated blood ETOH concentrations at 30 minutes

following the 1-hour intravenous administration (9 - 15 mg/dL) of Pfizer docetaxel were similar to the end-of-infusion estimated blood alcohol concentrations (13 - 16 mg/dL). *See the Clinical Pharmacology review filed under this NDA on January 28, 2014 for more detailed pharmacokinetic information.*

Clinical Significance of Ethanol (ETOH) Exposure

The predicted ETOH exposure level for Pfizer docetaxel results in low-to-moderate exposure levels that are clinically significant and may be a concern for patients who are sensitive to the effects of alcohol, or for patients in which ETOH exposure should be minimized or avoided. In a comprehensive review, Eckardt, et. al. assessed the effects of moderate alcohol consumption on the Central Nervous System (CNS). The lower level of moderate alcohol consumption was defined as 4.5 – 50 grams of ETOH per dose. The authors concluded that the threshold for negative effects on psychomotor tasks is generally around 40 mg/dL - 50 mg/dL. However, the authors also note complex tasks are more vulnerable to disruption following ingestion of alcohol. At blood ethanol concentrations of 20 mg/dL – 90 mg/dL; effects on GABA, glutamate, serotonin, dopamine, cholinergic, and opioid neurochemical pathways were detectable; and impairment of complex cognitive and/or motor function have been shown to occur. Additionally, the precision of these blood ETOH levels should be interpreted with an awareness that inter-patient variability will factor into how a patient responds since a number of factors, including genetic, pharmacokinetic, drinking experience, gender, smoking, concomitant medications, diet, age, and body habitus have all been reported to impact both individual CNS exposure and behavioral response to ETOH. [1],[2]

The European Guidelines for Excipients in the Label and Package Leaflet of Medicinal Products for Human Use (Ethanol and Propylene Glycol) (2003) recommend medicinal products with > 3 grams of ethanol per dose include the following information in labeling:

- This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... ml beer, ... ml wine per dose.
- Harmful for those suffering from alcoholism.
- To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy.
- The amount of alcohol in this medicinal product may alter the effects of other medicines.
- The amount of alcohol in this medicinal product may impair your ability to drive or use machines.

See Table 2 below for more information on the European Labeling Guidelines for Alcohol Content.

The Clinical Pharmacology Reviewer summarizes the safety concerns for the anticipated ETOH exposure from Pfizer docetaxel as follows:

> "The total ethanol dose and predicted end-of-infusion blood ethanol concentration following a maximum 200 mg dose of Docetaxel Injection were 6.4

g and 15 mg/dL (0.015%), respectively. Based on published literature, blood ethanol concentrations > 100 mg/dL are known to result in impairment of motor function, which includes altered perception, ataxia, impaired judgment, lack of coordination, mood, personality, and behavioral changes, nystagmus, prolonged reaction time and slurred speech. Blood ethanol concentrations > 50 mg/dL are associated with impairment of some tasks requiring skill, increased talkativeness and increased relaxation. A blood ethanol concentration of 40 mg/dL is considered the threshold for negative effects on psychomotor tasks, and is associated with significant effects on subjective and performance measures. A blood ethanol concentration of >10 mg/dL is associated with increased stimulation and the "feeling of intoxication" threshold. Therefore, the predicted end-of-infusion blood ethanol concentration (15 mg/dL) following a single 200 mg dose of Docetaxel Injection may produce mild CNS depression, and is below the legal blood alcohol concentration limit for driving (80 mg/dL in most states [3])."

"The European medicines agency (EMA, 2010) has published that ethanol content in herbal medicines used in children should not exceed a blood ethanol concentration of 12.5 mg/dL following a single dose. This recommendation is based on the impairment of psychomotor skills that can occur with blood ethanol concentrations > 12.5 mg/dL. The end-of-infusion blood ethanol concentration (15 mg/dL) following administration of a 200 mg maximum dose of Docetaxel Injection is similar to the 12.5 mg/dL concentration not to exceed in children recommended by the EMA. The labeling language proposed by the sponsor is

(b) (4)

Reviewer Comment: The conclusions reached by the Clinical Pharmacology reviewer and the Predictive Safety Team are consistent with the conclusions of the Clinical Review Team regarding the significance of the ethanol exposure related to Pfizer docetaxel administration.

The Clinical Reviewer conducted a search of the FDA AERS database to identify case reports of alcohol intoxication associated with currently approved and marketed docetaxel products (Accessed December 17, 2013). Two cases (#7541774; #6454788) of alcohol intoxication at least possibly related to docetaxel were identified.
Case #7541774 involved a 44-year old man being treated with 75 mg/m^2 (150 mg dose) of intravenous (IV) docetaxel once every three weeks (Q3W) for metastatic (bone) prostate cancer who experienced "alcohol intoxication" described as "feeling drunk" with symptoms of confusion, drowsiness, and dizziness. These events occurred "half-way" through his ninth infusion of docetaxel treatment. He had a past medical history significant for alcohol abuse, but reported being alcohol-free for a period of three years prior to his docetaxel treatment. No laboratory investigations were performed. The pharmacist reporter observed "signs of drunkenness" and noted that the docetaxel product was changed from the two-vial formulation (1.0 g/m^2 ETOH) to the one-vial

formulation (2.0 g/m^2 ETOH) for this administration. Information related to pre-medication was not included in the case report; so the contribution of specific pre-medications (e.g., antihistamines) could not be assessed. The docetaxel infusion was held for an unspecified amount of time, intravenous fluids were administered, and the infusion was restarted at a lower infusion rate. The patient completely recovered at an unspecified time on the day of the event. The decision was made to use a "non-alcoholic" version of docetaxel for the next and final cycle of therapy. The reporter's attribution to docetaxel was "highly probable". Clinical Reviewer attribution of these events to docetaxel is probable. Case #6454788 is a poorly documented report involving a 33-year old woman who experienced transient dementia during an infusion of docetaxel that includes only limited case details. The pharmacist reporter assessed the patient as being in a possible "state of drunkenness". The patient recovered and the pharmacist reported that a docetaxel formulation without alcohol would be used for the next scheduled cycle of therapy.

Reviewer Comment: These case reports further support inclusion of Warnings and Precautions information related to alcohol intoxication in docetaxel products. Since an alcohol-free version of docetaxel is not currently approved and marketed in the US, the reviewer recommends each docetaxel USPI include labeling content with a contextual statement describing the ETOH dose in g/m^2 to enable basic calculation of total ETOH dose for each patient and to compare potential ETOH exposures across docetaxel products. FDA OSE DPV-II was consulted to perform a more detailed review of the potential cases of alcohol intoxication related to docetaxel products and for advice on labeling content. A third case of alcohol intoxication (#8554908) possibly related to docetaxel was identified by the OSE DPV-II reviewer. See the OSE DPV-II review filed on February 14, 2014 for more information.

ii. The extent to which propylene glycol adds to ethanol intoxication

Propylene Glycol (PG) Exposure from Pfizer Docetaxel

The PG dose following a maximum 100 mg/m^2 dose of Pfizer docetaxel to a patient with a BSA of 2.0 m^2 (200 mg total dose) was 7.5 grams (g). The predicted end-of-infusion blood concentrations of PG are 10.8 mg/dL when using an elimination t ½ of 1.4 hours, and 12.4 mg/dL when using an elimination t ½ of 3.3 hours. [5] PG is partially (25%-45%) eliminated through renal clearance and may also be influenced by ETOH-mediated inhibition of ADH. The Applicant evaluated the differences in blood PG concentrations for the following three conditions: 1) No metabolic inhibition by ETOH; 2) Assuming only metabolic and no renal clearance (CLr); and 3) Assuming ETOH further inhibited metabolic clearance by 90%. The predicted end of infusion PG concentrations ranged from approximately 11 to 14 mg/dL when applying these three conditions. Therefore, ETOH-mediated inhibition of ADH and/or renal impairment are not predicted to result in a significant increase in PG blood concentrations.

