CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202356Orig1s000

OTHER REVIEW(S)

Division of Oncology Products 1

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 202356

Name of Drug: Docetaxel Injection Concentrate, 10 mg/mL

Applicant: Pfizer Labs

Labeling Reviewed

Dates of Submission: September 12, 2013; January 10, and 27, 2014; February 28, 2014, and March 11, 2014.

Receipt Dates: September 13, 2013; January 10, and 27, 2014; February 28, 2014, and March 11, 2014.

Background and Summary Description

This is the third review cycle for this 505(b)(2) NDA for Docetaxel Injection Concentrate, 10 mg/mL. The first Complete Response letter was sent on February 29, 2012. On September 13, 2013, the Applicant submitted a response to the Agency's second Complete Response action letter dated February 14, 2013. The Reference Listed Drug is Taxotere, NDA 020449.

This 505(b)(2) New Drug Application is indicated for:

- Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC
- Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC
- 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

Review

Applicant responses to the Agency's information requests of January 6, 15, and 23; February 24, and March 6, 2014, were received on January 10 and 27; February 28, and March 7, 2014

I compared the Applicant's January 27, 2014; proposed Package Insert to the last approved Package Insert for the RLD dated December 13, 2013 (S-071). No differences were noted other than those identified by the Applicant's in their submission, with the exception of FDA updates and minor formatting edits. The Applicant accepted the FDA revisions in their submission dated March 11, 2014. The attached Package Insert represents the agreed upon Package Insert between the FDA and the Applicant.

Recommendation

The Clinical team, V. Ellen Maher, Clinical Team Leader, and William Pierce, Clinical Reviewer, accepted the labeling revisions identified below, as reflected in the Clinical Review dated February 26, 2014.

The Nonclinical team, Todd Palmby, Nonclinical Team Leader, and Haw-Jyh (Brian) Chiu, Nonclinical Reviewer, accepted the labeling revisions identified below, as reflected in the Nonclinical Review dated February 24, 2014.

The Chemistry, Manufacturing and Controls (CMC) team, Ali Al Hakim, Branch Chief II, and Josephine Jee, CMC reviewer accepted the revisions identified below, as reflected in the CMC review dated January 24, 2014.

The Clinical Pharmacology team, Qi Liu, Clinical Pharmacology Team Leader, and Jeanne Fourie Zirkelbach, Clinical Pharmacology Reviewer, stated in their review dated January 28, 2014, that the current submission does not contain changes to the Clinical Pharmacology labeling previously reviewed and accepted by FDA clinical pharmacology reviewer during the second review cycle.

The Division of Pharmacovigilance team, Margaret Rand, Tracy Salaam, Allen Brinker and Scott Proestall of the Office of Surveillance and Epidemiology accepted the revisions as noted in their memo dated February 14, 2014.

The Division of Medication Error and Prevention and Analysis team in the Office of Surveillance and Epidemiology, Chi-Ming Tu, DMEPA Team Leader, and Jibril Abdus-Samad, DMEPA Reviewer, accepted the revisions denoted above, as reflected in their DMEPA reviews dated February 21, 2014, and March 7, 2014.

The Patent Labeling Team, Barbara Fuller, Patient Labeling Team Leader, and Nathan Caulk, Patient Labeling Reviewer, accepted the labeling revisions as reflected in their review of March 4, 2014.

Marybeth Toscano, Office of Prescription Drug Promotion (OPDP) reviewer, also reviewed and accepted these labeling revisions as reflected in her review dated February 21, 2014.

Therefore, I recommend that the changes identified in the attached Package Insert be approved. An Approval letter should issue for NDA 202356.

The attached package inserts are:

1. The Applicant's original proposed package insert with changes tracked, also incorporating FDA's revisions.
2. A clean copy of the agreed upon package insert between FDA and the Applicant.

Modupe Fagbami

Regulatory Project Manager
Date

Christy Cottrell

Chief, Project Management Staff
Date

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/s/

MODUPE O FAGBAMI
03/12/2014

CHRISTY L COTTRELL
03/12/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 7, 2014
Requesting Office or Division:	Division of Oncology Products I (DOP1)
Application Type and Number:	NDA 202356
Product Name and Strength:	Docetaxel Injection
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Pfizer
Submission Date:	February 28, 2014
OSE RCM #:	2013-2189-1
DMEPA Primary Reviewer:	Jibril Abdus-Samad, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

DOP1 requests DMEPA to evaluate the revised prescribing information for Docetaxel Injection NDA 202356 for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the revised prescribing information submitted on February 28, 2014.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

In OSE Review 2013-2189 dated February 20, 2014, we recommended deleting the word *Concentrate* from the established name in the prescribing information. The Applicant agreed to our recommendation. Additionally during a March 6, 2014 teleconference, the Applicant agreed to the following changes in the prescribing information:

- Highlights of Prescribing Information:
  Replace the abbreviation *IV* with the words *intravenously* or *intravenous infusion* accordingly.
- Preparation and Administration (Section 2.9):
  Revise the formatting to place the concentration of the final solution (0.3 mg/mL to 0.74 mg/mL) to appear on the same line.

4 CONCLUSION & RECOMMENDATIONS

The Applicant has addressed DMEPA's concerns with the prescribing information.

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/s/

JIBRIL ABDUS-SAMAD
03/07/2014

CHI-MING TU
03/07/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	March 4, 2014
To:	Anthony Murgo, MD Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nathan Caulk, MS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	Docetaxel Injection
Dosage Form and Route:	Intravenous Infusion (IV)
Application Type/Number:	NDA 202-356
Applicant:	Pfizer Laboratories, Inc.

1 INTRODUCTION

On September 13, 2013, Pfizer Laboratories, Inc. resubmitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 202-356 for Docetaxel Injection, Intravenous Infusion in response to a Complete Response (CR) letter issued on February 14, 2013. This Class 2 resubmission includes updated labels, responses to the product quality and labeling deficiencies, and data to support the combination of ethanol and propylene glycol in the proposed docetaxel formulation. The Applicants initial NDA submission dated April 29, 2011received a Complete Response (CR) letter on February 29, 2012. The Reference Listed Drug (RLD) is TAXOTERE (docetaxel) Injection Concentrate (IV), NDA 20-449. The proposed indication for Docetaxel Injection, Intravenous Infusion is for the treatment of:

- 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 Adenocacinoma (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

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Oncology Products 1 (DOP1) on November 5, 2013 for DMPP to provide a focused review of the Applicant's proposed Patient Package Insert (PPI) for Docetaxel Injection, Intravenous Infusion.

2 MATERIAL REVIEWED

- Draft Docetaxel Injection, Intravenous Infusion PPI received on September 13, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on February 28, 2014.
- Draft Docetaxel Injection, Intravenous Infusion Prescribing Information (PI) received on September 13, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on February 28, 2014.
- Approved TAXOTERE (docetaxel) Injection Concentrate, Intravenous Infusion (IV) comparator labeling dated December 13, 2013.

3 REVIEW METHODS

In our focused review of the PPI we have:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our focused review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
03/04/2014

BARBARA A FULLER
03/04/2014

LASHAWN M GRIFFITHS
03/04/2014

505(b)(2) ASSESSMENT

Application Information		
NDA # 202356	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Docetaxel Injection Concentrate 10 mg/mL Established/Proper Name: docetaxel Dosage Form: solution, injection Strengths: 20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL, 200 mg/20 mL		
Applicant: Pfizer Labs		
Date of Receipt: April 29, 2011-1st Cycle; August 14, 2012-2nd Cycle; September 13, 2013-3rd Cycle		
PDUFA Goal Date: February 29, 2012-1st cycle February 14, 2013-2nd cycle March 13, 2014-3rd cycle	Action Goal Date (if different): CR issued on February 29, 2012 for 1st cycle CR issued on February 14, 2013, for 2nd cycle 3rd cycle-pending (Approval Action in view)	
Proposed Indication(s): • Breast Cancer – single agent for the treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy. In combination with doxorubicin and cyclophosphamide for the adjuvant treatment of operable, node-positive breast cancer. • Non-Small Cell Lung Cancer – single agent for the treatment of locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. In combination with cisplatin for the treatment of patients unresectable, locally advanced or metastatic NSCLC who have not previously received chemotherapy for this condition. • Prostate Cancer – in combination with prednisone for the treatment of androgen independent (hormone refractory) metastatic prostate cancer. • Gastric Adenocarcinoma – in combination with cisplatin and fluorouracil 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 – in combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO X

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Taxotere 40 mg/mL NDA 020449	Clinical (efficacy & safety), nonclinical, clinical pharmacology

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Pfizer asked for and received a waiver of the need for bioequivalence studies.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO X

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES X NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Taxotere 40 mg/mL	020449	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A X YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO X

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO X

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO X

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☒ NO X

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Taxotere 40 mg/mL

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for an alternate formation to Taxotere. Pfizer's product is a 1-vial formulation that does not require a pre-mix step and is ready for immediate dilution and administration. The 1-vial formulation will reduce the number of aseptic manipulations required to prepare the final infusion fluid, which reduces the potential for contamination and, therefore, may improve patient safety.

