

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201195Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 201195	NDA Supplement #: N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: N/A		
Established/Proper Name: Docetaxel Injection (b) (4)		
Dosage Form: Injection		
Strengths: 20mg/0.5 mL and 80 mg/2.0 mL		
Applicant: Accord Healthcare, Inc.		
Date of Receipt: December 10, 2010		
PDUFA Goal Date: June 10, 2011 (Class 2 Resubmission)		Action Goal Date (if different): N/A
Proposed Indication(s): Breast Cancer (CA); Non-Small Cell Lung Cancer (NSCLC); Hormone Refractory Prostate Cancer (HRPC); Gastric Adenocarcinoma (GC); Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN).		

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

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 (docetaxel) Injection Concentrate, Intravenous Infusion (IV) 80 mg/2 mL and 20 mg/0.5 mL.	Clinical, statistical, pharmacokinetic, and nonclinical, CMC sections 2.10, 11, 16 (formulation-related sections are not relied upon), data rely on Taxotere label.

*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)

Based on the route of administration (intravenous) and the information provided on the formulation, the Clinical Pharmacology and the ONDQA/OPS Biopharmacology teams determined that a BE study will not be needed.

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

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 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 (docetaxel) Injection Concentrate, Intravenous Infusion (IV)	N20449	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 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

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

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

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

- c) Described in a monograph?

YES NO

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

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:

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 (b)(2) drug provides a minor change in formulation adding two new excipients, polyethylene glycol 400 and citric acid for (b) (4) and pH control. The presentation of two-vial solution for injection is the same as Taxotere. This application does not provide a new indication, or a change in dosage form. It is intended to increase/expand the supply of docetaxel.

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

*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):

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.

Listed drug/Patent number(s):	5438072	Nov. 22, 2013
	5438072*PED	May 22, 2014
	5698582	July 3, 2012
	5698582*PED	Jan. 3, 2013
	5714512	July 3, 2012
	5714512*PED	Jan. 3, 2013
	5750561	July 3, 2012
	5750561*PED	Jan. 3, 2013

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

Patent number(s):

- X** 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification) ****Paragraph III certification was previously submitted by the applicant to address Patents 4814470 (exp. May 14, 2010) and 4814470*PED (exp. November 14, 2010).**

Patent number(s):

Expiry date(s):

- 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.*

5438072	Nov. 22, 2013
5438072*PED	May 22, 2014
5698582	July 3, 2012
5698582*PED	Jan. 3, 2013
5714512	July 3, 2012
5714512*PED	Jan. 3, 2013
5750561	July 3, 2012
5750561*PED	Jan. 3, 2013

****The applicant previously submitted Paragraph III Certification to address the '582', '512', and '561' patents.**

- 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.
- 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 | Nov. 22, 2013 |
| 5438072*PED | May 22, 2014 |
| 5698582 | July 3, 2012 |
| 5698582*PED | Jan. 3, 2013 |
| 5714512 | July 3, 2012 |
| 5714512*PED | Jan. 3, 2013 |
| 5750561 | July 3, 2012 |
| 5750561*PED | Jan. 3, 2013 |

- (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 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 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): November 22, 2010

- (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

On May 17, 2011, Judge Gregory M. Sleet of the US District Court for the District of Delaware entered a signed consent decree in Civil Action Case NO. 11-18-GMS stating that U.S. Patent Nos. 5714512 and 5750561 for Taxotere, NDA 020449, are invalid, unenforceable or will not be infringed by Accord's manufacture, user or sale of drug product under their application.

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/s/

KIM J ROBERTSON

06/06/2011

505(b)(2) Assessment Form; NDA 201195; Docetaxel Inj.; Accord Healthcare

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

Date: June 3, 2011

Application Type/Number: NDA 201195

To: Robert Justice, MD, Director
Division of Drug Oncology Products

Through: Todd Bridges, RPh, Acting Deputy Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Memorandum

Drug Name and Strength: Docetaxel Injection
20 mg/0.5 mL and 80 mg/2 mL

Applicant: Accord Healthcare Inc.

OSE RCM #: 2011-282

This memorandum evaluates the revised container labels, blister labels and carton labeling received on June 1, 2011 for Accord's Docetaxel Injection in response to a request from the Division of Drug Oncology Products (see Appendices A through D). DMEPA finds the revised container labels and carton labeling acceptable. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this memorandum. If you have further questions or need clarification, please contact OSE Regulatory Project Manager, Sarah Simon, at 301-796-5205.