Clinical Significance of Propylene Glycol (PG) Exposure from Pfizer Docetaxel

The PG exposure attained when Pfizer docetaxel is administered at the recommended dose using a once every 3 weeks schedule is expected to be below the threshold of clinical relevance. The predicted PG blood concentrations attained following a maximum dose of Pfizer docetaxel remain below 15 mg/dL, even when applying conditions expected to significantly reduce PG clearance. PG has been associated with CNS depressant effects similar to ETOH and mild-to-moderate reversible metabolic acidosis. These events have occurred predominantly in patients in intensive care units receiving continuous infusions (> 24 hours) of benzodiazepines and significantly higher total doses (e.g., > 28 grams). Since Pfizer docetaxel is administered as a single IV infusion, at a lower dose, and with a washout period of approximately 3 weeks between each administration; the reported cases of PG intoxication and metabolic acidosis are unlikely applicable. [6] The CNS effects of PG have also been reported to be approximately one-third as intoxicating as ETOH. [7] Based on this assumption, the intoxicating effects of PG alone are not expected to be clinically relevant or to elicit behavioral effects in humans. The additive effects of PG to ETOH-related CNS depression or behavioral effects are also expected to be minimal at these exposure levels. The Clinical Review Team conclusions related to PG exposure are consistent with those of the FDA Clinical Pharmacology and OCP Predictive Safety Teams. *See the Applicant's Response to 14-FEBRUARY-2013 FDA Complete Response Letter (4.2.1) for a more detailed literature review of PG-related intoxication or the Clinical Pharmacology review for more information.*

iii. The potential interaction between these two agents (e.g., competition for alcohol dehydrogenase)

Review of Ethanol (ETOH)-Propylene Glycol (PG) Interactions

Based on the estimated end-of infusion blood ETOH and PG concentrations following docetaxel administration, and the Km values of ETOH and PG for alcohol dehydrogenase (ADH), pharmacokinetic (PK) drug interactions resulting in significant elevations in either blood ETOH or PG concentrations are unlikely. The Km constant for alcohol dehydrogenase (ADH) is reported to be the rate-limiting metabolic step for ETOH and PG metabolism and is 10- to 20- fold higher for ETOH compared to PG. [5] The Km is the concentration required for half the maximum velocity of an enzymatic reaction to occur. The end-of-infusion PG concentrations for Pfizer docetaxel are not predicted to result in significant elevations of the ETOH blood concentration or significant slowing of ETOH metabolic elimination. ETOH may reduce the metabolic clearance of PG through inhibition of ADH. However, the blood ETOH concentration estimated to cause complete inhibition of ADH is 100 mg/dL and substantially higher than the estimated peak concentration reached following administration of Pfizer docetaxel (15 mg/dL). [5] Therefore, increases in PG blood concentrations due to an interaction with ETOH are not expected to be significant at the concentrations of ETOH delivered by Pfizer docetaxel. *See the Clinical Pharmacology review filed under this NDA on January 28, 2014 for more information.*

Alcohol-related Toxicities in Prescribing Information

There are currently no applicable US regulations or guidelines for labeling related to the content of alcohol in intravenous prescription drug products. In response to the previous FDA Clinical Information Request, the Applicant stated that the proposed labeling related to the alcohol content in Pfizer docetaxel prescribing information was based primarily on the European Guidelines for Excipients in the Label and Package Leaflet of Medicinal Products for Human Use (2003). *See the Clinical Review filed under this NDA on January 13, 2013 for more information.* The European guidelines provide a tiered approach and recommend specific labeling statements for ETOH and PG toxicities based on the total dose administered. Table 2 summarizes the European labeling guidelines for ETOH and PG.

Table 2: European Guidelines for Excipients in the Label and Package Leaflet of Medicinal Products for Human Use (Ethanol and Propylene Glycol) (2003)

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Ethanol	Oral and parenteral	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per <dose>.	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
		100 mg – 3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... ml beer, ... ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.	The package leaflet should give the equivalent volume of beer and wine, nominally calculated assuming 5% vol and 12% vol ethanol respectively. Separate warning statements may be needed in different parts of the package leaflet.
		3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... ml beer, ... ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines.	

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
			The amount of alcohol in this medicinal product may impair your ability to drive or use machines.	
Propylene Glycol and Esters	Oral and parenteral	400 mg/kg adults; 200 mg/kg children	May cause alcohol-like symptoms	

Assuming a BSA of 2.0 and a body weight of 70 kg, administration of Pfizer docetaxel at the maximum dosage (100 mg/m^2) would result in an ETOH dose of 6.4 grams and a PG dose of 7.5 g (110 mg/kg). EMA-approved medicinal products with > 3 g of ETOH per dose (like Pfizer docetaxel) include warnings that the drug product may be harmful to pregnant, breast-feeding, or pediatric patients; patients suffering from alcoholism; and patients in a high-risk group such as liver disease or epilepsy. For > 3 g per dose exposures, additional EMA labeling recommendations include warnings that alcohol content may alter the effects of other medicines and impair a patient's ability to drive or use machines.

The proposed content of labeling related to alcohol content in the Pfizer docetaxel is consistent with the EMA guidelines. The Clinical Reviewer also notes that this information is included in the EMA Taxotere Summary of Product Characteristics (SPC) intended for prescribers, and EMA the Package Leaflet (PL) intended for patients. (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000073/WC500035264.pdf; Accessed: January 13, 2014) Additionally, other EMA-approved docetaxel products (e.g., Accord docetaxel, Mylan docetaxel, Teva docetaxel) consistently include ETOH-related warnings in each product's respective SPC and PL.

Reviewer Comment: The Clinical Reviewer recommends that all of the USPIs and PPIs for currently marketed docetaxel products are updated to include Warnings and Precautions related to alcohol content with contextual statements for ETOH exposure for each drug product formulation (e.g., g/m^2; total gram dose). This is supported by case narratives of alcohol intoxication associated with the currently marketed docetaxel formulations. In general, the OSE DPV-II Review Team concurs with this recommendation. During this review, the DOP1 Clinical Review Team provided this recommendation to the DOP1 Deputy Director for Safety for consideration and potential regulatory action.

Based on the drug formulation provided by Pfizer and reviewed by the FDA Clinical Reviewer, an FDA-approved drug product with comparable exposures per dose of both ETOH and PG could not be identified in a relevant clinical setting. Taxol (paclitaxel) is an example of a drug product with ETOH that includes adult and pediatric Warnings and Precautions related to alcohol content. However, paclitaxel does not include PG and

the relevance of this comparison is limited because the dosage of ethanol when paclitaxel is given to a person with a BSA of 2.0 m^2 is approximately 28 g (versus 6.4 g for Pfizer docetaxel); an approximate four-fold increase when considering only the ETOH content of these products.

During this review, the Clinical Reviewer identified two other approved drug products [Sandimmune® (cyclosporine) (IV) and Kaletra® (lopinavir/ritonavir) (oral solution)] that deliver similar or lower per dose ETOH exposure at the recommended doses administered. Sandimmune provides an ETOH dose of approximately 2.8 g at the maximum initial recommended IV dose (6 mg/kg) for a 70 kg patient. Kaletra oral solution delivers approximately 2.1 g of ETOH and 0.8 g of PG at the recommended daily adult dose (400 mg/100mg). Both of these drug products include Warnings and Precautions statements in the approved USPIs for patients sensitive to alcohol-related toxicities. Kaletra also includes pediatric (infants and young children) warnings related to PG.

Reviewer Comment: The EMA guidelines and the approved products contain lower dose thresholds for ETOH and PG exposure than those delivered by Pfizer Docetaxel. The EMA guidelines and the FDA labeling precedents established by Sandimmune and Kaletra support inclusion of specific warning statements for sensitive (and vulnerable) patients in the Pfizer docetaxel prescribing information.

Reviewer Comments/Conclusions

The total ethanol (ETOH) dose and estimated blood ETOH concentrations were higher for Pfizer docetaxel (15 mg/dL) than for the referenced drug product (Taxotere 2-vial formulation) (5 mg/dL) or for the currently marketed Taxotere 1-vial formulation (~10 mg/dL). For the low-moderate levels of ETOH exposure delivered by these docetaxel products, the small increase in the ETOH exposure for Pfizer docetaxel is not expected to result in significant differences in psychomotor dysfunction, CNS depression, or the overall safety profile when compared to other approved docetaxel products.

The total doses of propylene glycol (PG) appear to be below the threshold of clinical relevance. PG is not expected to produce alcohol intoxication at the recommended dose or schedule that Pfizer docetaxel is administered. Pharmacokinetic interactions resulting in further elevations in blood ETOH or PG concentrations are not predicted to significantly increase the exposure of ETOH or PG for Pfizer docetaxel. The additive effects of PG to ETOH-related CNS depression or behavioral effects are expected to be minimal at these exposure levels.

Since it is desirable to minimize the ETOH exposure in vulnerable or sensitive patients as much as possible, labeling that includes a contextual statement with ETOH dose level for each docetaxel product is expected to adequately manage the small differences in alcohol exposure. The labeling content incorporated into the Pfizer docetaxel prescribing information (USPI) and patient package insert (PPI) is expected to

adequately manage potential safety risks associated with alcohol exposure (*see Section 8 of this review*). The other approved docetaxel product USPI and PPIs should be updated with labeling content consistent with the alcohol content-related labeling in the Pfizer docetaxel USPI and PPI. This will enable adequate assessments of the ethanol content across these products by healthcare practitioners and facilitate appropriate management of alcohol related risks in sensitive or vulnerable patient populations.

8 Review of Labeling

This does not reflect the final, agreed upon labeling, but the labeling revisions initially recommended to the Applicant by the Agency.

> Reviewer Comment: To be consistent with the referenced product (Taxotere), an FDA information request was sent to the Applicant to update and resubmit the Pfizer Docetaxel USPI to include updated Warnings and Precautions for eye disorders and pediatric safety information.

The Applicant's labeling revisions for the Highlights of Prescribing Information, the existing Warnings and Precautions (W&Ps) subsection for neurologic reactions (5.8), a new W&Ps subsection (5.12) for alcohol content, and the Patient Counseling Information (17), and Patient Package Insert (PPI) are listed below. The FDA Reviewer revisions are annotated in track changes (i.e., removed text is in strikethrough font; new text is underlined):

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

- Neurologic reactions: (b) (4)

……

- Alcohol content: The alcohol content in a dose of Docetaxel Injection- (b) (4) may affect the central nervous system- (b) (4) ability to drive or use machines immediately after infusion.- (b) (4)

FULL PRESCRIBING INFORMATION

5. WARNINGS AND PRECAUTIONS

5.8 Neurologic Reactions

Severe neurosensory symptoms (e.g., paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued *[see Dosage and Administration (2.7)]*. Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

(b) (4)

Reviewer Comment: This deleted labeling content was moved to the subsection for Alcohol Content (5.12).