The active pharmaceutical ingredient in Docetaxel Injection Concentrate 10 mg/mL is docetaxel (anhydrous) instead of docetaxel (trihydrate) used in Taxotere.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO X

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☒

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):
~201195 Accord Hlthcare (ap 6/8/11)
~203551 Actavis Inc (ap 4/12/13)
~022234 Hospira Inc (ap 3/8/11)
~201525 Sandoz (ap 6/29/11)
~022534 Sun Pharma Globa (ap 5/3/11)

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

5698582 (7/3/12) 5698582*PED (1/3/13)
5714512 (7/3/12) 5714512*PED (1/3/13)
5750561 (7/3/12) 5750561*PED (1/3/13)
5438072 (5/22/14)

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 4814470

X 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): 5714512 Expiry date(s): 1-3-2013
5750561 1-3-2013

X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

Patent number: 5698582

Patent number: 5438072, expiry date of May 22, 2014
This patent is no longer listed in the Orange Book under NDA 20449.

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

From form 3542a

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5438072, 5698582
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES X NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES X NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): December 15, 2011

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval

See 2-9-2012 submission.

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/s/

MODUPE O FAGBAMI
02/27/2014

CHRISTY L COTTRELL
02/27/2014

MEMORANDUM
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

******Pre-decisional Agency Information******

Memorandum

Date: February 21, 2014

To: Modupe Fagbami, RPM
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

From: Marybeth Toscano, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on draft product labeling for Docetaxel
NDA 202356

In response to your consult request dated November 6, 2013, OPDP has reviewed the proposed product labeling (PI) for Docetaxel. OPDP's comments are based on the proposed, substantially complete version of the PI, available at the following link:

\\CDSESUB1\evsprod\NDA202356\202356.enx

OPDP has reviewed the proposed PI and has no comments.

If you have any questions, please contact Marybeth Toscano at 6-2617 or at Marybeth.Toscano@fda.hhs.gov.

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/s/

MARYBETH TOSCANO
02/21/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 20, 2014
Requesting Office or Division:	Division of Oncology Products I (DOP1)
Application Type and Number:	NDA 202356
Product Name and Strength:	Docetaxel Injection
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Pfizer
Submission Date:	September 13, 2013
OSE RCM #:	2013-2189
DMEPA Primary Reviewer:	Jibril Abdus-Samad, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

DOP1 consulted DMEPA to evaluate the proposed container labels, carton labeling, and prescribing information for Docetaxel Injection NDA 202356 for areas of vulnerability that could lead to medication errors. Additionally, DOP1 asked DMEPA to recommend appropriate labeling for the specific Docetaxel formulation because it contains more ethanol and propylene glycol than all other currently marketed Docetaxel formulations.

2 REGULATORY HISTORY

The Applicant, Pfizer, submitted labels and labeling in their initial NDA submission dated April 29, 2011. The Applicant received a Complete Response (CR) letter for the application on February 29, 2012 for non-clinical and product quality issues. DMEPA's comments for the container labels and carton labeling from OSE review # 2011-1613 were included in this CR letter. On August 14, 2012, Pfizer responded to the CR in a Class II resubmission. DMEPA provided comments on the labels and labeling via OSE Review 2012-2284 for the resubmission. However the August 14, 2012 resubmission also received a CR on February 14, 2013 due to concerns the amounts of alcohol and propylene glycol and additional product quality issues. On September 13, 2013, the Applicant responded to the CR with another Class II resubmission which included updated labels and labeling, data to support product quality, and amounts of alcohol and propylene glycol.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Alcohol Warning

We find the proposal to add a warning regarding alcohol content in *Warnings and Precautions* (section 5) of the prescribing information acceptable considering the Division of Pharmacovigilance II (DPV2) recommends that DOP1 label all docetaxel formulations uniformly with regard to the risks of alcohol intoxication. Adding alcohol content warnings in *Warnings and Precautions* (section 5) of the prescribing information is consistent with currently marketed products that contain similar amounts of alcohol such as Paclitaxel, Sandimmune, and Kaletra.

Use of *Concentrate* in the Established Name (Docetaxel Injection Concentrate)

The established name in the prescribing information (Docetaxel Injection Concentrate) is inconsistent with the container label and carton labeling (Docetaxel Injection). In previous OSE Review 2011-1613 dated January 19, 2012, we recommended removal of the word *Concentrate* from the established name to be consistent with similar Docetaxel formulations that are 1-vial and 10 mg/mL concentration. The Docetaxel formulations that are 1-vial and 20 mg/mL contain the word *Concentrate* in the established name. However, we note that there is no clear consistency between all the Docetaxel Injection formulations with regard to the use of the word *Concentrate* within the established name as it relates to 1-vial vs. 2-vial formulations or varying final concentrations (See Table 3). DMEPA will continue post-marketing surveillance of medication errors to determine if the inconsistent use of *Concentrate* in the established names contributes to medication errors.

5 CONCLUSION & RECOMMENDATIONS

The proposal to add a warning regarding alcohol content in *Warnings and Precautions* (section 5) of the prescribing information is acceptable. Additionally, the container labels and carton labeling are acceptable. However, we recommend deleting the word *Concentrate* from the established name in the prescribing information.

5.1 COMMENTS TO THE DIVISION

We recommend deleting the word *Concentrate* from the established name in the prescribing information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Docetaxel that Pfizer submitted on September 13, 2013.

Table 2. Relevant Product Information for Docetaxel	
Active Ingredient	Docetaxel
Indication	**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.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL, and 200 mg/20 mL
Dose and Frequency	**Breast Cancer (BC):** 60 mg/m^2 to 100 mg/m^2 single agent intravenously over 1 hour every 3 weeks. **Non-Small Cell Lung Cancer (NSCLC):** 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks. **Hormone Refractory Prostate Cancer (HRPC):** 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5 mg orally twice daily is administered continuously.

	Gastric Adenocarcinoma (GC): 75 mg/m^2 as a 1 hour intravenous infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as a 24-hour continuous intravenous infusion for 5 days, starting at the end of the cisplatin infusion **Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN)**: 75 mg/m^2 as a 1 hour intravenous infusion followed by cisplatin 75 mg/m^2 intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles
How Supplied	Single-vial and Five-vial packs 20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL, and 200 mg/20 mL
Storage	Store between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.
Container Closure	Polypropylene vials

Table 3: Comparison of Docetaxel products

NDA	Applicant	Formulation	Concentration	Status
202356 Docetaxel Injection Concentrate	Pfizer	1 vial	10 mg/mL	Pending
20449 Taxotere (Docetaxel Injection Concentrate) RLD	Sanofi-Aventis	1 vial	20 mg/mL	Approved
	Sanofi-Aventis	2 vial	10 mg/mL after initial dilution	No longer marketed
201195 Docetaxel Injection Concentrate	Accord Healthcare	2 vial	10 mg/mL after initial dilution	Approved
		1 vial	20 mg/mL	Approved
022234 Docetaxel Injection, USP	Hospira	1 vial	10 mg/mL	Approved
201525 Docetaxel Injection	Sandoz	1 vial	10 mg/mL	Approved
022534 Docefrez (Docetaxel for Injection)	Sun Pharma Global (b) (4)	Lyophilized powder plus diluent	**20 mg vial** 20 mg/0.8 mL (25 mg/mL) **80 mg vial** 24 mg/mL	Approved
022312 Docetaxel Injection	Apotex	2 vial	10 mg/mL after initial dilution	Approved
203551 Docetaxel Injection Concentrate	Actavis	1vial	20 mg/mL	Approved

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on February 11, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]

Table 3: FAERS Search Strategy	
Date Range	**September 23, 2013 (latest date searched in last Docetaxel review) to February 11, 2014**
Drug Names	**Docetaxel** [active ingredient]
MedDRA Search Strategy	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.2 Results

Our search identified five cases. None of the cases described errors possibly associated with the current labels and labeling for Docetaxel. We excluded all the cases because they described adverse events unrelated to medication errors (n=3) and Clinical Trials reports (n=2).