APPENDICES

Appendix A: Container Labels (20 mg/0.5 mL and 80 mg/2 mL)

(b) (4)



Appendix B: Diluent Container Labels for (20 mg/0.5 mL and 80 mg/2 mL)

(b) (4)



Appendix C: Blister Labels (20 mg/0.5 mL and 80 mg/2 mL)

(b) (4)



Appendix D: Carton Labeling (20 mg/0.5 mL and 80 mg/2 mL)

(b) (4)



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/s/

LORETTA HOLMES
06/03/2011

TODD D BRIDGES
06/03/2011

Internal Consult

Pre-decisional Agency Information

To: Kim J. Robertson, Division of Drug Oncology Products, (DDOP)

From: Adam George, Regulatory Reviewer Officer
Division of Drug Marketing, Advertising, and Communications,
(DDMAC)

CC: Karen Rulli, Professional Review Group II Leader, DDMAC

Date: April 22, 2011

Re: Comments on draft labeling (Package Insert) for Docetaxel for
intravenous infusion

NDA 201195

In response to your consult request via email on March 17, 2011, we have reviewed the draft Package Insert for Docetaxel for intravenous infusion (Docetaxel). We offer the following comments.

Specific comments on the proposed labeling:

Section	Statement from draft	Comment
<ul style="list-style-type: none">FULL PRESCRIBING INFORMATION: CONTENTS, Section 14 CLINICAL STUDIES	14 CLINICAL STUDIES <ul style="list-style-type: none">14.1 Locally Advanced or Metastatic Breast Cancer14.2 Adjuvant Treatment of Breast Cancer14.3 Non-Small Cell Lung Cancer (NSCLC)14.4 Hormone Refractory Prostate Cancer14.5 Gastric Adenocarcinoma14.6 Head and Neck Cancer	<ul style="list-style-type: none">In the reference label drug (RLD) 14.1 states "Breast Cancer" and 14.4 states "Prostate Cancer". Unless there is a specific reason for these section titles to be changed DDMAC recommends that the label for 201195 match

Section	Statement from draft	Comment
		the RLD.
<ul style="list-style-type: none"> 6 ADVERSE REACTIONS, Table 11 		<ul style="list-style-type: none"> Adverse event “Constipation” Grade 3/4 rate is listed as (b) (4) in the label for 201195. In the RLD it is listed as 2%. DDMAC recommends changing the rate of Grade 3/4 constipation to match the RLD
<ul style="list-style-type: none"> 14 CLINICAL STUDIES, Table 16 	30%**†	<ul style="list-style-type: none"> For the 201195 label the column for table 16 titled “TAX320” for Docetaxel 75 mg/m² the % 1-year Survival 95% CI data has two asterix. According to the RLD there should only be one asterix. DDMAC recommends deleting an asterix.

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/s/

ADAM GEORGE
04/22/2011

**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: April 5, 2011

To: Robert Justice, MD, Director
Division of Drug Oncology Products

Through: Irene Z. Chan, PharmD, BCPS, Team Leader
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name: Docetaxel Injection
20 mg/0.5 mL and 80 mg/2 mL

Application Type/Number: NDA 201195

Applicant: Accord Healthcare Inc.

OSE RCM #: 2011-282

1 INTRODUCTION

This review evaluates the revised labels and labeling for Accord Healthcare's Docetaxel Injection submitted on January 19, 2011 for areas of vulnerability that could lead to medication errors. This review is written in response to a request from the Division of Drug Oncology Products.

1.1 REGULATORY HISTORY

DMEPA previously provided label and labeling recommendations for this product in OSE Review 2010-530, dated September 27, 2010. This application subsequently received a Complete Response (CR) action on October 22, 2010; however, our label and labeling recommendations were never forwarded to the Applicant.

This NDA is a 505(b)(2) application. The reference listed drug (RLD) is Taxotere (Docetaxel) Injection Concentrate (NDA 020449) in the two-vial formulation.

1.2 BACKGROUND ON DOCETAXEL PRODUCTS

Taxotere, a Sanofi Aventis product, was approved on May 14, 1996, as 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. The Docetaxel Injection by Hospira is also a one-vial formulation like the one-vial formulation of Taxotere. An important difference between these two products is their concentration. Taxotere's one-vial formulation is available in a concentration of 20 mg/mL, whereas Hospira's one-vial formulation of docetaxel is available in a concentration of 10 mg/mL. The reference listed drug for Hospira's product is Taxotere. Since approval, we have received complaints concerning this disparity in concentrations.

Sanofi Aventis intends to discontinue the two-vial Taxotere formulation now that a one-vial Taxotere formulation has been introduced to the market. Although the two-vial Taxotere will be discontinued, (b) (4), including this one, which propose a two-vial formulation of docetaxel. These two-vial formulations will yield a 10 mg/mL concentration after the initial reconstitution step which is the same as two-vial Taxotere. (b) (4)

1.3 PRODUCT INFORMATION FOR ACCORD HEALTHCARE'S DOCETAXEL INJECTION

Docetaxel Injection is 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 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 A).

Docetaxel Injection is a two-vial formulation which will be available in 20 mg/0.5 mL and 80 mg/2 mL strengths which must be diluted with the supplied diluent to yield a concentration of 10 mg/mL. The required amount is withdrawn from the vial(s) and must be further diluted by adding it to the infusion solution. Docetaxel Injection diluted 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 active drug plus diluent will be packaged in a blister pack in one carton. The diluent for Docetaxel Injection contains ingredients that differ from those in the diluent of the RLD.