.....

5.12 Alcohol Content

Cases of alcohol intoxication have been reported with docetaxel. (b) (4)
(b) (4)

The alcohol content in a dose (b) (4) (b) (4) of Docetaxel Injection may affect the central nervous (b) (4) and (b) (4) should be taken into account for patients in whom alcohol intake should be avoided or minimized. (b) (4)

Consideration should be given to the alcohol content in Docetaxel Injection (b) (4) on the ability to drive or use machines immediately after the infusion. Each administration of Docetaxel Injection at 100 mg/m^2 delivers 3.2 g/m^2 of ethanol. For a patient with a BSA of 2.0 m^2, this would deliver 6.4 grams of

ethanol *[see Description (11)]*. [redacted] other docetaxel products [redacted] have a lesser amount of alcohol.

Reviewer Comment: Cases of alcohol intoxication have been reported for the currently marketed docetaxel formulations. [8] Pfizer docetaxel has more alcohol than all of the currently marketed docetaxel products at the present time, so these cases are relevant, and warrant labeling statements in the Pfizer docetaxel USPI.

8. USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

…….

The alcohol content of Docetaxel Injection should be taken into account when given to pediatric patients. *[see Warnings and Precautions (5.12)]*

8.6 Hepatic Impairment

…….

The alcohol content of Docetaxel Injection should be taken into account when given to patients with hepatic impairment. *[see Warnings and Precautions (5.12)]*

…….

17. PATIENT COUNSELING INFORMATION

…….

- Explain to patients the possible effects of the alcohol content in Docetaxel Injection [redacted] including possible effects on the central nervous system [redacted] atients in whom alcohol should be avoided or minimized should consider the alcohol content of docetaxel injection. Alcohol could impair their ability to drive or use machines immediately after infusion.

…….

Patient Information

[redacted] Docetaxel Injection Concentrate

[redacted]

.....

What is the most important information I should know about Docetaxel?
Docetaxel can cause serious side effects, including death.

.....

[redacted]

9 References

[1] Eckardt, MJ. Et. al. Effects of Moderate Alcohol Consumptions on the Central Nervous System. Alcohol Clin and Env Res. 1998;(22)(5):998-1040.

[2] Ferrara, SD., Zancaner, S., Gioretti, R. Low blood alcohol concentrations and driving impairment. Int J Leg Med 1994; (106):169-177.

[3] Ethanol. Micromedex 2.0 POISONDEX® Managements. Truven Health Analytics. www.thompsonhc.com/micromedex2. Accessed January 8, 2013.

[4] *Excipients in the label and package leaflet of medicinal products for human use.* Medicinal Products for Human Use: Safety, Environment and Information. European Commission. Enterprise Directorate-General (2003) Vol. 3B, Rev.1.

[5] Speth PA et al. Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. Ther Drug Monit 1987:9(3):255-8.

[6] Kraut and Kurtz. Toxic alcohol ingestions: Clinical features, diagnosis and management. Clin J AM soc Nephrol 2008;3(1):208-25.

[7] Rowe, RC., Sheskey, PJ., Quinn, ME. Propylene Glycol. Handbook of Pharmaceutical Excipients, Sixth Edition. American Pharmacists Association. 2009:592-593.

[8] Mirza A, Mithal N. Alcohol intoxication with the new formulation of docetaxel. Clinical Oncology 2011;23:560-61

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/s/

WILLIAM F PIERCE
02/26/2014

VIRGINIA E MAHER
02/26/2014

Cross-Discipline Team Leader Review

DATE	31-JAN-2013
From	Nallaperumal Chidambaram, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	202356
Applicant	Pfizer, Inc.
Date of Submission	14-AUG-2012
PDUFA Goal Date	14-FEB-2013
Proprietary Name/ Established (USAN) names	Docetaxel Injection
Dosage forms / Strength	20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL and 200 mg/20 mL
Proposed Indication(s)	1. Breast cancer 2. Non-small cell lung cancer 3. Prostate cancer 4. Gastric adenocarcinoma 5. Head and neck cancer
Recommendation:	**Complete response** (1) Deficiencies related to Chemistry, manufacturing and controls. (2) Unresolved safety issue. (3) Pending information request dated 12-DEC-2012. (4) Pending overall acceptable recommendation from the Office of Compliance.

1. Introduction

Pfizer submitted a complete response on 14-AUG-2012 to the issues noted in the complete response letter dated 29-FEB-2012 to NDA (b) (4) for Docetaxel Injection. This application was filed on 13-OCT-2012.

This CDTL memo serves to summarize the critical issues noted in all review disciplines and recommends a "**complete response**" action for this application. All individual discipline reviews may be found in DARRTS. Due to intended complete response action, information requests from CMC and Clinical were not conveyed to the applicant. Furthermore, PI was not negotiated during this review cycle.

2. Background

The Reference Listed Drug for this submission is the one-vial formulation of Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), which is currently marketed by Sanofi Aventis. The proposed drug product is a "ready to use" product containing the drug substance (in solution) in one vial. The solution is intended for reconstitution and subsequent intravenous injection. Docetaxel Injection is supplied in four presentations (20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL and 200 mg/20 mL). All four presentations utilize the same concentration of 10 mg/mL. The proposed drug product is formulated with polysorbate 80 as a [(b) (4)], propylene glycol and ethanol as [(b) (4)], disodium edentate as a [(b) (4)], and citric acid for pH adjustment. The proposed formulation contains higher levels of ethanol (40% v/v, compared with [(b) (4)]% v/v present in Taxotere), as well as polysorbate-80 ([(b) (4)]% in Taxotere compared to [(b) (4)]% in the proposed formulation). In addition, the proposed formulation contains propylene glycol, disodium edentate, and anhydrous citric acid, which are not present in the innovator product.

Dosing Regimen and Administration

Multiple indications and dosing regimens are associated with this NDA. Please refer to the Medical Officer's 11-JAN-2013 review for additional details.

3. CMC

General product quality considerations

The CMC reviewer (Ms. Josephine Jee) in her review #3 dated 18-JAN-2013 and signed 30-JAN-2013 recommended a Complete Response for this application due to (1) four Chemistry deficiencies, (2) safety concerns expressed by the Medical Officer and (3) pending compliance recommendation.

The four Chemistry deficiencies are related to:
(1) components/composition statement to indicate the exact amount of ethanol, propylene glycol and polysorbate-80, (2) acceptance criteria for ethanol, (3) testing for ethanol on stability and (4) in-use stability data.

ONDQA Biopharm review

The Biopharm reviewer (Dr. Elsbeth Chikhale) noted in her review dated 19-NOV-2012 that the CR letter dated 29-FEB-2012 did not include Biopharmaceutics deficiencies and that there is no change to the drug product formulation to that was submitted in the original submission, therefore the request to waive the *in vivo* bioequivalence study requirement remains acceptable and that this application is recommended for approval.

Facilities review/inspection

The Office of Compliance is yet to issue an overall acceptable recommendation. The inspection status is pending since 17-AUG-2012.

Microbiology

The microbiology reviewer (Dr. J. Metcalfe) NAI'd the submission on 31-JAN-2013 and noted that the resubmission did not contain any new product quality Microbiology issues to review.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer (Dr. Haw-Jay Chiu) in his review dated 15-JAN-2013 noted that the applicant satisfactorily responded to the non-clinical deficiencies related to impurities and leachables that were noted in the complete response letter dated 29-FEB-2012. However, adequate justification for the level of ethanol and propylene glycol in the formulation was not provided for the non-clinical review team to conclude with a reasonable level of certainty that there will not be a change in the associated risk to benefit ratio compared to the RLD. The non-clinical reviewer further concluded that conducting additional non-clinical studies to address this issue is not warranted, and therefore, this application was deemed approvable from his perspective.

5. Clinical Pharmacology

The Clinical Pharmacology reviewer (Dr. Jeanne Fourie Zirkelbach) noted no new Clinical Pharmacology information was provided. Based on the original submission, this submission was found to be acceptable (refer to her review dated 17-JAN-2013). The reviewer however summarized Clinical Pharmacology labeling recommendations for this application. Due to the intended complete response action, no labeling comments were forwarded.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Not applicable.

8. Safety

There are no new clinical data submitted in the application. However, during review of updated USPI and PPI and a comparison of the proposed labeling to approved labeling for the RLD, the Clinical reviewer (Dr. W. Pierce) noted the following in his memo dated 11-JAN-2013:

The proposed NDA for docetaxel injection, in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic (F, D, and C) Act, was submitted to request approval of Pfizer docetaxel. This 505(b)(2) application relies on the efficacy and safety findings from Taxotere (docetaxel) (i.e., referenced drug product) reviewed and approved under NDA 20-449. The ethanol and propylene glycol in the proposed Pfizer docetaxel formulation may result in a difference in the safety profiles of this product and the referenced drug (Taxotere) being relied upon for this 505(b)(2). Based on this concern, Pfizer proposed new safety information, including a new Warning and Precaution, related to potential alcohol-related toxicities not found in the reference drug product or in any of the USPIs for other docetaxel drug products currently approved and marketed in the US.