B.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on February 12, 2014 using the term Docetaxel to identify reviews previously performed by DMEPA.

C.2 Results

We retrieved 2 reviews for this specific NDA 202356 (OSE Review 2012-2284, dated January 31, 2013 and OSE Review 2011-1613, dated January 19, 2012). We provided recommendations to decrease the potential for confusion between the multiple formulations of Docetaxel varying in concentration and preparation instructions. The Applicant accepted our recommendations. Additionally, there were multiple Docetaxel reviews for different manufacturers that also addressed the aforementioned potential for confusion.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on February 12, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Date Range	January 30, 2013 (date of last search) to February 12, 2014
ISMP Newsletter Search Strategy	Match Exact word or phrase: Docetaxel, Taxotere
Search Terms	Docetaxel AND Taxotere

E.2 Results

No results retrieved.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Docetaxel labels and labeling submitted by Pfizer on September 13, 2013.

- Container labels
- Carton labeling
- Carton labeling 5-count pack

G.2 Label and Labeling Images

- Container label

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JIBRIL ABDUS-SAMAD
02/20/2014

CHI-MING TU
02/21/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memo

Date:	February 13, 2014
Reviewer:	Margaret Rand, PharmD, BCOP, Safety Evaluator Division of Pharmacovigilance II (DPV II)
Team Leader:	Tracy Salaam, PharmD, Team Leader, DPV II Allen Brinker, MD, Team Leader DPV II
Division Director:	Scott Proestel, MD, Division Director DPV II
Product Name:	Docetaxel
Subject:	Postmarketing Reports of Alcohol Intoxication
Application Type/Number:	NDA 020-449, NDA 022-534, NDA 022-234, NDA 201-195, NDA 201-525, NDA 203-551 *Discontinued: NDA 022312*
Applicant/Sponsor:	Multiple Sponsors
OSE RCM #:	2014-122

1 INTRODUCTION

The Division of Oncology Products 1 (DOP 1) consulted the Division of Pharmacovigilance II (DPV II) to review the FDA Adverse Event Reporting System (FAERS) and the literature for an association between treatment with parenteral docetaxel (containing ethanol) and symptoms of alcohol intoxication. The purpose of this memorandum is to determine if regulatory action is necessary.

2 BACKGROUND

Taxotere® (docetaxel) is a microtubule inhibitor in the taxane drug class approved on May 14, 1996. Docetaxel is indicated to treat breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck. There are presently six FDA-approved formulations of docetaxel available in the US.

The current FDA-approved docetaxel product labels have no warnings about the risk of alcohol intoxication even though they all contain ethanol in various concentrations. The Pfizer docetaxel formulation under review has the highest alcohol concentration of any of the approved products. It is also the only docetaxel formulation containing propylene glycol. See Table 1.

Table 1. Description of US docetaxel formulations and excipient content[a]

Product	Manufacturer	NDA	Approval Date	Ethanol content (Grams)*	Propylene Glycol content (Grams)*
Taxotere two vial formulation	Sanofi	020449	5/14/1996	2.0	0
Taxotere one vial formulation	Sanofi	020449	8/2/2010	4.0	0
Docetaxel	Hospira	022234	3/8/2011	3.7	0
Docefrez	Sun Pharma	022534	5/3/2011	2.9	0
Docetaxel	Accord	201195	6/8/2011	4.0	0
Docetaxel	Sandoz	201525	6/29/2011	5.5	0
Docetaxel	Actavis	203551	4/12/2013	4.0	0
Docetaxel	Pfizer	202356	Approval pending	6.4	7.5

*Assumes maximum dose of 100mg/m^2, BSA = 2.0m^2, 200mg dose administered

NDA 202356 for Docetaxel injection concentrate was originally submitted to FDA on April 29, 2011, for approval under Section 505(b)(2) as an alternative formulation to the reference listed drug (RLD) Taxotere. After a standard review, a Complete Response letter was issued on February 29, 2012, due to multiple Chemistry, Manufacturing and Controls (CMC) deficiencies. A re-submission was received on August 14, 2012, however due to clinical concerns about safety and CMC deficiencies, a Complete Response action was again taken on February 14, 2013.[b]

[a] Modified from Pfizer docetaxel Midcycle meeting slides presented by William Pierce on January 15, 2014

[b] Summary Review for Regulatory Action, Deputy Director Review, NDA 202356, Docetaxel Injection Concentrate, Amna Ibrahim. February 14, 2013.

On September 12, 2013, Pfizer Inc. re-submitted NDA 202356 for review, with labeling that included high alcohol content in the Warnings and Precautions section. Pfizer proposed the following labeling for NDA 202356 on January 10, 2014:

Highlights

Alcohol content: The alcohol content in a dose of Docetaxel Injection (b) (4) (b) (4) *(5.12)*

Warnings and Precautions

5.8 Neurologic Reactions (b) (4)

5.12 Alcohol Content (b) (4)

Patient Information (b) (4)

17. Patient Counseling Information

Explain to patients the possible effects of the alcohol content in Docetaxel Injection (b) (4) *including possible effects on the central nervous system,* (b) (4) [redacted]

3 METHODS AND RESULTS

3.1 FAERS SEARCH STRATEGY

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 2.[c]

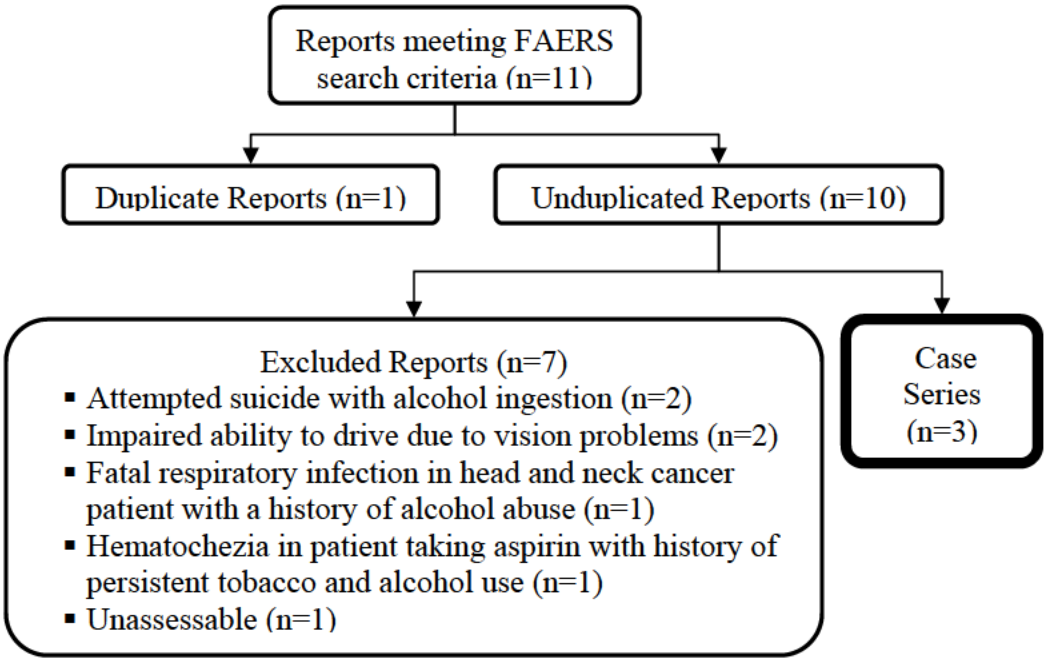
Table 2. FAERS Search Strategy	
Date of search	January 22, 2014
Time period of search	January 1, 1969* - January 22, 2014
Product Terms	Active Ingredient: Docetaxel, Docetaxel Anhydrous
MedDRA version 16.0 Search Terms (Preferred Terms)	• Accidental poisoning • Alcoholic hangover • Alcohol interaction • Alcohol poisoning • Alcohol problem • Alcoholic psychosis • Alcohol use • Alcohol withdrawal syndrome • Blood alcohol abnormal • Blood alcohol increased • Blood ethanol increased • Breath alcohol test positive • Chemical poisoning • Feeling drunk • Idiosyncratic alcohol intoxication • Impaired driving ability • Saliva alcohol test positive • Urine alcohol test positive

*Date FDA began receiving postmarket reports for all drugs

[c] FAERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population. FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

3.2 FAERS SEARCH RESULTS

Figure 1. FAERS case selection for alcohol intoxication associated with docetaxel



Descriptions of the three FAERS cases of alcohol intoxication associated with docetaxel are as follows:

1) Case 6454788, Foreign (Japan), Expedited, October 2007: A 33 year-old female taking docetaxel to treat an unknown indication developed symptoms of dementia. The patient experienced these symptoms during the administration of docetaxel and they were transient; the patient had no memory of the event and the physician felt she could have been in a state of drunkenness. Plans were made to continue docetaxel treatment with a formulation containing a lower alcohol content. The patient recovered from the event.
Reviewer's comment: RLD Taxotere (Aventis) was the product identified in this report, and based on the event date, it was likely the original formulation.