2 METHODS AND MATERIALS

DMEPA previously conducted an AERS search to identify medication errors involving Taxotere or docetaxel (see OSE review 2007-548 dated March 23, 2007). Results of the previous search were used to inform label and labeling recommendations for Taxotere two-vial formulation in order to minimize medication errors that were occurring at that time. Since 2007, an updated search for docetaxel medication errors has not been completed. Given the changes to the labels and labeling for Taxotere since 2007, (b) (4), and complicated safety issues concerning docetaxel products, DMEPA conducted a new search of the FDA Adverse Event Reporting System (AERS) database. We also reviewed a medication error report from the Institute for Safe Medication Practices (ISMP). The proposed labels and labeling were reviewed as well.

2.1 AERS SELECTION OF MEDICATION ERROR CASES

An AERS search was conducted on March 21, 2011 using the MedDRA High Level Group Terms “Medication Errors” and “Product Quality Issues”, active ingredient “Doce%”, trade name “Taxo%”, and verbatim “Taxo%” and “Doce%”. The search was limited to the dates March 23, 2007 through March 21, 2011. This time period covers the time since our last AERS search conducted for OSE Review 2007-548.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. Cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If the root cause(s) could be associated with the labels, labeling, or packaging of the product, the cases were considered pertinent to this review. Those cases that did not describe a medication error or did not describe an error applicable to this review (e.g. adverse drug event not resulting from a medication error, product quality complaints, etc.), were excluded from further analysis.

2.2 ISMP MEDICATION ERROR REPORT

The article “Dosing error with the new Taxotere concentration” in the March 24, 2011 issue of ISMP Medication Safety Alert¹ was reviewed.

¹ “Dosing error with new Taxotere concentration,” *ISMP Medication Safety Alert*, Vol. 16, Issue 6, March 24, 2011.

2.3 LABEL AND LABELING RISK ASSESSMENT

DMEPA uses Failure Mode and Effects Analysis (FMEA) to evaluate the container labels and carton and insert labeling. This review focuses on the container labels and carton labeling submitted on January 19, 2011 (see Appendices D through G):

- Container Labels (Docetaxel Injection): 20 mg/0.5 mL and 80 mg/2 mL
- Diluent Labels for Docetaxel Injection 20 mg/0.5 mL and 80 mg/2 mL
- Blister Labeling for Blister Pack Containing Active Drug and Diluent
- Carton Labeling (Docetaxel Injection): 20 mg/0.5 mL and 80 mg/2 mL

We reserve review of and recommendations for the insert labeling for the labeling meetings scheduled with the Division of Drug Oncology Products. Our recommendations will be made to the working insert labeling that is available on the shared (N) drive.

3 RESULTS AND DISCUSSION

The following sections describe the findings and assessment of the AERS data, ISMP medication error report, and the label and labeling review.

3.1 FDA ADVERSE EVENTS REPORTING SYSTEM (AERS) CASES

The AERS search conducted on March 21, 2011, retrieved 26 cases (see Appendix B for ISR numbers). Of the 26 cases, 23 were excluded (see Appendix C). Thus, three reports remained for our evaluation:

Potential Error (n=2)

- The reporter stated the product packaging of Taxotere is confusing because the 80 mg/2 mL active drug plus the 7.1 mL of diluent adds up to 9.1 mL, not the 80 mg/8 mL needed for a 10 mg/mL concentration. The reporter further explained that this could lead to errors if a person didn't closely read the entire box prior to final product preparation. (ISR #5581415)
- The reporter stated the concentration of the new Taxotere [one-vial] formulation (20 mg/mL) could cause an overdose because this is an increase from the two-vial Taxotere which is 10 mg/mL after the initial dilution step. (ISR #7092480)

Improper Dose or Wrong Technique (n=1)

- The reporter stated students made 3 doses of Taxotere incorrectly, all of which were caught prior to patient administration. The details of the error were not reported; therefore, it is difficult to determine whether an improper dose was made or if wrong technique was used in preparing the doses (ISR # 5403737).

Our AERS results indicate there is still confusion with the two-vial formulation of Taxotere between the concentration of the active drug vial and the resultant concentration after the initial dilution step. The concentration of the active drug is necessary on the vial label in order to inform healthcare practitioners of its contents. Additionally, it is due to the physical characteristics of the product that the volume of active drug plus the volume of diluent, when they are combined, do not add up to the expected volume. This is explained in the insert labeling, and it is not feasible to put all of this additional information on the container labels and carton labeling due to space limitations. However, the instructions for preparation are highlighted on the container labels and carton labeling so that they are readily available and if they are read, the

product can be prepared correctly. We will ensure this is included for the container labels and carton labeling for Docetaxel Injection.