The Applicant has not provided adequate information to conclude that the safety findings from Pfizer docetaxel would be consistent with safety of Taxotere due to potential alcohol-related toxicities that may be a unique safety issue for the reformulated Pfizer docetaxel product. The Applicant has created a new formulation of docetaxel that delivers a two- or three-fold increase in the amount of ethanol administered per dose compared to the ethanol that is delivered with each dose of the referenced drug. The magnitude of this alcohol exposure exceeds the alcohol exposure of all of the previously approved docetaxel products currently marketed in the United States (US) and maybe clinically relevant. When factoring in the potential additive effects and metabolic interactions between ethanol and propylene glycol, also unique to the Pfizer docetaxel formulation, additional intensification of alcohol-related toxicities is possible.

The Applicant did not provide comparable product experience with similar levels of exposure for both ethanol and propylene glycol (e.g., blood alcohol estimates/levels or clinical experience). The magnitude and clinical significance of potential alcohol-related toxicities, and the difference between this docetaxel product and the referenced or other marketed docetaxel drug products, remains uncertain without additional clinical information.

Based on this unresolved safety issue, which appears to be unique to Pfizer docetaxel, the Clinical Reviewer recommends that this 505(b)(2) resubmission receive a Complete Response.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

Not applicable

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP): This application is not in the AIP list.
Exclusivity or patent issues of concern: No issues were noted for this NDA.
Financial disclosures: None submitted or needed
Other GCP issues: None
DSI audits: Not applicable
Other discipline consults: DMPP

DMPP:

The DMPP reviewer (Nathan Caulk) noted in his memo dated 29-JAN-2013 that owing to intended CR action he would defer his comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter.

Any other outstanding regulatory issues: None

12. **Labeling**

An information request with labeling comments were sent to the applicant on 12-DEC-2012 and applicant's response is still pending.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

This reviewer recommends **complete response** for this NDA

Risk Benefit Assessment

The review of this NDA is based primarily on chemistry, manufacturing and controls data. However, there are deficiencies related to (1) Chemistry, manufacturing and controls and (2) unresolved safety issue. In addition, an overall acceptable recommendation is pending from the office of Compliance. Therefore, this application cannot be recommended for approval until all the above deficiencies are satisfactorily addressed, and an overall acceptable recommendation is received from the Office of Compliance.

Recommendation for Postmarketing Risk Management Activities

This does not apply to this NDA.

Recommendation for other Postmarketing Study Commitments

None

Recommended Comments to Applicant

Please forward the deficiencies noted in the CMC review (Ms. Josephine Jee) dated 18-JAN-2013 signed 30-JAN-2013 (p. 33), and the comments noted by the Clinical reviewer (Dr. W. Pierce) dated 11-JAN-2013 (p. 18). Also indicate the pending information request sent on 12-DEC-2012.

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/s/

NALLAPERUM CHIDAMBARAM
01/31/2013

CLINICAL REVIEW

Application Type	NDA 505(b)(2) (Resubmission)
Application Number(s)	202356
Priority or Standard	Not Applicable
Submit Date(s)	August 14, 2012
Received Date(s)	August 14, 2012
PDUFA Goal Date	February 14, 2013
Division / Office	DOP1 / OHOP
Clinical Reviewer	William Pierce, PharmD
Clinical Team Leader	V. Ellen Maher, MD
Review Completion Date	January 11, 2013
Established Name	docetaxel
(Proposed) Trade Name	Docetaxel Injection
Therapeutic Class	Microtubule inhibitor
Applicant	Pfizer, Inc.
Formulation(s)	IV
Dosing Regimen	Multiple (see product information, 2.1)
Indication(s)	Multiple (see product information, 2.1)
Intended Population(s)	Multiple (see product information, 2.1)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The proposed NDA for docetaxel injection, in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic (F, D, and C) Act, was submitted to request approval of Pfizer docetaxel. This 505(b)(2) application relies on the efficacy and safety findings from Taxotere (docetaxel) (i.e., referenced drug product) reviewed and approved under NDA 20-449. The ethanol and propylene glycol in the proposed Pfizer docetaxel formulation may result in a difference in the safety profiles of this product and the referenced drug (Taxotere) being relied upon for this 505(b)(2). Based on this concern, Pfizer proposed new safety information, including a new Warning and Precaution, related to potential alcohol-related toxicities not found in the reference drug product or in any of the USPIs for other docetaxel drug products currently approved and marketed in the US.

The Applicant has not provided adequate information to conclude that the safety findings from Pfizer docetaxel would be consistent with safety of Taxotere due to potential alcohol-related toxicities that may be a unique safety issue for the reformulated Pfizer docetaxel product. The Applicant has created a new formulation of docetaxel that delivers a two- or three-fold increase in the amount of ethanol administered per dose compared to the ethanol that is delivered with each dose of the referenced drug. The magnitude of this alcohol exposure exceeds the alcohol exposure of all of the previously approved docetaxel products currently marketed in the United States (US) and maybe clinically relevant. When factoring in the potential additive effects and metabolic interactions between ethanol and propylene glycol, also unique to the Pfizer docetaxel formulation, additional intensification of alcohol-related toxicities is possible.

The Applicant did not provide comparable product experience with similar levels of exposure for both ethanol and propylene glycol (e.g., blood alcohol estimates/levels or clinical experience). The magnitude and clinical significance of potential alcohol-related toxicities, and the difference between this docetaxel product and the referenced or other marketed docetaxel drug products, remains uncertain without additional clinical information.

Based on this unresolved safety issue, which appears to be unique to Pfizer docetaxel, the Clinical Reviewer recommends that this 505(b)(2) resubmission receive a Complete Response.

1.2 Risk Benefit Assessment

Please refer to NDA 20449.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: docetaxel

Proprietary Name: Docetaxel Injection, solution

Applicant: Pfizer, Inc.
235 East 42nd Street
New York, NY 10017
Tel: (212) 733-2061
Fax: (212) 833-5567

Drug Class: Microtubule inhibitor

Proposed Indications

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.

Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic 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 Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN.

Proposed Dosage and Administration
Administered IV over 1 hr every 3 weeks (1 cycle) for the following cancers:

- BC, locally advanced or metastatic: 60-100 mg/m^2 single agent
- BC adjuvant: 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 for 6 cycles
- NSCLC, after platinum failure: 75 mg/m^2 single agent
- NSCLC, chemotherapy-naive: 75 mg/ m^2 followed by cisplatin 75 mg/ m^2
- HRPC: 75 mg/ m^2 with 5 mg prednisone twice a day continuously

- 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
- Induction chemotherapy of inoperable SCCHN followed by radiotherapy: 75 mg/ m^2 followed by cisplatin 75 mg/ m^2 IV (day 1), followed by fluorouracil 750 mg/ m^2 per day as a continuous 24-hr IV infusion (days 1-5) for 4 cycles.
- Induction chemotherapy followed by chemoradiotherapy of locally advanced SCCHN: 75 mg/ m^2 followed by cisplatin 100 mg/ m^2 IV (day 1), followed by fluorouracil 1000 mg/ m^2 per day as a continuous 24-hr IV infusion (days 1-4) for 3 cycles.

Premedication Regimen

- Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice a day) for 3 days starting 1 day before administration
- HRPC: oral dexamethasone 8 mg at 12 hours, 3 hours, and 1 hour before treatment

For dosage adjustments during treatment see full prescribing information.

Dosage Forms and Strengths

- 20 mg/2 mL single-dose vial
- 80 mg/8 mL single-dose vial
- 130 mg/13 mL single-dose vial
- 200 mg/20 mL single-dose vial

Contraindications

- Hypersensitivity to docetaxel injection or polysorbate 80
- Neutrophil counts of <1500 cells/mm^3

Warnings and Precautions

- Secondary acute myeloid leukemia (when administered with anthracycline and/or cyclophosphamide)
- Cutaneous reactions (erythema, desquamation)
- Neurologic reactions (paresthesia, dysesthesias, pain, [redacted] (b) (4))
- [redacted] (b) (4)
- Asthenia
- Alcohol content*

Reviewer Comment: New alcohol-related safety information, including a new Warning and Precaution, have been proposed by Pfizer due to an increase in the ethanol content in the Pfizer docetaxel product compared to the RLD. See Section 7 of this review for more information.

Adverse Reactions
The most common adverse reactions are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

2.2 Availability of Proposed Active Ingredient in the United States

Taxotere (docetaxel) is marketed in the US. Multiple other drug products containing the docetaxel active ingredient are marketed in the US. See Table 1 for more information.

2.3 Summary of Presubmission Regulatory Activity Related to Submission

On November 1, 2010, a pre-IND (109,463) meeting was held to discuss a proposal for a 505(b)(2) submission. On April 29, 2011, the original NDA 202356 was submitted under the 505(b)(2) pathway by Pfizer, Inc. On February 29, 2012, FDA issued a Complete Response (CR) to the Applicant due to the numerous nonclinical and product quality deficiencies as conveyed in the CR letter. Due to these deficiencies, a review of the proposed prescribing information for this docetaxel product was not conducted during the original NDA review. On June 7, 2012, a Type A meeting was held between the FDA and the Applicant to discuss this proposed resubmission. On August 14, 2012, the Applicant submitted a Class 2 NDA resubmission in accordance with 21 CFR 314.110.