2) Case 7541774, Foreign (Great Britain), Expedited, Literature report, July 2010[d]: 44 year-old male taking docetaxel 75mg/m2 every three weeks to treat prostate cancer had a history of alcohol abuse, but was alcohol free for 3 years prior to docetaxel treatment. Halfway through the patient's 9th cycle of docetaxel (recently changed from "two vial sets" to "one vial sets") the patient showed signs of drunkenness. The infusion was stopped and intravenous fluids were administered. After an unspecified period of time, the infusion was restarted at a slower rate and the patient did not show any further signs of drunkenness. A decision was made to use "non-alcoholic" docetaxel in the future.

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

Reviewer's comment: The "new formulation" of RLD Taxotere (Aventis) was the product identified in this report. . This new formulation was introduced in September 2009 in Europe (August 2010 in the US) to simplify the preparation of the infusion solution.[e]

3) Case 8554908, Foreign (France), Expedited, Clinical study case, (b) (6): A 64 year-old male taking docetaxel and erlotinib to treat non-small cell lung cancer experienced vertigo, a drunken sensation, and two consecutive falls requiring hospitalization within 24 hours of receiving docetaxel. The symptoms resolved and the patient was discharged from the hospital after 4 days. A cerebral CT scan was performed which did not show brain metastases. The investigator assessed the fall due to vertigo and drunken sensation related to docetaxel.
Reviewer's comment: It is unclear what formulation of docetaxel was used because this report was sent from the sponsor for erlotinib.

3.3 LITERATURE SEARCH RESULTS

A literature search for alcohol intoxication associated with docetaxel identified one of the three FAERS cases described above (#2). Additionally, there is one study published in Japan which evaluated breath alcohol concentrations (BRAC) following paclitaxel and docetaxel infusions.[f] In this study undertaken in 2003, fifty-two subjects were enrolled (36 paclitaxel and 16 docetaxel patients) and breath samples were measured three times immediately following drug infusion. Twenty of the paclitaxel patients tested positive for BRAC, three of which reached the illegal level for driving in Japan. Six of these patients were tested 30 minutes after the initial positive measurement and in four of the six subjects BRAC were not detected. The authors therefore recommend that patients should be advised not to drive for at least 30 minutes after receiving paclitaxel. None of the docetaxel patients tested positive for BRAC which the authors concluded was due to lower alcohol content in the docetaxel formulation compared to paclitaxel as well as a different dosing regimen.
Reviewer's comment: Each mL of paclitaxel contains 49.7% (v/v) dehydrated alcohol (396 mg/mL). As a comparison, the most recent formulation of Taxotere (which was not available at the time of this study) contains 395 mg/mL of dehydrated alcohol solution.[g,h]

4 DISCUSSION AND CONCLUSION

We identified three cases consistent with alcohol intoxication associated with docetaxel in FAERS. They are all foreign reports involving at least two different formulations of docetaxel. There is a strong temporal association between the docetaxel infusion and symptoms of alcohol intoxication in these cases (two occurred during the infusion and one within 24 hours of drug administration). The symptoms of alcohol intoxication were listed as "transient" in one case and in another case the symptoms resolved in time for the patient to finish his treatment using a

[e] European Medicines Agency. Evaluation of medicines for human use, EMA/774985/2009. London: European Medicines Agency; 2009
[f] Komagata H, Yoneda S, Sakai H et al. Breath alcohol concentrations in Japanese outpatients following paclitaxel and docetaxel infusion. Int J Clin Pharmacol Res 2005;25(4):195-202
[g] Taxol® product information, last updated 5/2/2011
[h] Taxotere® product information, last updated 12/13/2013

slower infusion rate. In two of the three cases, the reporters planned to use a different docetaxel formulation with lower alcohol content for future treatments.

The literature from Japan supports an association between alcohol intoxication and the taxanes. This study documented positive breath alcohol concentrations immediately after paclitaxel administration which showed a pattern of subsiding after 30 minutes. The authors did not note the same effect with docetaxel, however the study used the older formulation of RLD Taxotere. The newer formulations of docetaxel contain comparable amounts of alcohol to paclitaxel per mL and could very well exhibit the same effects as this study showed, depending on what dosages are used.

Addtionally, we identified four FDA-approved drugs that contain labeling for alcohol toxicity: IV ethanol in dextrose,[i] Sandimmune (cyclosporine),[j] Taxol (paclitaxel),[f] and Kaletra (lopinavir/ritonavir) oral solution.[k] See Appendix 1 for detailed product labeling on the risk of alcohol intoxication with these agents. While paclitaxel only contains a precaution for adults that consideration should be given to possible CNS and other effects of alcohol, the other drugs share several things in common; warnings for use in pregnant and breast feeding women, pediatrics, patients with a history of alcohol abuse, and those presenting with liver disease or epilepsy. (b) (4). Additionally, intravenous ethanol carries a warning for cautious use following cranial surgery or in the presence of significant renal impairment as well as monitoring for postural hypotension due to vasodilating effects. None of the four drugs mentioned above caution against operating machinery or driving.

In addition to alcohol content, Kaletra also contains propylene glycol which shares a metabolic pathway with ethanol[l] and the combination could potentiate adverse events. A statement to this effect is in the Kaletra product label. Propylene glycol on its own exhibits 1/3 the intoxicating effect of alcohol.[m] Pfizer's docetaxel is the first formulation which would contain both alcohol and propylene glycol, and this potential pharmacodynamic effect should be addressed in product labeling.

In conclusion, there are postmarketing cases of alcohol intoxication associated with docetaxel and literature to support this potential adverse event. Four currently approved drugs (IV ethanol, Sandimmune, Taxol, and Kaletra) which contain alcohol can serve as a guide for labeling Pfizer's docetaxel formulation. Lastly, regardless of the amount of alcohol in the various docetaxel formulations, the product labels should be standardized to warn practitioners and patients of the risk of alcohol intoxication.

[i] IV Alcohol and dextrose product label, updated 6/1999
[j] Sandimmune® product label, updated 5/3/2013
[k] Kaletra® product label, updated 9/15/2000
[l] Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis and management. Clin J Am Soc Nephrol 2008 Jan;3(1):208-25.
[m] Handbook of Pharmaceutical Excipients 6th edition, 2009. Edited by R Rowe, P Sheskey et al.

5 RECOMMENDATIONS

DPV II finds the proposed Pfizer docetaxel product labeling with warnings for alcohol intoxication generally acceptable. We recommend adding language to convey the potential additive effects of propylene glycol and alcohol. Also, it may be helpful to add a time frame, such as "immediately after infusion" to the statement cautioning against operating machinery or driving. Finally, for the purposes of patient education and practitioner monitoring during drug administration, we recommend that all docetaxel formulations be uniformly labeled regarding the risks of alcohol intoxication.

6 APPENDIX 1. SECTIONS OF PRODUCT LABELING FOR IV ETHANOL, SANDIMMUNE, TAXOL, AND KALETRA WHICH RELATE TO ALCOHOL INTOXICATION RISK

IV Ethanol and dextrose (approved 1946):

WARNINGS

Alcohol should be used cautiously, if at all, in patients with liver impairment, in the presence of shock, following cranial surgery, in actual or anticipated postpartum hemorrhage, or in the presence of significant renal impairment. Alcohol decreases blood sugar in diabetic patients. In the untreated diabetic, the rate of alcohol metabolism is slowed. As a nutrient, alcohol supplies only calories. Given alone, it may cause or potentiate vitamin deficiencies and certain liver alterations. Alcohol crosses the placenta rapidly and enters the fetal circulation. It may also be found in the milk of lactating women. The use of these solutions in pregnancy should be carefully considered.