DMEPA is aware that the Taxotere one-vial formulation (20 mg/mL), approved on August 2, 2010, may cause confusion that can lead to medication errors due to differences in concentration and preparation instructions from the two-vial formulation. Additionally, Hospira's one-vial formulation for Docetaxel Injection (10 mg/mL) compounds the confusion because its concentration is different from one-vial Taxotere. We make recommendations in section 4 below based on previous recommendations implemented for Taxotere two-vial formulation to minimize the risk of confusion.

3.2 ISMP MEDICATION ERROR REPORT

ISMP published a report dated March 24, 2011, that described a medication error in which a patient on Taxotere received twice the intended dose, 100 mg/m², rather than the reduced dose of 50 mg/m². This error occurred soon after an ambulatory cancer center pharmacy began to transition from the two-vial Taxotere which yields a concentration of 10 mg/mL after initial dilution to the new one-vial Taxotere which has a 20 mg/mL concentration. The physician ordered 50 mg/m² although the dose administered was 100 mg/m², which is within safe dosing limits. The patient suffered febrile neutropenia which necessitated hospitalization. There are a number of factors that could lead to such an error including long-time familiarity with the two-vial Taxotere formulation, confirmation bias, delays in updating computer software to reflect the new concentration, stocking of both products concurrently, calculating the dose based on the 10 mg/mL concentration but using the 20 mg/mL concentration to prepare the infusion, and lack of knowledge regarding the new concentration of Taxotere.

3.3 LABEL AND LABELING RISK ASSESSMENT

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

- The colors used for strength differentiation overlap with those of one-vial Taxotere. This is concerning because the concentration per mL differs between the two products. Using similar colors can lead practitioners to believe the products have the same concentration per mL before addition to an infusion solution.
- The abbreviation (b) (4) is present. This is considered a dangerous abbreviation.
- Some statements necessary for minimizing confusion differ from those on the two-vial Taxotere.
- Some statements necessary for minimizing confusion that are on the two-vial Taxotere are not present on the proposed labels and labeling.
- The "Rx Only" statement is too prominent.

Due to the availability of multiple formulations in varying concentrations that require differing instructions for drug preparation, the potential for confusion among these products is a significant safety concern for DMEPA. 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

We provide recommendations for color changes and other revisions that we believe will help to minimize the potential for confusion between the varying formulations, concentrations, and preparation instructions among the different docetaxel products in Section 4 below.

4 CONCLUSION AND RECOMMENDATIONS

Our evaluation identified areas where information on the container labels and carton labeling can be improved to minimize the potential for medication errors. The most recently approved Taxotere labels and labeling for the two-vial formulation (see Appendices H through K) reflect DMEPA's most recent recommendations for minimizing the risk of medication errors. Thus, we believe the proposed labels and labeling should be consistent with the labels and labeling of the two-vial Taxotere. Section 4.1, *Comments to the Applicant*, contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 4.1 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 clarifications, please contact OSE Regulatory Project Manager, Sarah Simon, at 301-796-5205.

4.1 COMMENTS TO THE APPLICANT

A. General Comments for all Container Labels and Carton Labeling

1. Due to the availability of multiple formulations of docetaxel in varying concentrations that require differing instructions for drug preparation, the potential for confusion among these products is a significant safety concern for DMEPA. 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 colors you propose for strength differentiation of the 20 mg/0.5 mL and 80 mg/2 mL strengths are similar to those utilized for the currently marketed one-vial Taxotere. This may lead to confusion due to the differences in formulation (one-vial vs. two-vial) and concentration per mL. (b) (4)

Therefore, the strengths can also be confused, leading to wrong dose errors. Thus, we request that you choose colors for strength differentiation that do not overlap with the currently marketed one-vial Taxotere or one-vial Docetaxel Injection marketed by Hospira.

2. The "Rx Only" statement is very prominent and detracts from other important information on the principal display panel. Decrease the prominence of the statement

by decreasing its size, unbolding it, and relocating it to a less prominent area on the principal display panel.

3. Revise all instances of the abbreviation (b) (4) to read “Intravenous” or “Intravenously”, as appropriate. (b) (4)

(b) (4) As part of a national campaign to reduce medication errors related to error-prone medical abbreviations and dose designations, the FDA agreed not to approve labels and labeling that included the use of error prone abbreviations or dose designations. Thus, we request you revise accordingly.

B. Container Labels, 20 mg/0.5 mL and 80 mg/2 mL

1. There is a typographical error in the Caution statement. In the first sentence, the word “concentration” is misspelled as (b) (4). Revise the word (b) (4) to read “concentration”.
2. Increase the prominence of the statement “For Intravenous Infusion Only After Final Dilution”
3. (b) (4) the storage conditions statements.
4. Box the caution statement to increase its prominence.