2.4 Pediatric Waiver

The original pediatric exclusivity of Taxotere ended on November 14, 2010. The pediatric use information for the referenced drug product is based on data submitted in response to a pediatric Written Request and is protected by pediatric exclusivity under the Best Pharmaceuticals for Children Act (BPCA) until May 13, 2013.

The innovator product was issued a pediatric Written Request (WR), fairly complied with the terms of the WR, and received pediatric exclusivity, but no pediatric indication was sought. The labeling provides information regarding safety and dosing (including dose-limiting toxicity). The question of whether pediatric language in labeling should be "carved-out" or retained in 505(b)(2) applications resulted in a consult to the Pediatric and Maternal Health staff regarding another 505(b)(2) application (NDA 200795) and its referenced drug product (Gemcitabine). The Best Pharmaceuticals for Children Act (BPCA) does not address the protected pediatric information of 505(b)(2) products, only generic products. Therefore, the PMH staff believes omitting pediatric language may be appropriate for a 505(b)(2) product when removal of the language will not result in a safety concern for pediatric patients.

Because the referenced drug product (Taxotere) is not indicated for use in the pediatric population and toxicities seen in pediatric patients were similar to those seen in adults,

Docetaxel Injection, if used in the pediatric oncology population, is unlikely to pose a significant or unknown safety risk. The pediatric information protected under the BPCA act can be carved out of the docetaxel labeling consistent with previous docetaxel NDA labeling reviews and approvals.

2.5 Other Relevant Background Information

The sponsor of NDA 20449 for Taxotere is Sanofi-Aventis, Inc. The Taxotere NDA, NDA 20449, has been previously reviewed for efficacy and safety for multiple therapeutic indications. In addition to the approval of Taxotere, other drug products containing the docetaxel active ingredient have been approved and were deemed therapeutically equivalent to Taxotere or to the 10 mg/mL docetaxel injection product (Hospira, Inc.). Table 1 lists the current docetaxel products with therapeutic equivalence according to the Orange Book.

Table 1: Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Appl No	TE Code[4]	RLD[5]	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N201195		No	DOCETAXEL	INJECTABLE; INJECTION	160MG/8ML (20MG/ML)	DOCETAXEL	ACCORD HLTHCARE
N201195	AP	No	DOCETAXEL	INJECTABLE; INJECTION	20MG/0.5ML (40MG/ML)	DOCETAXEL	ACCORD HLTHCARE
N201195	AP	No	DOCETAXEL	INJECTABLE; INJECTION	20MG/ML (20MG/ML)	DOCETAXEL	ACCORD HLTHCARE
N201195	AP	No	DOCETAXEL	INJECTABLE; INJECTION	80MG/2ML (40MG/ML)	DOCETAXEL	ACCORD HLTHCARE
N201195	AP	No	DOCETAXEL	INJECTABLE; INJECTION	80MG/4ML (20MG/ML)	DOCETAXEL	ACCORD HLTHCARE
N022312	AP	No	DOCETAXEL	INJECTABLE; INJECTION	20MG/0.5ML (40MG/ML)	DOCETAXEL	APOTEX INC
N022312	AP	No	DOCETAXEL	INJECTABLE; INJECTION	80MG/2ML (40MG/ML)	DOCETAXEL	APOTEX INC
N022234	AP	Yes	DOCETAXEL	INJECTABLE; INJECTION	160MG/16ML (10MG/ML)	DOCETAXEL	HOSPIRA INC
N022234	AP	Yes	DOCETAXEL	INJECTABLE; INJECTION	20MG/2ML (10MG/ML)	DOCETAXEL	HOSPIRA INC
N022234	AP	Yes	DOCETAXEL	INJECTABLE; INJECTION	80MG/8ML (10MG/ML)	DOCETAXEL	HOSPIRA INC
N201525	AP	No	DOCETAXEL	INJECTABLE; INJECTION	160MG/16ML (10MG/ML)	DOCETAXEL	SANDOZ
N201525	AP	No	DOCETAXEL	INJECTABLE;	20MG/2ML	DOCETAXEL	SANDOZ

Appl No	TE Code[4]	RLD[5]	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
				INJECTION	(10MG/ML)		
N201525	AP	No	DOCETAXEL	INJECTABLE; INJECTION	80MG/8ML (10MG/ML)	DOCETAXEL	SANDOZ
N020449	AP	Yes	DOCETAXEL	INJECTABLE; INJECTION	20MG/ML (20MG/ML)	TAXOTERE	SANOFI AVENTIS US
N020449	AP	Yes	DOCETAXEL	INJECTABLE; INJECTION	80MG/4ML (20MG/ML)	TAXOTERE	SANOFI AVENTIS US
N022534		Yes	DOCETAXEL	INJECTABLE; INJECTION	20MG/VIAL	DOCEFREZ	SUN PHARMA GLOBAL
N022534		Yes	DOCETAXEL	INJECTABLE; INJECTION	80MG/VIAL	DOCEFREZ	SUN PHARMA GLOBAL

Source: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm.
Accessed January 5, 2013.

3 Ethics and Good Clinical Practices

Not applicable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

None identified.

5 Sources of Clinical Data

No new clinical data was submitted for this NDA.

6 Review of Efficacy

Not applicable.

7 Review of Safety

On October 31, 2012, the Applicant submitted (STN #13; eCTD 0012) an updated Docetaxel USPI and PPI to NDA 202356 for the proposed docetaxel product. The Applicant also provided a comparison of the proposed labeling to the approved labeling

text for the referenced drug. During review of the proposed docetaxel USPI and these documents, FDA identified that Pfizer proposed new safety information related to potential alcohol-related toxicities. This new safety information included a Warnings and Precautions (W& P) subsection for alcohol content (5.11) not found in the reference drug product or in any of the USPIs for other docetaxel drug products currently approved and marketed in the US. The Applicant's rationale for this new safety labeling is "Pfizer's formulation contains propylene glycol and higher levels of ethanol, both of which can contribute to alcohol-like symptoms."

The Applicant's labeling revisions for the Highlights of Prescribing Information, the existing W&P subsection for neurologic reactions (5.8), a new W&P subsection (5.11), and the Patient Counseling Information (17) and Patient Package Insert (PPI) are listed below (new text is underlined):

----------WARNINGS AND PRECAUTIONS----------

- Neurologic reactions: (b) (4)
- Alcohol content: (b) (4)

5.8 Neurologic Reactions

Severe neurosensory symptoms (*e.g.,* paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued *[see Dosage and Administration (2.7)]*. Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

(b) (4)

5.11 Alcohol Content

(b) (4)

17. PATIENT COUNSELING INFORMATION

- Explain to patients the possible effects of the alcohol content in Docetaxel, including possible effects on the central nervous system, (b) (4)

Patient Information

(b) (4)
(b) (4) **Docetaxel Injection Concentrate**

What is the most important information I should know about Docetaxel?
Docetaxel can cause serious side effects, including death.

(b) (4)

Reviewer Comment: The Applicant did not provide any additional information to support the new safety information related to alcohol-related toxcities in the proposed Pfizer docetaxel labeling.

On October 9, 2012, FDA sent the following Clinical information Request (CIR) to request additional information related to potential alcohol-related toxicities:

> With regards to the proposed labeling in subsections 5.8 and 5.11, Section 17, and the Patient Information that relate to new safety information due to the propylene glycol and ethanol content in this docetaxel formulation, provide a more detailed rationale that includes at least the following:
>
> 1. Estimations of the blood alcohol levels (BALs) and propylene glycol levels that will result in patients who are treated with this docetaxel product
>
> 2. A discussion of the clinical significance of the estimated BAL and propylene glycol levels
>
> 3. A discussion comparing the estimated levels to the reference listed drug product and other approved docetaxel formulations
>
> 4. A rationale that supports the additional warning labeling proposed in this resubmission
>
> 5. A discussion of any other additional actions that may be required based on the findings provided in items #1 - #4.

On October 24, 2012, Pfizer submitted a response (STN #14; eCTD 0013) to the FDA CIR.

Pfizer's response to FDA Comment #1 stated that "the actual blood concentrations of ethanol following a high dose infusion of Pfizer Docetaxel (maximum TDI of 6.4 g ethanol, or 0.09 g/kg for a 70 kg individual, administered over 1 hour) are difficult to estimate" and are "likely to be substantially less than 50 mg/dL" based on zero order kinetics and the data listed in Table 2.

Table 2: Estimated Blood Alcohol Concentration after Intravenous Infusion with Ethanol

(copied from Applicant's response to CIR- October 24, 2012)

Study Author	Infusion Rate	Approximate total daily intake	Duration of infusion	Blood alcohol level at the end of infusion
Jones et al[1]	0.4 g ethanol per kg body weight	28 g ethanol for a 70 kg individual	0.5h	84.7 mg/dL*
Jones et al[2]	0.6 g ethanol per kg body weight	42 g ethanol for a 70 kg individual	1h	108 mg/dL*
Rangno et al[3]	0.375 g ethanol per kg body weight	26.3 g ethanol for a 70kg individual	0.5h	88 mg/dL†

* *Venous blood alcohol level reported*

† *Plasma alcohol level reported*

[1] Jones AW, Norberg A, Hahn RG. Concentration-time profiles of ethanol in arterial and venous blood and end-expired breath during and after intravenous infusion. J Forensic Sci. 1997 Nov; 42(6):1088-94.