PRECAUTIONS

General

Alcohol and Dextrose Injections USP should be administered slowly, and the patient observed for restlessness or narcosis. The half lives of phenytoin, warfarin and tolbutamide may be shortened 50% to 75% by concurrent administration of alcohol. Alcohol increases serum uric acid and can precipitate acute gout. The vasodilating effect of alcohol may potentiate postural hypotension, particularly in association with some antihypertensive drugs. If the administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result. To minimize the risk of possible incompatibilities arising from mixing this solution with other additives that may be prescribed, the final infusate should be inspected for cloudiness or precipitation immediately after mixing, prior to administration, and periodically during administration. Use only if solution is clear and vacuum is present.

ADVERSE REACTIONS

Alcoholic intoxication may occur with too rapid infusion. Vertigo, flushing, disorientation (especially in elderly patients), or sedation may also occur. An alcoholic odor may be noted in the breath. Generally, these effects can be avoided by slowing the rate of infusion.

Too rapid infusion of hypertonic solutions may cause local pain and, rarely, vein irritation. Use of the largest available peripheral vein and a well-placed, small bore needle is recommended.

Sandimmune (cyclosporine, approved 1983)

Warnings: Alcohol (ethanol)

The alcohol content (See DESCRIPTION) of Sandimmune should be taken into account when given to patients in whom alcohol intake should be avoided or minimized, e.g. pregnant or breast feeding women, in patients presenting with liver disease or epilepsy, in alcoholic patients, or pediatric patients. For an adult weighing 70 kg, the maximum daily oral dose would deliver about 1 gram of alcohol which is approximately 6% of the amount of alcohol contained in a standard drink. The daily intravenous dose would delivery approximately 15% of the amount of alcohol contained in a standard drink.

Care should be taken in using Sandimmune (cyclosporine) with nephrotoxic drugs.

Taxol (paclitaxel, approved 1992)

Precautions

Nervous System: TAXOL contains dehydrated alcohol USP, 396mg/mL; consideration should be given to possible CNS and other effects of alcohol (See Precautions: Pediatric Use)

Pediatric Use: There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which TAXOL was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. The toxicity is most likely attributable to the high dose of the ethanol component of the TAXOL vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of TAXOL for use in this population.

Kaletra (lopinavir/ritonavir, approved 2000)

5.2 Toxicity in Preterm Neonates

KALETRA oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. Postmarketing life-threatening cases of cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving KALETRA oral solution.

KALETRA oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of KALETRA oral solution in this patient population has not been established. However, if the benefit of using KALETRA oral solution to treat HIV infection in infants immediately after birth outweighs the potential risks, infants should be monitored closely for increases in serum osmolality and serum creatinine, and for toxicity related to KALETRA oral solution including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis. Total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients *[see Dosage and Administration (2.2) and Overdosage (10)]*.

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/s/

MARGARET L RAND
02/13/2014

TRACY M SALAAM
02/13/2014

ALLEN D BRINKER
02/14/2014

SCOTT E PROESTEL
02/14/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 202356

Application Type: New NDA (505(b)(2)

Name of Drug/Dosage Form: Docetaxel Injection Concentrate, 10 mg/mL

Applicant: Pfizer Labs

Receipt Date: September 13, 2013

Goal Date: March 13, 2014

Regulatory History and Applicant's Main Proposals

This is the 3rd review cycle for this 505(b)(2) NDA for Docetaxel Injection Concentrate, 10 mg/mL. The first Complete Response letter was sent on February 29, 2012. On September 13, 2013, the Sponsor submitted a response to the Agency's February 14, 2013, Complete Response action letter. The Reference Listed Drug is Taxotere, NDA 020449.

This 505(b)(2) New Drug Application is indicated for:

- Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC (1.1)
- 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 (1.2)
- Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer (1.3)
- Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction (1.4)
- Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN (1.5)

The application received a Standard Review Designation, thereby making the PDUFA date March 13, 2013.

Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI) of January 10, 2014. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

1. Highlights Limitation Statement:
   Name of drug product is not in UPPER CASE letters

2. Initial U. S. Approval in Highlights:
   Not followed by 4-digit representing the year such as "XXXX"

3. Table of Content:
   Table of content is not in two columns.

4. Adverse Reactions:

   a) Clinical Trials: Verbatim statement is not included. See below:

   "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

   b) Post-marketing Experience: Verbatim statement is not included. See below:

   "The following adverse reactions have been identified during post approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the drug exposure."

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 27, 2014. PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *Waiver granted for the RLD, Taxotere.*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: The name of *drug product is not in UPPER CASE letters*

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

NO 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Not followed by 4-digit year*

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

NO 25. The TOC should be in a two-column format.

Comment: *TOC not in two columns*

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

NO 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: *Verbatim statement not included.*

NO 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *Verbatim statement not included.*

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MODUPE O FAGBAMI
01/23/2014

ALICE KACUBA
01/23/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	January 31, 2013
Reviewer:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Docetaxel Injection Concentrate 20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL, 200 mg/20 mL
Application Type/Number:	NDA 202356
Applicant:	Pfizer, Inc.
OSE RCM #:	2012-2284

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label and carton labeling of Docetaxel Injection Concentrate 20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL, and 200 mg/20 mL (NDA 202356) submitted in the Class II resubmission dated August 14, 2012.

1.1 REGULATORY BACKGROUND

The Applicant, Pfizer, submitted labels and labeling in their initial NDA submission dated April 29, 2011. The Applicant received a Complete Response (CR) letter for the application on February 29, 2012. DMEPA's comments for the carton labeling and container labels from OSE review # 2011-1613 were included in this CR letter. Pfizer responded to the CR in a Class II resubmission dated August 14, 2012.

In this review DMEPA is providing comments on the labels and labeling that Pfizer submitted in their August 14th submission. The comments for the Package Insert in OSE Review # 2011-1613 have not yet been incorporated in labeling discussions with the Division of Oncology Products 1 (DOP1).

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 14, 2012 (Appendix A)
- Carton Labeling submitted August 14, 2012 (Appendix B)

3 CONCLUSION

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. If you have questions or need clarifications, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

4 RECOMMENDATIONS

A. Comments to the Applicant

Carton Labeling (1 count and 5 count)

1. Add the concentration per mL statement "10 mg/mL" just below the total drug content in all places that it appears. Highlight the "(10 mg/mL)" statement by placing it in a red color block background with "(10 mg/mL)" in white lettering to provide emphasis on the concentration of the product. Ensure the font size

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

of the per mL concentration is smaller than the font size of the total drug content. Refer to the Unites States Pharmacopeia General Chapter <1> Injections for additional guidance, if needed.

For example:

White lettering with red color background

80 mg/ 8 mL

(10 mg/mL)

2. In red color block and in white lettering add "xx mg/xx mL (10 mg/mL)" to the top of all panels of the carton labeling as a continuous banner to provide further emphasis on the concentration of the product (see example below). Additionally, delete the statement "((b) (4))" at the top of each carton.

3. Increase the font size of the following statements on the 1 count and 5 count cartons, respectively:

   "xx mL single-use vial; discard unused portion"

   "5 x xx mL single-use vials; discard unused portion"

4. With regards to the statement "Docetaxel Injection", bold "Injection" as you did on the container labels.

Carton Labeling (5 count)

1. Increase the font size of the statements on the side panels. As currently presented, the statements are all within the top half of the side panel. Utilizing large font sizes for these statements and more of the side panel will increase readability of these statements.

Container Label and Carton Labeling for the 130 mg/13 mL Product

1. Due to the availability of multiple formulations of docetaxel in varying concentrations that require different instructions for drug preparation, the potential for confusion among these products is a significant safety concern. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized. One important feature of the container labels and carton labeling, that may help to differentiate these products, is color. Thus, in an effort to help minimize the potential for confusion that can lead to dosing errors due to similarities or overlaps in color

between the products, we take into consideration that colors should not overlap between the following:

- One-vial vs. two-vial formulations
- Concentration of 10 mg/mL vs. concentration of 20 mg/mL prior to dilution in infusion bag

The color you propose for your 130 mg/13 mL strength is similar to the color currently utilized for a two-vial docetaxel product of a different concentration and strength (see sample of color to avoid below). Therefore, not only could the concentrations get confused but the strengths could get confused as well. This could lead to wrong dose errors. Thus, we request you choose a different color for strength differentiation for your 130 mg/13 mL product.

(b) (4)

(b) (4)

Container Label and Carton Labeling for the 200 mg/20 mL Product

1. The color you propose for your 200 mg/20 mL (10 mg/mL) strength is similar to a (b) (4) color currently utilized for a different docetaxel concentration and strength. Therefore, not only could the concentrations get confused (10 mg/mL vs. 20 mg/mL) but the strengths could get confused as well. This could lead to wrong dose errors. Thus, we request you choose a different color for strength differentiation for your 200 mg/20 mL product. A sample of the color used by the other docetaxel product that should be avoided is provided below.