C. Carton Labeling

1. Revise the statement (b) (4) to read: “see side panel for concentration obtained after initial dilution step.”
2. Add the statements “Before Initial Dilution*” and “see side panel for concentration obtained after initial dilution step” on the back panel like it is currently presented on the front panel.
3. See B.4 above

D. Diluent Labels

1. The diluent labels are not well differentiated from the active drug vials which could cause healthcare practitioners to confuse the diluent as the active drug vial and vice versa. The “docetaxel” established name and strength are too prominent on the diluent labels and the trade dress highlights the established name of the active drug, not the ingredients in the diluent. Therefore we request you revise as follows:
 - a. Delete the statement of strength from the diluent labels.
 - b. Increase the prominence of the word “Diluent” so that it is the most prominent word on the label.
 - c. Revise the name to read “Diluent for Docetaxel Injection 20 mg” or 80 mg as appropriate. Additionally, use a bold font for the word “Diluent” or make it much larger than the rest of the statement.
2. In the Caution statement, place the following in bold font: “entire”, “1.95 mL” and “7.2 mL”.
3. The storage conditions statements are too prominent due to the red font used. Use a black, unbolded font for the storage conditions statements.

E. Blister Labels

See comments B.2, B.4, and D.3 above.

REFERENCES

Oleszczuk, Zachary. Docetaxel Injection Concentrate Label and Labeling Review, OSE Review 2010-530, dated September 27, 2010.

APPENDICES

Appendix A: 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

Appendix B: AERS Database ISR Report Numbers (one report was a duplicate)

Report	ISR Number
1	5316842
2	5338548
3	5403737
4	5455743
5	5490684
6	5581415
7	5621594
8	5684161
9	5744074
10	5788965
11	6082771
12	6134156
13	6221946

14	6392206
15	6607952
16	6611878
17	6673107
18	7033529
19	7092480
20	7153486
21	7206114
22	7206129
23	7206142
24	7235796
25	7241888
26	7270819
27	7355206

Appendix C: Excluded AERS Search Results

The AERS search conducted on March 21, 2011 yielded 26 cases. Of these cases, 23 were excluded from further evaluation for the reasons below:

- Adverse drug reactions not related to a medication error (n=11)
- Taxotere was a concomitant medication and not involved in a medication error (n=6)
- Cases reported both an adverse drug reaction not related to a medication error and product quality complaint (n=4)
- Wrong route of administration. Foreign case (Germany). There was not enough information provided to evaluate the case. (n=1)
- Improper dose (overdose). The patient was in a study protocol and there was not enough information provided to evaluate the case. (n=1)

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

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

/s/

IRENE Z CHAN on behalf of LORETTA HOLMES
04/05/2011

IRENE Z CHAN
04/05/2011

CAROL A HOLQUIST
04/06/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 201195	NDA Supplement #: S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: N/Z Established/Proper Name: Docetaxel Dosage Form: Injection Strengths: 20mg/0.5 mL and 80 mg/2.0 mL		
Applicant: Accord Healthcare, Inc.		
Date of Receipt: December 22, 2009		
PDUFA Goal Date: October 22, 2010		Action Goal Date (if different): N/A
Proposed Indication(s): Breast Cancer (CA); Non-Small Cell Lung Cancer (NSCLC); Hormone Refractory Prostate Cancer (HRPC); Gastric Adenocarcinoma (GC); Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN).		

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

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 (docetaxel) Injection Concentrate, Intravenous Infusion (IV) 80 mg/2 mL and 20 mg/0.5 mL.	New information consists of CMC data and impurities. Except for formulation-related sections of the label, other information in the label is the same as that described for the reference listed drug (RLD).

*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)

Based on the route of administration (intravenous) and the information provided on the formulation, the Clinical Pharmacology and the ONDQA/OPS Biopharmacology teams determined that a BE study will not be needed.

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
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 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 (docetaxel) Injection Concentrate, Intravenous Infusion (IV)	N20449	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 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

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

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

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

- c) Described in a monograph?

YES NO

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

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:

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 (b)(2) drug provides a minor change in formulation adding two new excipients, polyethylene glycol 400 and citric acid for (b) (4) and pH control. The presentation of two-vial solution for injection is the same as Taxotere. This application does not provide a new indication, nor a change in dosage form. It is intended to increase/expand the supply of docetaxel.

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 **X** NO

*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 **X** NO

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

YES **X** 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 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):

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.