[2] Jones AW, Hahn RG, Stalberg HP. Pharmacokinetics of ethanol in plasma and whole blood: estimation of total body water by the dilution principle. Eur J Clin Pharmacol. 1992; 42(4):445-8.

[3] Rangno RE, Kreeft JH, Sitar DS. Ethanol 'dose-dependent' elimination: Michaelis-Menten v classical kinetic analysis. Br J Clin Pharmacol. 1981 Nov;12(5):667-73.

Pfizer's response to FDA Comment #2 acknowledged that patients who receive the Pfizer docetaxel product may have higher blood alcohol levels than patients administered the referenced drug product. Based on the assumption that the blood alcohol levels will be "significantly less than 50 mg/dL", the applicant stated that "modestly higher levels of ethanol in Pfizer docetaxel are therefore considered unlikely to elicit clinically appreciable differences when compared to Taxotere". The clinical relevance and resultant alcohol intoxication effects for higher levels of exposure ($\geq$ 100 mg/dL) are well established. Blood alcohol levels of 50 mg/dL or less may also result in "increased talkativeness, increased relaxation, and impairment of some tasks requiring skill" [1], and may therefore be clinically relevant.

Reviewer Comment: The alcohol exposure that would result from administration of the proposed Pfizer docetaxel product has not been well characterized. The Applicant's estimation of blood alcohol concentration and the conclusion that the blood alcohol levels for this docetaxel product will be less than 50 mg/dL are plausible; but significantly confounded by multiple factors and have not been well established.

The Applicant did not provide evidence for alcohol exposure consistent with the levels administered with the proposed docetaxel product (i.e., 6.4 g; 0.9 g/kg body weight). Variability in the pharmacokinetics (e.g., rate and extent of absorption, distribution, elimination) of ethanol is well documented. [2] Projecting blood alcohol levels to predict alcohol-related toxicities for patients treated with the higher doses of ethanol, in the absence of propylene glycol, is problematic.

Potential pharmacodynamic and pharmacokinetic interactions between ethanol and propylene glycol exist for the proposed docetaxel drug formulation. The significance of propylene glycol and potential additive alcohol-related toxicities has not been well characterized by the Applicant. Propylene glycol is estimated to be one-third as intoxicating as ethanol. [3] Additionally, the magnitude of the pharmacokinetic interaction on blood alcohol levels is also unclear. The rate limiting step in oxidation and conversion of ethanol to acetaldehyde involves alcohol dehydrogenase (ADH); which becomes saturated quickly. This is also the primary pathway for propylene glycol metabolism and clearance. [4]

In the response to FDA Comment #3, the Applicant provided Table 3, which lists the total intake of ethanol for the referenced product and other docetaxel products when a 200 mg dose (100 mg/m^2 dosage for person with a BSA of 2.0 m^2) is administered. The FDA reviewer verified the ethanol intake (per gram) for each docetaxel product was accurate.

Table 3: Total Daily Intake of Ethanol from Docetaxel Injection Drug Products

(copied from Applicant's response to CIR- October 24, 2012)

Product Name (Sponsor)	Total Daily Intake of Ethanol*
Taxotere 2-vial, RLD (Sanofi) †	2.0 g
Docetaxel 1-vial (Hospira)	3.7 g
Docetaxel 1-vial (Accord)	4.0 g
Taxotere 1-vial (Sanofi)	4.0 g
Docetaxel 1-vial (Sandoz)	5.5 g
Docetaxel 1-vial (Pfizer)	6.4 g

* *Total Daily Intake assumes that the maximum dose of 200 mg docetaxel is administered.*
† *RLD: Reference Listed Drug*

Reviewer Comment: The FDA reviewer reviewed the USPIs for the docetaxel products listed in Table 1 and Table 3. With the exception of the Sandoz docetaxel, for the 200 mg dose, all of the docetaxel products result in ≤ 4.0 grams of ethanol exposure. The Sandoz product results in a difference in ethanol exposure of approximately only 1 g per dose. However, the Pfizer docetaxel product would also result in 7.5 g of propylene glycol exposure. With the exception of the proposed Pfizer docetaxel product, none of the currently marketed docetaxel products include propylene glycol in addition to ethanol in their drug formulations.

Pfizer concludes that "any differences in blood alcohol levels between the use of Pfizer Docetaxel versus Taxotere are likely to be minimal, and insufficient to produce clinically significant differences in the safety profile of Pfizer Docetaxel relative to Taxotere." Pfizer also states that the "additive effect of propylene glycol in Pfizer Docetaxel on alcohol-like symptoms are minimal" based on the requirement for high levels of propylene glycol to contribute to alcohol-like symptoms. This assumption is supported with a reference to the European guidance document [Volume 3B (July 2003)], *Excipients in the label and package leaflet of medicinal products for human use.* The European guidance recommends labeling should include a "may cause alcohol-like symptoms" if a drug product results in the administration of a ≥ 400 mg/kg dose of propylene glycol. For the Pfizer docetaxel product, the dosage of propylene glycol for a 200 mg dose administered to a 70 kg patient with a BSA of 2.0 is 7.5 g and would result in an approximate 110 mg/kg dose of propylene glycol.

Reviewer Comment: The Pfizer assumption relies on an estimation of propylene glycol toxicities for "alcohol-like symptoms" in the absence of ethanol. This assumption does not take into account the combined additive effects of propylene glycol and the potential pharmacokinetic interaction between the ethanol and the propylene glycol present in this docetaxel formulation. The FDA reviewer could not identify other relevant experience with drug products that included comparable exposures for both ethanol and propylene glycol (i.e., ~6.4 g ethanol with ~7.5 g of propylene glycol)

In the response to FDA Comment #4 from the FDA CIR, Pfizer states that there are currently no FDA Guidance documents related to the ethanol and propylene glycol drug excipients. The proposed labeling in the USPI was based on European guidance recommendations for labeling of products with > 3 g of ethanol per dose. Table 4 shows the European Guidance recommendations for ethanol and propylene glycol for the "Package Leaflet".

Table 4: 2003 European Guidelines for Excipients in the Label and Package Leaflet of Medicinal Products for Human Use (ethanol and propylene glycol)

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Ethanol	Oral and parenteral	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per <dose>.	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
		100 mg – 3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... ml beer, ... ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.	The package leaflet should give the equivalent volume of beer and wine, nominally calculated assuming 5 % vol and 12% vol ethanol respectively. Separate warning statements may be needed in different parts of the PL.
		3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... ml beer, ... ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may impair your ability to drive or use machines.	
Propylene Glycol and	Oral and parenteral	400 mg/kg adults; 200 mg/kg	May cause alcohol-like symptoms	

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Esters		children		

Based on the drug formulations provided by Pfizer and reviewed by the FDA clinical reviewer, an FDA-approved drug product with comparable exposures per dose of both ethanol and propylene glycol could not be identified in a relevant clinical setting. Pfizer provided Taxol (paclitaxel) as an example of a drug product with ethanol that includes adult and pediatric Warnings and Precautions that are related to alcohol content and toxicities. However, Taxol does not include propylene glycol and the relevance of this comparison is limited because the dosage of paclitaxel for a person with a BSA of 2.0 m^2 is approximately 23 g (versus 6.4 g for Pfizer docetaxel) of ethanol; an approximate four-fold increase when considering only the ethanol content of these products. Pfizer also identified Phenytoin Injection for comparison, but the relevance of this product is also limited since the dosage for a 70 kg patient includes only 1.6 g of ethanol with 8.7 g of propylene glycol. Phenytoin Injection does not have Warnings and Precautions included in the package insert related to propylene glycol content or alcohol-like symptoms. Therefore, these products are not comparable to the proposed Pfizer docetaxel product with respect to the levels of exposure for both ethanol and propylene glycol.

Reviewer Comments/Conclusions/Recommendations

The ethanol and propylene glycol in the proposed Pfizer docetaxel formulation may result in a difference in the safety profiles between Pfizer docetaxel and the referenced drug (Taxotere). A 505(b)(2) NDA application requires full reports of investigations of safety (and effectiveness) are provided to determine if the proposed product can rely on the safety (and efficacy) findings from the referenced product (i.e., Taxotere). For this 505(b)(2) NDA, the Applicant proposed unique Warnings and Precautions related to potential alcohol-related toxicities in the Pfizer docetaxel labeling, despite the absence of this information in all of the previously approved docetaxel products currently marketed in the US; all of which result in lower ethanol and propylene glycol (none) exposures per dose. The labeling for 505(b)(2) submissions are not required to be identical to the referenced listed drug product. However, the proposal to add a unique Warning and Precaution to labeling by the Applicant, as in this case, is highly suggestive of a significant difference in the clinical safety of the proposed Pfizer docetaxel and the referenced product Taxotere. This is problematic since the premise of this (b)(2) NDA relies solely on the clinical findings for safety from the referenced drug, Taxotere.