(b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JAMES H SCHLICK
01/31/2013

TODD D BRIDGES
02/01/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	January 29, 2013
To:	Robert Justice, MD Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nathan Caulk, MS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI)
Drug Name (established name):	Docetaxel Injection Concentrate
Dosage Form and Route:	Intravenous Infusion (IV)
Application Type/Number:	NDA 202-356
Applicant:	Pfizer Laboratories, Inc.

1 INTRODUCTION

On August 14, 2012, Pfizer Laboratories, Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 202-356 for Docetaxel Injection Concentrate, Intravenous Infusion. The purpose of the Applicant's submission is to provide a Class 2 Resubmission in response to a Complete Response (CR) letter issued from the Agency on February 29, 2012.

On September 27, 2012, the Division of Oncology Products (DOP1) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for Docetaxel Injection Concentrate, Intravenous Infusion. The proposed indication for Docetaxel Injection Concentrate, Intravenous Infusion is for the treatment of:

- 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
- 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 Adenocacinoma (GC): with cisplatin and fluorouracil for untreated, adnvaced GC, including the gastroesophageal junction
- Squamous Cell Carinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) for Docetaxel Injection Concentrate, Intravenous Infusion.

2 CONCLUSIONS

Due to outstanding chemistry deficiencies , DOP1 plans to issue a Complete Response (CR) letter. Therefore, DMPP defers 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. Please send us a new consult request at such time.

Please notify us if you have any questions.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NATHAN P CAULK
01/29/2013

BARBARA A FULLER
01/29/2013

LASHAWN M GRIFFITHS
01/29/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 19, 2012
To:	Patricia Keegan, MD, Director Division of Oncology Products 2
Through:	Todd Bridges, RPh, Team Leader Irene Z Chan, PharmD, BCPS, Team Leader Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	James Schlick, RPh, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name:	Docetaxel Injection Concentrate 20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL, 200 mg/20 mL
Application Type/Number:	NDA 202356
Applicant:	Pfizer
OSE RCM #:	2011-1613

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the labels and labeling for Pfizer's proposed Docetaxel Injection Concentrate, submitted on April 29, 2011, for areas of vulnerability that can lead to medication errors. This review is written in response to a request from the Division of Oncology Products 1.

1.1 REGULATORY HISTORY

This NDA is a 505 (b)(2) application. The Reference Listed Drug is 2-vial Taxotere (Docetaxel) Injection Concentrate, NDA 020449.

1.2 BACKGROUND ON DOCETAXEL PRODUCTS

Taxotere, a Sanofi Aventis product, was approved on May 14, 1996. It is a two-vial configuration consisting of one vial of active drug solution (40 mg/mL) and one vial of diluent that must be mixed together to yield a concentration of 10 mg/mL before being added to the infusion solution. The two-vial configuration has undergone numerous label and labeling changes in addition to educational interventions to address medication errors that resulted from confusion with the unusual two-step dilution.

On August 2, 2010, a new one-vial formulation of Taxotere was approved by the FDA. This one-vial formulation does not require a two step dilution process, and the drug can be withdrawn from the vial and added directly to the infusion solution. However, whereas the two-vial formulation yielded a concentration of 10 mg/mL before being added to the infusion solution, the new one-vial formulation was approved with a concentration of 20 mg/mL.

On March 8, 2011, a 505 (b)(2) application for Docetaxel Injection manufactured by Hospira was approved by the FDA. On June 29, 2011, another 505 (b)(2) application for Docetaxel Injection manufactured by Sandoz was approved by the FDA. The Docetaxel Injection products by Hospira and Sandoz are also one-vial formulations like the one-vial formulation of Taxotere. An important difference between these two products as compared to the one vial Taxotere formulation by Sanofi Aventis is their concentration. Taxotere's one-vial formulation is available in a concentration of 20 mg/mL, whereas Hospira's and Sandoz's one-vial formulations are available in a concentration of 10 mg/mL. Additionally, there is one pending 505 (b)(2) application submitted by Pfizer (the application evaluated in this review) for a one vial formulation containing 10 mg/mL, the same as Hospira's and Sandoz's products. Since approval, we have received complaints concerning this disparity in concentrations.

Although Sanofi Aventis intends to discontinue the two-vial Taxotere formulation now that a one-vial Taxotere formulation has been introduced to the market, an additional product like the two-vial Taxotere was approved by the FDA. This application, submitted by Accord Healthcare, was approved on June 8, 2011 as a 505 (b)(2) application. Accord Healthcare's Docetaxel Injection is a two-vial formulation that yields a 10 mg/mL concentration after the initial reconstitution step, the same as the two-vial Taxotere by Sanofi Aventis. There is also one product by Apotex*** pending FDA approval that is also a two-vial formulation, like the two-vial Taxotere by Sanofi Aventis.

Lastly, the FDA approved a 505 (b)(2) application, submitted by Sun Pharma Global as a powder for injection, which differentiates it from all the other approved and pending docetaxel products. Appendix A summarizes the approved and pending docetaxel injection products.

*** This document contains proprietary and confidential information that should not be released to the public.

1.3 PRODUCT INFORMATION FOR PFIZER'S DOCETAXEL INJECTION CONCENTRATE

Docetaxel Injection Concentrate is a microtubule inhibitor indicated for the treatment of breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck. Docetaxel Injection Concentrate has a boxed warning concerning toxic deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention. The dosing regimens vary depending on the indication of use (see Appendix B). Docetaxel Injection Concentrate solution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered intravenously through polyethylene-lined administration sets over one hour. The inactive ingredients in the active drug and diluent differ from those in the Reference Listed Drug.

Docetaxel Injection Concentrate is a one-vial formulation available in a 10 mg/mL concentration. The appropriate amount is withdrawn from the vial and can be added directly to either a 5% dextrose solution or a 0.9% sodium chloride solution. Docetaxel Injection Concentrate is available in the following strengths: 20 mg/2 mL, 80 mg/8 mL,130 mg/13 mL, and 200 mg/20 mL.

2 METHODS AND MATERIALS REVIEWED

DMEPA previously conducted an AERS search to identify medication errors involving Taxotere or docetaxel on March 21, 2011(see OSE review 2010-2465 dated, April 5, 2011). Given the number of approved docetaxel products, pending applications, and complicated safety issues concerning these products, DMEPA conducted a new search of the FDA Adverse Event Reporting System (AERS) database. The container labels, carton labeling, and insert labeling were reviewed as well.

2.1 AERS SELECTION OF MEDICATION ERROR CASES

An AERS search was conducted on October 20, 2011 using the MedDRA High Level Group Term "Medication Errors", High Level Term "Product Label Issues", and Preferred Term "Product Quality Issues", active ingredient "Docetaxel", trade name "Taxotere", and verbatim "Taxot%" and "Doce%". The search was limited to the dates March 22, 2011 through October 20, 2011. This time period covers the time since our last AERS search was conducted in OSE Review 2010-2465. The results of the AERS search can be found in OSE review 2011-2624, dated December 21, 2011.

2.2 LABEL AND LABELING RISK ASSESSMENT

DMEPA uses Failure Mode and Effects Analysis (FMEA) to evaluate container labels and carton and insert labeling. This review summarizes our evaluation of the following labels and labeling (see Appendices C through E).

- Container Labels: 20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL, and 200 mg/20 mL
- Carton Labeling: 20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL, and 200 mg/20 mL
- Insert Labeling: No image

3 RESULTS AND DISCUSSION

3.1 LABEL AND LABELING RISK ASSESSMENT

The following deficiencies were noted in the container labels and/or carton labeling:

- The color scheme for the Pfizer 200 mg product overlaps with that of one-vial Taxotere 80mg product. Due to the availability of multiple formulations in varying concentrations that require

different instructions for drug preparation, the potential for confusion among these products is a significant safety concern. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized. One important feature of the container labels and carton labeling that may help to differentiate these products is color. Thus, in an effort to help minimize the potential for confusion that can lead to dosing errors due to similarities or overlaps in color between the products, we take into consideration that colors should not overlap between the following:

  - One-vial vs. two-vial formulations
  - Concentration of 10 mg/mL vs. concentration of 20 mg/mL prior to dilution in infusion bag

- There is a lack of statements that highlight and caution healthcare providers about the product concentration.
- There are statements on the labels and labeling that are not optimally positioned and/or need to be revised.
- There is clutter on the container labels that competes with the prominence of other important information.
- The established name lacks prominence.
- The use of "Concentrate" in the established name could lead to confusion with the two vial concentrate preparations which have two dilution steps.