Listed drug/Patent number(s):	4814470*PED	Nov.14, 2010
	5438072	Nov. 22, 2013
	5438072*PED	May 22, 2014
	5698582	July 3, 2012
	5698582*PED	Jan. 3, 2013
	5714512	July 3, 2012
	5714512*PED	Jan. 3, 2013
	5750561	July 3, 2012
	5750561*PED	Jan. 3, 2013

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

Patent number(s):

- (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 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): March 11 and 12, 2010

- (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

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

/s/

KIM J ROBERTSON

10/14/2010

505(b)(2) Assessment Form NDA 201195 Docetaxel Inj. Accord Healthcare

**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: September 27, 2010

Application Type/
Number: NDA 201195

To: Robert Justice, MD, Director
Division of Drug Oncology Products

Through: Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis

From: Zachary Oleszczuk, Pharm.D., Team Leader
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Docetaxel Injection Concentrate
20 mg/0.5 mL and 80 mg/2 mL

Applicant/sponsor: Accord

OSE RCM #: 2010-530

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EXECUTIVE SUMMARY

Our Label and Labeling Comparative Analysis and Label and Labeling Risk Assessment noted important areas (e.g., the color scheme and prominence of important information) where the labels/labeling of Docetaxel Injection Concentrate differ from those of Taxotere Injection, the reference listed drug (RLD). This is a safety concern because the Taxotere labels/labeling have undergone several revisions over the years in order to address medication error reports concerning drug preparation errors. These errors were due to confusing presentation of the active drug concentration and volume, diluent volume, and instructions for preparation. We believe the current Taxotere labels/labeling are better designed as a result of the revisions they have undergone. Having the proposed Docetaxel Injection Concentrate reflect those changes in specific areas will also make for better designed labels/labeling of Docetaxel Injection as well. The Division of Medication Error Prevention and Analysis provides recommendations in Section 4 of this review and request these recommendations be implemented prior to approval.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from the Division of Drug Oncology Products dated March 7, 2010, for DMEPA evaluation of the container label, blister labeling, carton labeling and package insert labeling for Docetaxel Injection Concentrate for the potential to contribute to medication errors. There is no proposed proprietary name for this product at this time.

1.2 REGULATORY HISTORY

Docetaxel Injection Concentrate is the subject of a 505(b)(2) application submitted on December 21, 2009, that references Taxotere (Docetaxel) Injection. Taxotere Injection (NDA 020449) was approved on May 14, 1996. The diluent of Docetaxel Injection Concentrate differs from the diluent of Taxotere Injection Concentrate. However, the products share the same indications of use, dosing, route of administration, frequency of administration, and method of preparation.

DMEPA has completed 9 reviews on the reference listed drug, Taxotere between 1999 and 2009 and 3 on other 505(b)(2) applications of the active ingredient Docetaxel (see references). The reviews focus on minimizing the risk of medication errors due to the confusing presentation of the active drug concentration and volume, diluent volume, and instructions for preparation. DMEPA has recommended label and labeling revisions to the reference listed drug and other 505(b)(2) products aimed at minimizing these risks. The Applicants for these drugs have incorporated all of DMEPA's recommendations into their labels and labeling.

1.3 PRODUCT INFORMATION

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 certain precautions, contraindications, and adverse reactions. For dosage information, see Appendix A.

Docetaxel Injection Concentrate is to be administered intravenously over 1 hour every 3 weeks. Contact of Docetaxel Injection Concentrate with plasticized PVC (polyvinyl chloride) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the Docetaxel Injection diluted solution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Docetaxel Injection Concentrate requires two dilutions prior to administration. Docetaxel infusion solution, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours. Fully prepared Docetaxel infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour intravenous administration).

Docetaxel will be available in single-dose vials containing 20 mg/0.5 mL and 80 mg/2 mL. The unopened vials can be stored at (b) (4) 25°C (b) (4) 77°F and should be retained in the original package to protect from light. The product will be supplied in cartons containing 1 vial of active drug and 1 vial of diluent.

2 METHODS AND MATERIALS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Since the active ingredient Docetaxel has been on the US market since May 14, 1996, DMEPA would typically conducted a search of the Adverse Event Reporting System (AERS) Database to identify any medication errors occurring with the currently marketed product that may be indicative of errors that could occur with the proposed product. However, DMEPA has extensive postmarketing experience with the active ingredient Docetaxel because we have conducted multiple AERS searches in previous reviews. Therefore, DMEPA did not conduct a new AERS search. We reviewed all of the previous reviews related to the active ingredient Docetaxel and the AERS searched in those reviews to identify possible errors that may occur with this product and can be minimized by label and labeling revisions.

2.2 LABELS AND LABELING RISK ASSESSMENT

We use Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling.

For Docetaxel Injection Concentrate, the Applicant submitted the following container labels, carton labeling, and blister labeling on December 21, 2009 , (See Appendices B and D for container labels and carton labeling images) and insert labeling on June 11, 2010 (no image):

- Container Labels for Docetaxel for 20 mg/0.5 mL and 80 mg/2mL
- Container Labels for the Diluent for Docetaxel 20 mg/0.5 mL and 80 mg/2mL
- Carton Labeling for 20 mg/0.5 mL and 80 mg/2mL
- Blister Labeling for 20 mg/0.5 mL and 80 mg/2mL

3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

DMEPA's search of the of the previous reviews determined that errors related to confusing presentation of the active drug concentration and volume, diluent volume, and instructions for preparation.