The magnitude of the potential effect and the difference between this docetaxel product and the referenced drug remains uncertain without additional clinical information. Based on the European Guidance, the Pfizer docetaxel product will likely result in clinically relevant blood alcohol levels. Compared to Taxotere, Pfizer docetaxel delivers a two- to three- fold increase in the amount of ethanol per dose. This increases to

approximately four-fold per dose when theoretically factoring in the additive effect of propylene glycol. The magnitude and/or the duration of the alcohol-related toxicities may be further increased due to a potential interaction between ethanol and propylene glycol via the primary metabolic elimination pathway, alcohol dehydrogenase, for both substances.

The reviewer recommends that this 505(b)(2) resubmission receive a Complete Response. The Complete Response letter should request that the Applicant provide additional information to better characterize potential alcohol-related toxicities. This information could include new references that enable adequate estimation of the blood alcohol levels and assessments of the safety profile for the Pfizer docetaxel product. If additional clinical references are provided, this information must be based on experience using drug formulations that have comparable exposure levels for both ethanol and propylene glycol in a relevant clinical setting. Alternatively, or in the absence of this existing clinical information, the Applicant may consider conducting a clinical trial to assess the safety of Pfizer docetaxel. A study measuring blood alcohol levels to compare to the referenced product may be acceptable if combined with adequate safety monitoring and assessment strategies for alcohol-related toxicities. Another alternative would be to for the Applicant to reformulate the Pfizer docetaxel product to deliver exposure levels for both ethanol and propylene glycol that are comparable to other docetaxel products.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

[1] Ethanol. Micromedex 2.0 Poisondex® Managements Truven Health Analytics. http://www.thomsonhc.com/. Accessed January 8, 2013.

[2] Norberg A, Jones AW, Hahn RG, Gabrielsson JL. Role of variability in explaining ethanol pharmacokinetics: research and forensic applications. Clin Pharmackinet. 2003;42(1):1-31

[3] Rowe RC, Sheskey PJ, et. al. Propylene glycol. Handbook of Pharmaceutical Excipients. 7th ed. London: Pharmaceutical Press; 2012: p.407-408

[4] Speth PA, Vree TB, Neilen NF. Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. Ther Drug Monit. 1987 Sep; 9(3):255-258

9.2 Labeling Recommendations

Not applicable.

9.3 Advisory Committee Meeting

Not applicable.

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/s/

WILLIAM F PIERCE
01/11/2013

VIRGINIA E MAHER
01/13/2013

Cross-Discipline Team Leader Review

Date	24-FEB-2012
From	Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	202356
Applicant	Pfizer, Inc.
Date of Submission	29-APR-2011
PDUFA Goal Date	29-FEB-2012
Proprietary Name / Established (USAN) names	Docetaxel Injection
Dosage forms / Strength	10 mg/mL (20 mg/2 mL, 80 mg/8 mL, 200 mg/20 mL)
Proposed Indication(s)	1. Breast cancer 2. Non-small cell lung cancer 3. Prostate cancer 4. Gastric adenocarcinoma 5. Head and neck cancer
Recommended:	**Complete Response**

1. Introduction

Pfizer, Inc. submitted NDA 202356 for Docetaxel Injection on 29-APR-2011. The NDA was subsequently filed on 06-JUL-2011, and the PDUFA date is 29-FEB-2012.

This CDTL memo serves as an update to the previous 06-FEB-2012 memo and confirms a "Complete Response" recommendation for this application. All individual discipline reviews may be found in DARRTS. Due to the intended "Complete Response" action, final PI labeling was not negotiated during this review cycle.

2. Background

See CDTL memo dated 06-FEB-2012. There is no update to this section.

3. CMC

Reference is made to the previous CMC Review #1 (25-JAN-2012). CMC Review #2 (23-FEB-2012) presents updated CMC deficiencies based on subsequent review of the Applicant's 01-DEC-2011 submission. While two of the previous deficiencies were resolved with the 01-DEC-2011 amendment, the majority of the remaining deficiencies remain as approvability issues for the application. Note that several of the remaining deficiencies have not yet been conveyed to the Applicant, as the team's decision on a

"Complete Response" action was based on early identification of other unresolvable CMC issues.

4. Nonclinical Pharmacology/Toxicology

See CDTL memo dated 06-FEB-2012. There is no update to this section.

5. Clinical Pharmacology

See CDTL memo dated 06-FEB-2012. There is no update to this section.

6. Clinical Microbiology

See CDTL memo dated 06-FEB-2012. There is no update to this section.

7. Clinical/Statistical- Efficacy

See CDTL memo dated 06-FEB-2012. There is no update to this section.

8. Safety

See CDTL memo dated 06-FEB-2012. There is no update to this section.

9. Advisory Committee Meeting

See CDTL memo dated 06-FEB-2012. There is no update to this section.

10. Pediatrics, Geriatrics, and Special Populations

See CDTL memo dated 06-FEB-2012. There is no update to this section.

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): See CDTL memo dated 06-FEB-2012.
- Exclusivity or patent issues of concern: See CDTL memo dated 06-FEB-2012.
- Financial disclosures: See CDTL memo dated 06-FEB-2012.
- Other GCP issues: See CDTL memo dated 06-FEB-2012.
- DSI audits: See CDTL memo dated 06-FEB-2012.
- Other discipline consults: See CDTL memo dated 06-FEB-2012.
- Any other outstanding regulatory issues: None, with the exception of updated deficiencies for the action letter.

12. Labeling

Due to the intended "Complete Response" action, PI labeling negotiations were not conducted during this review cycle. However, the identified container/carton labeling deficiencies should be provided to the Applicant in the Complete Response letter. This was not the original strategy delineated in the 06-FEB-2012 CDTL memo, but conveyance of the deficiencies as part of the current action will allow the Applicant additional time to consider for forthcoming submissions.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  This reviewer recommends a "Complete Response" action for this NDA. There are outstanding Chemistry, Manufacturing and Controls and Pharmacology/Toxicology deficiencies. Due to this recommended action, labeling discussions were not conducted during this review cycle.

- Risk Benefit Assessment
  See CDTL memo dated 06-FEB-2012.

- Recommendation for Postmarketing Risk Management Activities
  This does not apply to this NDA.

- Recommendation for other Postmarketing Study Commitments
  See CDTL memo dated 06-FEB-2012.

- Recommended Comments to Applicant
  Specific language for current and updated outstanding deficiencies is located in the Chemistry, Manufacturing and Controls review (see Deficiencies #1-7, pages 8-9, 23-FEB-2012) and the previous Pharmacology/Toxicology review (page 5, 26-JAN-2012). In the previous CDTL review, this reviewer recommended that the labeling deficiencies #8-13 identified in the CMC review be deferred until a later review cycle. However, in the interim, the multidisciplinary team has agreed to send container/carton labeling deficiencies as part of the Agency's Complete Response letter. Therefore, the labeling deficiencies #8-13 should be included in the Complete Response letter, as stated in the 23-FEB-2012 CMC review.

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/s/

SARAH P MIKSINSKI
02/24/2012

Cross-Discipline Team Leader Review

Date	03-FEB-2012
From	Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	202356
Applicant	Pfizer, Inc.
Date of Submission	29-APR-2011
PDUFA Goal Date	29-FEB-2012
Proprietary Name / Established (USAN) names	Docetaxel Injection
Dosage forms / Strength	10 mg/mL (20 mg/2 mL, 80 mg/8 mL, 200 mg/20 mL)
Proposed Indication(s)	1. Breast cancer 2. Non-small cell lung cancer 3. Prostate cancer 4. Gastric adenocarcinoma 5. Head and neck cancer
Recommended:	**Complete Response**

1. Introduction

Pfizer, Inc. submitted NDA 202356 for Docetaxel Injection on 29-APR-2011. The NDA was subsequently filed on 06-JUL-2011, and the PDUFA date is 29-FEB-2012.

This CDTL memo serves to highlight the critical approvability issues discussed in all review disciplines and recommends a "Complete Response" action for this application. All individual discipline reviews may be found in DARRTS. Due to the intended "Complete Response" action, final PI and container/carton labeling was not negotiated during this review cycle.

2. Background

The Reference Listed Drug for this submission is the one-vial formulation of Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), which is currently marketed by Sanofi Aventis. The proposed drug product is a "ready to use" product containing the drug substance (in solution) in one vial. The solution is intended for reconstitution and subsequent intravenous injection. Docetaxel Injection is supplied in three presentations (20 mg/2 mL, 80 mg/8 mL, 200 mg/20 mL). All three presentations utilize the same concentration of 10 mg/mL. The proposed drug product is formulated with polysorbate 80 as a (b) (4), propylene glycol and ethanol as (b) (4), disodium edentate as (b) (4) (b) (4), and citric acid as pH adjustment. The proposed formulation contains higher levels of ethanol (40% v/v, compared with (b) (4)% v/v present in Taxotere), as well as polysorbate-

80 ((b) (4) % in Taxotere compared to (b) (4) % in the proposed formulation). In addition, the proposed formulation contains propylene glycol, disodium edentate, and anhydrous citric acid, which are not present in the innovator product.

Dosing Regimen and Administration
There are various indications and dosing regimens associated with this NDA. Please refer to the Medical Officer's 17-JAN-2012 review for additional details.