4 CONCLUSION AND RECOMMENDATIONS

Our evaluation identified areas where information on the container labels, carton labeling, and package insert can be improved to minimize the potential for medication errors. Section 4.2 *Comments to the Applicant* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarification, please contact OSE Safety Regulatory Project Manager, Mark Liberatore, at 301-796-2221.

4.1 COMMENTS TO THE DIVISION

A. General Comments on Package Insert Labeling

1. Revise all instances of the abbreviation "hr" to read "hour" to minimize misinterpretation of the abbreviation.

2. Add the full name "granulocyte - colony stimulating factor" immediately before the first appearance of "G-CSF" in the insert and place the abbreviation in parentheses to minimize confusion. Subsequent abbreviations of "G-CSF" are not required to have the full name immediately before the abbreviation.

3. Add the full name "polyvinyl chloride" immediately before the first appearance of "PVC" in the insert and place the abbreviation in parentheses to minimize confusion. Subsequent abbreviations of "PVC" are not required to have the full name immediately before the abbreviation.

4. Revise all instances of the abbreviation "IV" to be written as "intravenous" or "intravenously" and all instances of "<", ">", "≤" and "≥" to be written in text instead of a symbol (e.g. "≥" should be revised to "greater than or equal to"), because they are considered dangerous abbreviations. The abbreviation "IV" appears on the Institute for Safe Medication Practices (ISMP) List of Error-Prone Abbreviations, Symbols, and Dose Designations[1] because it has been confused as 'IM', the abbreviation for intramuscular. Additionally, the symbols "<", ">", "≤" and "≥" also appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because they have been confused for the opposite meaning (e.g. "<" has been misinterpreted as great than). On June 14, 2006, the FDA and ISMP launched a campaign to reduce medication errors related to error prone medical abbreviations and dose designations. As part of that campaign the FDA agreed not to approve labels and labeling that included the use of error prone abbreviations or dose designations.

B. Specific Comments on Package Insert Labeling

Revise the package insert as follows: [DMEPA's revisions to the package insert are in red print and underlined.]

2.9 Preparation and Administration

Docetaxel Injection Concentrate (10 mg docetaxel/mL) requires NO prior dilution with a diluent and is ready to add to the infusion solution.

1. Docetaxel Injection Concentrate (10 mg docetaxel/mL) should be stored between 2 and 25°C (36 and 77°F).
2. If Docetaxel Injection vials are stored under refrigeration, allow the vial(s) to come to room temperature prior to use.
3. Aseptically withdraw the required amount of Docetaxel Injection Concentrate (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL.
   If a dose greater than 200 mg of Docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL Docetaxel is not exceeded.
4. Thoroughly mix the infusion by manual rotation.
5. As with all parenteral products, Docetaxel Injection Concentrate and final dilution for intravenous infusion should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the Docetaxel Injection concentrate or final dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.

The Docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

2.10 Stability

[1] www.**ismp**.org/tools/**errorproneabbreviations**.pdf

[redacted] controlled [redacted] (20℃ to 25℃ or 68℉ to 77℉).

16.1 How Supplied

Docetaxel Injection Concentrate is supplied in single-use CYTOSAFE® polypropylene vials as a sterile, pyrogen-free, non-aqueous, solution. [redacted]

4.2 COMMENTS TO THE APPLICANT

A. General Comments for the Container Labels and Carton Labeling

1. Due to the availability of multiple formulations of docetaxel in varying concentrations that require different instructions for drug preparation, the potential for confusion among these products is a significant safety concern. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized. One important feature of the container labels and carton labeling, that may help to differentiate these products, is color. Thus, in an effort to help minimize the potential for confusion that can lead to dosing errors due to similarities or overlaps in color between the products, we take into consideration that colors should not overlap between the following:

    - One-vial vs. two-vial formulations
    - Concentration of 10 mg/mL vs. concentration of 20 mg/mL prior to dilution in infusion bag

    The color you propose for your 200 mg/ 20 mL strength is similar to the red color currently utilized for the one-vial Taxotere 80 mg/4 mL product by Sanofi Aventis. Therefore, not only could the concentrations get confused but the strengths could get confused as well. This could lead to wrong dose errors. Thus, we request you choose a color for strength differentiation that does not overlap with the currently marketed 80 mg/4 mL one-vial Taxotere by Sanofi Aventis.

2. Remove "Concentrate" from the established name. This could lead to confusion with the two vial concentrate preparations which have two dilution steps. Additionally, change the color of "Docetaxel Injection" to black to make the name more prominent.

3. Revise the statement "[redacted]" to "For Intravenous Infusion Only" and bold the words "Infusion Only". For example: "For Intravenous **Infusion Only**".

4. Remove "[redacted]" because it competes with other important information and clutters the labels and labeling.

5. Change the statement "single-use" to "single-use vial".

6. Highlight the "(10 mg/mL)" statement by placing it in a red color block background with "(10 mg/mL)" in white lettering wherever it appears on the container or carton labeling to provide emphasis on the concentration of the product.

B. Container Labels

1. Place the volume, in mL, immediately in front of the statement "single use vial" (see A.6 above). For example: "2 mL single use vial" on the 20 mg/2 mL product and so forth.

2. Relocate the statement "Caution: Cytotoxic Agent" to the side panel of the 80 mg/8 mL, 130 mg/13 mL, and 200 mg/20 mL labels.

3. Ensure there is one character space between "10" and "mg/mL" in the strength presentation.

4. To highlight the difference between docetaxel products, add the following statement – "Ready to add to infusion solution. Check concentration prior to preparation. See package insert for complete instructions." Additionally, bold and box the statement.

5. Consider using a different orientation for the layout of the information on the principal display panel in order to accommodate the above recommended revisions to the container labels. The Sandoz and Hospira marketed docetaxel container labels are a good resource on guidance for making changes to the Pfizer product to ensure patient safety. In addition, since the container labels are small like Hospira and Sandoz labels, the applicant may wish to remove the statements "Store between…", "Protect from light,…" and "Dosage and Use:…" statements by applying 21 CFR 201.10 (h)(2)(i) for minimum label requirements.

C. General Comments for Carton Labeling

1. In red color block and in white lettering add "xx mg/xx mL (10 mg/mL)" to the top of all panels of the carton labeling as a continuous banner to provide further emphasis on the concentration of the product. The Sandoz and Hospira marketed docetaxel products are a good resource on guidance for this change. Do not include the "New Strength and Preparation" banner found on the Hospira and Sandoz products.

2. As a continuous banner in red color block and in white lettering add the following statement – "Ready to add to infusion solution. Check concentration prior to preparation. See package insert for complete instructions."

D. Comments for One-Count Carton Labeling

See Comment B1 above.

E. General Comments for Five Count Carton Labeling

1. Remove "(b) (4)" and combine with the statement below.

2. Change the statement "(b) (4)." to "5 x XX mL single use vials; discard unused portion." Place the corresponding total volume where the XX is located (i.e., "5 x 2 mL single use vials; discard unused portion" for the 20 mg/2 mL carton and so forth). This statement should be located below the NDC numbers.

REFERENCES

Schlick, James. Docetaxel Injection Labeling Review, OSE Review 2011-2624, dated December 21, 2011.