3.2 LABELS AND LABELING

We compared the container labels and carton labeling of the proposed Docetaxel Injection Concentrate and Taxotere Injection Concentrate for the purpose of determining their similarities and differences.

The Taxotere Injection Concentrate container labels and carton labeling were obtained from the Annual Report for Taxotere Injection Concentrate submitted on July 10, 2009 which covers the period May 14, 2008 through May 13, 2009 (see Appendices E through G). The Applicant states in their July 13, 2010 Annual report that no label or labeling changes have been made during the reporting period of May 14, 2009 to May 13, 2010.

- Container Labels (active drug): 20 mg/0.5 mL and 80 mg/2 mL
- Diluent Container Labels for the 20 mg and 80 mg active drug vials
- Carton Labeling: 20 mg/0.5 mL and 80 mg/2 mL
- Blist Labeling: 20 mg/0.5 mL and 80 mg/2 mL

4 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed container labels, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors. Overall our comparison of the proposed Docetaxel Injection Concentrate container labels and carton labeling with the corresponding labels and labeling of Taxotere Injection Concentrate determined that important information can be revised to mimic those of Taxotere to help minimize the risk of medication errors with this product. The Taxotere labels/labeling have undergone several revisions since approval to highlight areas of confusion on the container and diluent labels and carton labeling that led to medication errors in the clinical setting. Maintaining consistency among Docetaxel products should help minimize the risk of medication errors that have been identified in the postmarketing setting.

Section 4.1 *Comments to the Division* contain our recommendations for the package insert labeling. Section 4.2 *Comments to the* contains our recommendations for the carton labeling and container labels. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. 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 clarifications, please contact OSE Regulatory Project Manager Sarah Simon at 301-796-5205.

4.2 COMMENTS TO THE DIVISION

1. We note that the package insert contains the dangerous abbreviations and symbols (b) (4)



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.

Thus, DMEPA recommends revising all instances of the abbreviation (b) (4) to be written as “intravenous” or “intravenously”. Additionally, DMEPA recommends revising all instances of (b) (4) to be written in text instead of a symbol (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

4. We note that section 16 *How Supplied/Storage and Handling* only lists the NDC number of the Carton Labeling for each strength of Docetaxel. We defer to the Division if the NDC numbers of the active ingredient container and the diluent container need to appear in this section.
5. We note that the Applicant has used the color (b) (4) for the designation of the 80 mg/2 mL and a (b) (4) color for the 20 mg/0.5 mL strength. DMEPA is concerned that this color scheme may be confusing because (b) (4)

(b) (4)

DMEPA recommends either reversing the color scheme (b) (4) or pick two colors that do not overlap with Taxotere.

4.1 COMMENTS TO THE APPLICANT

The labels and labeling of Taxotere Injection Concentrate (the RLD) have undergone several revisions over the years in order to address medication error reports concerning drug preparation errors. These errors were due to confusing presentation of the active drug concentration and volume, diluent volume, and instructions for preparation. We believe the current Taxotere labels/labeling are better designed as a result of the revisions they have undergone. Having the proposed Docetaxel Injection Concentrate reflect those changes in specific areas will also make for better designed labels/labeling of Docetaxel Injection as well. Therefore, we have the following recommendations.




A. All Container Labels, Carton Labeling, and Blister Labeling

1. We note that you use the color (b) (4) for the 80 mg/2 mL and a (b) (4) color for the 20 mg/0.5 mL strength. We are concerned that this color scheme may be confusing because (b) (4)
(b) (4) We recommend either reversing the color scheme (b) (4) or pick two colors that do not overlap with Taxotere labels or labeling.
2. We also note that the amount of color differentiation can be improved between the two strengths. (b) (4) We recommend increasing the amount of differentiation between the two strengths with the use of more color, boxing, or some other means. Increasing color differentiation can be accomplished by carrying whichever colors are chosen for differentiation onto the strength for the container labels, carton labeling and blister labeling. The solid strip of color and the strength would be the same color for a given strength and help to further differentiate these products.
3. Revising all instances of the abbreviation (b) (4) to be read “intravenous” or “intravenously”. The abbreviation (b) (4) appears on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because it has been confused (b) (4) As such, we request you revise the labels and labeling accordingly
4. The NDC number is distracting and competes for prominence with other important information on the label. Decrease the prominence by decreasing the size and unbolding any text if it is bolded.