3. CMC

Summarized below are the major issues identified and resolved in the Quality (CMC) review:

- The current CMC reviewer (Josephine Jee) identified numerous outstanding deficiencies in her review dated 25-JAN-2012. The CMC reviewer recommends a "Complete Response" action for this NDA, pending resolution of nine (9) outstanding deficiencies. Briefly, these deficiencies relate to missing CMC manufacturing information, missing leachables and extractables data for the drug product, missing in-use stability and compatibility data for the drug product, discrepancies in the proposed release and stability specifications for the drug product, missing test methods and acceptance criteria in the drug product release and stability specifications, lack of clarity regarding vial supplier(s) for the provided batch and stability data, and missing drug product stability data. Additionally, the CMC reviewer identifies a cross-referenced Drug Master File (DMF (b) (4)) as "inadequate" to support the NDA, as the DMF is currently in a "closed" status. This CDTL has re-confirmed this status in DARRTS prior to finalization of this summary review.

  Several CMC deficiencies were conveyed to the Applicant early in the review cycle (see Information Request dated 07-OCT-2011), in hopes of quick resolution and a possible "approval" recommendation. However, as of the date of the CMC reviewer's review, these deficiencies remain outstanding. Several other deficiencies were identified later in the review and were not conveyed subsequently, due to the intended "Complete Response" action. The Applicant submitted a 01-DEC-2011 amendment in response to the Agency's 07-OCT-2011 Information Request. However, the significant delay in timing of this significant amendment rendered it impossible for the reviewer to fully review by the established GRMP completion date of 25-JAN-2012. Additionally, the inadequacy of DMF (b) (4) was not ever addressed by the NDA Applicant or DMF Holder; hence, the inadequate status of the DMF remained an outstanding approvability issue, and further attempts to resolve additional CMC issues were not undertaken during this review clock.

- Reference is made to the review filed in DARRTS (see review dated 23-DEC-2011, by Dr. E. Chikhale), which grants the Applicant's requested biowaiver.

- Facilities review/inspection

An overall "acceptable" recommendation was issued by the Office of Compliance on 23-OCT-2011. The summary report for this recommendation can be located in the 25-JAN-2012 CMC review.

- Microbiology
  The Microbiology reviewer (Dr. S. Fong) conducted a review of this submission and recommended approval in a 25-JAN-2012 review.

- Other notable issues (resolved or outstanding)
  While the current recommendation for CMC is "Complete Response", the CMC reviewer indicates an intent to review the 01-DEC-2011 amendment in the remaining review clock. While this amendment will not resolve the inadequacy of DMF (b) (4), other identified deficiencies may be resolved. Therefore, the CDTL recommendation is to issue a "Complete Response" action; however, an auxiliary recommendation is that the team await the CMC reviewer's second review before finalizing the actual outstanding deficiencies for the action letter.

4. Nonclinical Pharmacology/Toxicology

Reference is made to the Pharmacology/Toxicology review (Dr. H. Chiu) which states the following:

The Applicant has provided inadequate scientific justification for the levels of impurities proposed in this NDA submission. The proposed acceptance criteria for all identified impurities in the Pfizer Docetaxel Injection Concentrate drug product exceed the ICH Q3B(R2) qualification limit of 0.2%. Impurity specifications that exceed the qualification limit should be lowered to either meet the current ICH Q3B(R2) Guidance or not to exceed the levels detected in Taxotere®. Alternatively, data from nonclinical studies to qualify the safety of the levels of these impurities may be required, or their safety adequately justified based on literature citations. This issue needs to be addressed before this NDA can be recommended for approval.

The reviewer recommends a "Complete Response" action and captures the following language (page 5 of the Pharmacology/Toxicology review) for inclusion in the action letter:

You have provided inadequate scientific justification for the levels of impurities proposed in this NDA submission. The proposed acceptance criteria for all identified impurities in the Pfizer Docetaxel Injection Concentrate drug product exceed the ICH Q3B(R2) qualification limit of 0.2%. Impurity specifications that exceed the qualification limit should be lowered to either meet the current ICH Q3B(R2) Guidance or not to exceed the levels detected in Taxotere®. Alternatively, either conduct nonclinical studies to qualify these impurities, or provide data from the literature to adequately justify these proposed impurity levels.

5. Clinical Pharmacology

There was no clinical pharmacology data submitted to this NDA. The clinical pharmacology reviewer (Dr. L. Zhang) recommends approval of this NDA in her review dated 13-JAN-2012.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

There are no new clinical data provided in the current submission. The clinical reviewer (Dr. W. Pierce) states the following in his 17-JAN-2012 memo:

The clinical reviewer concurs with the recommendations made by the CMC reviewer for this 505(b)(2) application, and recommends that the specific CMC deficiencies be provided to the applicant in a Complete Response letter. There are no additional clinical deficiencies or comments to communicate to the Applicant at this time.

8. Safety

No new clinical data were provided for this submission.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

Not applicable

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): This was not raised during the pre-approval inspections for this NDA.
- Exclusivity or patent issues of concern: No issues were noted for this NDA.
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None
- Any other outstanding regulatory issues: None, with the exception of outstanding deficiencies for the action letter.

12. Labeling

Not applicable. Due to the intended "Complete Response" action, labeling negotiations were not conducted during this review cycle.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  This reviewer recommends a "Complete Response" action for this NDA. There are outstanding Chemistry, Manufacturing and Controls and Pharmacology/Toxicology deficiencies. Due to this recommended action, labeling discussions were not conducted during this review cycle.

- Risk Benefit Assessment
  The review of this NDA is based primarily on Chemistry, Manufacturing and Controls data. The presence of outstanding deficiencies for both Chemistry, Manufacturing and Controls and Pharmacology/Toxicology results in an unacceptable risk with regard to possible marketing of the proposed drug product.

- Recommendation for Postmarketing Risk Management Activities
  This does not apply to this NDA.

- Recommendation for other Postmarketing Study Commitments
  None

- Recommended Comments to Applicant
  Specific language for current outstanding deficiencies is located in the Chemistry, Manufacturing and Controls review (see Deficiencies #1-9, pages 8-11, 25-JAN-2012) and the Pharmacology/Toxicology review (page 5, 26-JAN-2012). This reviewer recommends that the labeling deficiencies #10-15 identified in the CMC review be deferred until a later review cycle. All other deficiencies are the basis for the recommended "Complete Response" action.

  As mentioned above in Section 3, the CMC reviewer indicates an intention to review the 01-DEC-2011 amendment in the remaining review clock. While this amendment will not resolve the inadequacy of DMF (b) (4), other identified deficiencies may be resolved as a result of this review. This CDTL's recommendation is to issue a "Complete Response" action; however, an auxiliary recommendation is that the team await the CMC reviewer's second review before finalizing the actual outstanding deficiencies for the action letter.

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/s/

SARAH P MIKSINSKI
02/06/2012

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	202356
Priority or Standard	Standard
Submit Date(s)	April 29, 2011
Received Date(s)	April 29, 2011
PDUFA Goal Date	February 29, 2012
Division / Office	DOP2 / OHOP
Clinical Reviewer	William Pierce, PharmD
Clinical Team Leader	Steven Lemery, MD, MHS
Review Completion Date	January 17, 2012
Established Name	docetaxel
(Proposed) Trade Name	Docetaxel Injection
Therapeutic Class	Microtubule inhibitor
Applicant	Pfizer, Inc.
Formulation(s)	IV

Clinical Review / Recommendations

This 505(b)(2) application (NDA 202356) seeks approval of Docetaxel Injection 10 mg/mL in product sizes of 20 mg/2 mL, [redacted] (b) (4) The reference listed drug (RLD) identified by the applicant (Pfizer, Inc.) is Taxotere (Sanofi-Aventis, NDA 20-449). The Applicant's proposed labeling indications are the same as the RLD. No clinical data was submitted in this NDA. The Taxotere NDA 20449 has been previously reviewed for efficacy and safety.

A complete review of the Applicant's proposed labeling was not conducted due to identification of significant chemistry, manufacturing, and controls (CMC) deficiencies that would not permit this NDA to proceed to an approval action. See CMC reviews filed by Josephine Jee for more information.

The clinical reviewer concurs with the recommendations made by the CMC reviewer for this 505(b)(2) application, and recommends that the specific CMC deficiencies be provided to the applicant in a Complete Response letter. There are no additional clinical deficiencies or comments to communicate to the Applicant at this time.

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/s/

WILLIAM F PIERCE
01/17/2012

STEVEN J LEMERY
01/17/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-356/N-000 **Applicant:** Pfizer, Inc. **Stamp Date:** April 29, 2011

Drug Name: Docetaxel Injection Concentrate 10 mg/mL **NDA/BLA Type:** Original NDA [505(b)(2)]

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.			X	eCTD format \\Cdsesub1\evsprod\NDA202356\202356.enx
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			The Applicant has provided a summary of the referenced product's efficacy and safety findings with the referenced medical literature used to complete this summary.
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Clinical Overview 2.5.6
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	505(b)(2): The filing will rely on the findings of safety and effectiveness of the reference product Taxotere® (NDA 020449).
DOSE					
13.	If needed, has the applicant made an appropriate attempt to			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

No review issues at this time.

Reviewing Medical Officer	Date
Clinical Team Leader	Date

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/s/

WILLIAM F PIERCE
06/07/2011

STEVEN J LEMERY
06/07/2011