APPENDICES

Appendix A: Table of Docetaxel Injection Products

NDA	Applicant	Formulation	Concentration	Status
20449/S-054 Taxotere	Sanofi-Aventis	1 vial	20 mg/mL	Approved
20449 Taxotere	Sanofi-Aventis	2 vial	10 mg/mL after initial dilution	Approved
201195	Accord Healthcare	2 vial	10 mg/mL after initial dilution	Approved
022234	Hospira	1 vial	10 mg/mL	Approved
201525	Sandoz	1 vial	10 mg/mL	Approved
022534 Docefrez	Sun Pharma Global (b) (4)	Lyopholized powder plus diluent	**20 mg vial** 20 mg/0.8 mL (25 mg/mL) **80 mg vial** 24 mg/mL	Approved
202356	Pfizer	1 vial	10 mg/mL	Pending
022312	Apotex	2 vial	10 mg/mL after initial dilution	Pending

Appendix B: Docetaxel Injection Indications of Use and Dosage Information

Indication of Use	**Dosage**
Breast cancer: locally advanced or metastatic	60 mg to 100 mg/m^2 single agent
Breast cancer adjuvant	75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles
Non-small cell lung cancer, after platinum therapy failure	75 mg/m^2 single agent
Non-small cell lung cancer, chemotherapy naïve	75 mg/m^2 followed by cisplatin 75 mg/m^2
Hormone refractory prostate cancer	75 mg/m^2 with 5 mg prednisone twice a day continuously
Gastric adenocarcinoma	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 intravenous infusion (days 1-5), starting at end of cisplatin infusion
Squamous cell carcinoma of the head and neck	75 mg/m^2 followed by cisplatin 75 mg/m^2 intravenously (day 1), followed by fluorouracil 750 mg/m^2 per day as a 24-hour intravenous infusion (days 1-5), starting at end of cisplatin infusion; for 4 cycles
Squamous cell carcinoma of the head and neck	75 mg/m^2 followed by cisplatin 100 mg/m^2 intravenously (day 1), followed by fluorouracil 1000 mg/m^2 per day as a 24-hour intravenous infusion (days 1-4); for 3 cycles
Premedication Regimen	Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day before administration. Hormone refractory prostate cancer: oral dexamethasone 8 mg, at 12 hours, 3 hours, and 1 hour before treatment

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES H SCHLICK
01/19/2012

IRENE Z CHAN
01/20/2012

TODD D BRIDGES
01/20/2012

CAROL A HOLQUIST
01/20/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 202356	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Docetaxel Injection Concentrate 10 mg/mL Established/Proper Name: docetaxel Dosage Form: solution, injection Strengths: 20 mg/2mL, 80 mg/8mL, 130 mg/13mL, 200 mg/20mL		
Applicant: Pfizer Labs		
Date of Receipt: April 29, 2011		
PDUFA Goal Date: February 29, 2012	Action Goal Date (if different):	

Proposed Indication(s):

- Breast Cancer – single agent for the treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy. In combination with doxorubicin and cyclophosphamide for the adjuvant treatment of operable, node-positive breast cancer.
- Non-Small Cell Lung Cancer – single agent for the treatment of locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. In combination with cisplatin for the treatment of patients unresectable, locally advanced or metastatic NSCLC who have not previously received chemotherapy for this condition.
- Prostate Cancer – in combination with prednisone for the treatment of androgen independent (hormone refractory) metastatic prostate cancer.
- Gastric Adenocarcinoma – in combination with cisplatin and fluorouracil 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 – in combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO X

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Taxotere 40 mg/mL NDA 20-449	Clinical (efficacy & safety), nonclinical, clinical pharmacology

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Pfizer asked for and received a waiver of the need for bioequivalence studies.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO X

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES X NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Taxotere 40 mg/mL	20-449	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A X YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO X

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO X

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO X

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☒ NO X

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Taxotere 40 mg

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for an alternate formation to Taxotere. Pfizer's product is a 1-vial formulation that does not require a pre-mix step and is ready for immediate dilution and administration. The 1-vial formulation will reduce the number of aseptic manipulations required to prepare the final infusion fluid, which reduces the potential for contamination and, therefore, may improve patient safety.

The active pharmaceutical ingredient in Docetaxel Injection Concentrate 10 mg/mL is docetaxel (anhydrous) instead of docetaxel (trihydrate) used in Taxotere.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO X

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO X

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

5698582 (7/3/12)	5698582*PED (1/3/13)
5714512 (7/3/12)	5714512*PED (1/3/13)
5750561 (7/3/12)	5750561*PED (1/3/13)
5438072 (5/22/14)	

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO X

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 4814470

X 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): 5714512 Expiry date(s): 1-3-2013

X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

Patent number: 5698582

Patent number: 5438072, expiry date of May 22, 2014
This patent is no longer listed in the Orange Book under NDA 20449.

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

From form 3542a

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5438072, 5698582
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES X NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES X NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): December 15, 2011

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☒ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval

See 2-9-2012 submission.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMO

Date:	January 17, 2012
To:	Patricia Keegan, MD, Director **Division of Oncology Products 2 (DOP 2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
From:	Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
Subject:	Review Deferred: Patient Package Insert
Drug Name(s):	Docetaxel Injection Concentrate, 10 mg/mL
Application Type/Number:	NDA 202356
Applicant/Sponsor:	Pfizer Inc.
OSE RCM #:	2011-1614

This memorandum documents the deferral of our review of Docetaxel Injection Concentrate, 10 mg/mL. On May 19, 2011, the Division of Oncology Products 2 (DOP 2) requested that DMPP review the Applicant's proposed Patient Package Insert (PPI).

Due to outstanding chemistry deficiencies, DOP 2 plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's PPI at this time. DMPP will provide a complete review of proposed patient labeling after the Applicant submits a Complete Response to the Agency's Complete Response letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA A FULLER
01/17/2012
DMPP Deferral memo docetaxel injection NDA 202356

LASHAWN M GRIFFITHS
01/17/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202356 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Docetaxel In jection Concentrate 10 mg/mL Established/Proper Name: docetaxel Dosage Form: Solution, injection Strengths: 20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL & 200 mg/20 mL		
Applicant: Pfizer Labs Agent for Applicant (if applicable):		
Date of Application: 4-29-2011 Date of Receipt: 4-29-2011 Date clock started after UN:		
PDUFA Goal Date: 2-29-2012	Action Goal Date (if different):	
Filing Date: 6-28-2011	Date of Filing Meeting: 6-7-2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5		
Proposed indications: treatment of breast cancer, prostate cancer, NSCLC, head & neck cancer & gastric adenocarcinoma		

Type of Original NDA: AND (if applicable)	☐ 505(b)(1) X505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	X Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 109463	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: X Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	X			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
20449	Taxotere	PED (pediatric exclusivity)	11-13-2013
20449	Taxotere	M-61 (labeling revisions based on data submitted in response to pediatric written request)	5-13-2013

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year

exclusivity will only block the approval, not the submission of a 505(b)(2) application.				
Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				
Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) X CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: X legible XEnglish (or translated into English) Xpagination X navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?		X		Info submitted on 5-20-2011
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?				Submitted on 6-2-2011.
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			

Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			X	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** Clinical microbiology 5-16-2011	X			
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)?		X		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Date(s): ***If yes, distribute minutes before filing meeting***				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** November 1, 2010 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			X	

ATTACHMENT

MEMO OF FILING MEETING

DATE: 6-7-2011

BLA/NDA/Supp #: 202356

PROPRIETARY NAME: Docetaxel Injection Concentrate 10 mg/mL

ESTABLISHED/PROPER NAME: docetaxel

DOSAGE FORM/STRENGTH: 20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL & 200 mg/20 mL

APPLICANT: Pfizers Labs

PROPOSED INDICATIONS: treatment of breast cancer, prostate cancer, NSCLC, head & neck cancer & gastric adenocarcinoma (same indications as for Taxotere).

BACKGROUND: Pfizer's Docetaxel Injection is a 1-vial formulation that does not require the the pre-mix step that Taxotere requires and is thus ready for immediate dilution and administration.

The active pharmaceutical ingredient in Docetaxel Injection Concentrate 10 mg/mL is docetaxel (anhydrous), instead of docetaxel (trihydrate) used in Taxotere.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sharon Sickafuse	Y
	CPMS/TL:	Karen Jones	N
Cross-Discipline Team Leader (CDTL)	Sarah Pope		N
Clinical	Reviewer:	Bill Pierce	Y
	TL:	Steve Lemery	Y
Clinical Pharmacology	Reviewer:	Lillian Zhang	Y
	TL:	Hong Zhao	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Brian Chiu	Y
	TL:	Anne Pilaro	Y

Product Quality (CMC)	Reviewer:	Josephine Jee	Y
	TL:	Liang Zhou	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Steven Fong	N
	TL:	Jim McVey	N
CMC Labeling Review	Reviewer:	Tu-Van Lambert	Y
	TL:	Liang Zhou	N
OSE/DRISK	Reviewer:	Sharon Mills	Y
	TL:	LaShawn Griffiths	N
OSE/DMEPA	Reviewer:	Loretta Holmes	Y
	TL:	Irene Chan	N
DDMAC	Reviewer:	Carole Broadnax	Y
	TL:		
Bioequivalence	Reviewer:	Elsbeth Chikhale	Y
	TL:	Angelica Dorantes	N

Other reviewers		
Other attendees	Sue Kang, OSE RPM	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES X NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable

CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: N/A	☐ YES X NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: X NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS	X Not Applicable

Comments:	☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable XYES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable XYES ☐ NO X YES ☐ NO

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Patricia Keegan, M.D. **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): Review Classification: X Standard Review ☐ Priority Review

ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON K SICKAFUSE
06/09/2011