B. Container Labels and Carton Labeling for Active Drug

1. The Accord company logo (b) (4)
(b) (4)
2. The ‘Rx only’ statement (b) (4)
(b) (4)
3. Place an asterisk next to the “Before Initial Dilution” statement and place the accompanying notation (that directs practitioners to the caution statement for information on the concentration that results after the initial dilution step) immediately below it. See the following example:
Statement of Strength
Before Initial Dilution*
*see side panel for concentration obtained after initial dilution step

C. Container Labels and Carton Labeling for the Diluent

1. The Accord company logo (b) (4)

2. The Diluent label and labeling (b) (4)

3. Highlight the word “entire” on the side panel of the diluent to help make it more prominent and reinforce to healthcare practitioners that the entire vial should be used during dilution.
4. The ‘Rx only’ statement (b) (4)


D. Blister Labeling

1. The blister labeling is not well differentiated for the two strengths. Increase the differentiation by using color for the different strengths, boxing, or some other means. The colors, boxing, etc., should be consistent on all the labels and labeling.
2. (b) (4)

3. Increase the prominence of “Docetaxel Injection” as currently presented this information is not prominent and hard to locate. The active ingredient, strength, and the word diluent should be the most prominent information on this labeling.

REFERENCES

1. OSE Review #1999-012, *Taxotere Postmarketing Review*; May 13, 1999; Park, C.
2. OSE Review #1999-012-3, *Taxotere Postmarketing Review*; September 24, 2002; Mahmud, A.
3. OSE Review #2004-0208, *Medication Error Postmarketing Safety Review for Taxotere*; December 29, 2005; Pedersen, K.
4. OSE Review #2007-548, *Taxotere Label and Labeling Review*; March 23, 2009; Holmes, L.
5. OSE Review #2009-118, *Taxotere Label and Labeling Review*; January 16, 2009; Holmes, L.
6. OSE Review #2009-122, *Taxotere Label and Labeling Review*; June 19, 2009; Holmes, L.
7. OSE Review #2009-122, *Taxotere Label and Labeling Review (2)*; January 8, 2010; Holmes, L.
8. OSE Review #2009-122, *Taxotere Label and Labeling Review (3)*; January 14, 2010; Holmes, L.
9. OSE Review #2009-118, *Taxotere Label and Labeling Review (2)*; May 12, 2010; Holmes, L.
10. OSE Review #2008-410, *Docetaxel Label and Labeling Review*; August 4, 2009; Holmes, L.
11. OSE Review #2008-836, *Docetaxel Label and Labeling Review*; February 27, 2009; Holmes, L.
12. OSE Review #2009-1868, *Docetaxel Label and Labeling Review*; January 26, 2010; Holmes, L.

APPENDICIES

Appendix A: Dosing Information for Docetaxel

Indication	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 IV (days 1-5), starting at end of cisplatin infusion
Squamous cell carcinoma of the head and neck	<p><u>Induction chemotherapy followed by radiotherapy:</u> 75 mg/m² followed by cisplatin 75 mg/m² IV (day 1), followed by fluorouracil 750 mg/m² per day as a 24 hour IV (days 1-5), starting at end of cisplatin infusion; for 4 cycles</p> <p><u>Induction chemotherapy followed by chemoradiotherapy:</u> 75 mg/m² followed by cisplatin 100 mg/m² IV (day 1), followed by fluorouracil 1000 mg/m² per day as a 24 hour IV (days 1-4); for 3 cycles</p>
Premedication Regimen	<p>Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice a day) for 3 days starting 1 day before administration.</p> <p>Hormone refractory prostate cancer: oral dexamethasone 8 mg, at 12, 3, and 1 hours before treatment</p>

10 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

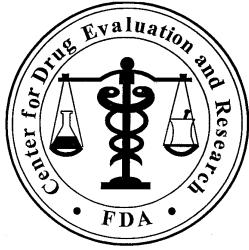
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZACHARY A OLESZCZUK
09/27/2010

DENISE P TOYER
09/27/2010

CAROL A HOLQUIST
09/28/2010



**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: July 9, 2010

To: Robert Justice, M.D., Director
Division of Drug Oncology Products (DDOP)

Through: Sharon Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: John Hubbard, MPAS
Patient Labeling Reviewer
Division of Risk Management

Subject: Close-out Memo re: DRISK Review of Patient Labeling
(Patient Package Insert)

Drug Name(s): Docetaxel Injection Concentrate

Application Type/Number: NDA 201-195

Applicant/sponsor: Accord Healthcare, Inc.

OSE RCM #: 2010-531

The Division of Drug Oncology Products (DDOP) requested that the Division of Risk Management review the proposed patient labeling for a 505 (b) (2) New Drug Application (NDA) 201-195 submitted by Accord Healthcare Inc., for Docetaxel Injection Concentrate submitted on December 22, 2009.

DDOP and DRISK have determined that the submitted patient labeling does not need to be reviewed by DRISK at this time, because the labeling is identical to the labeling for the Reference Listed Drug, Taxotere (docetaxel) Injection Concentrate. This memo serves to close-out the consult request for Docetaxel Injection Concentrate.

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201195	ORIG-1	ACCORD HEALTHCARE INC	DOCETAXEL INJECTION 20 MG and 80 MG

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

/s/

JOHN C HUBBARD
07/09/2010
Docetaxel close out memo.

SHARON R MILLS
07/09/2010