# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022234Orig1s000**

# OTHER REVIEW(S)

# REGULATORY PROJECT MANAGER LABELING REVIEW
## Division of Drug Oncology Products

**Application Number:** NDA 022234

**Name of Drug:** Docetaxel Injection, 20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL

**Applicant:** Hospira. Inc.

## Material Reviewed:

**Submission Date(s):** September 23, 2010

**Receipt Date(s):** September 23, 2010

**Submission Date of Structure Product Labeling (SPL):** N/A

**Type of Labeling Reviewed**: WORD

## Background and Summary

NDA 022234 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

This Resubmission after 2 Tentative Approvals has been reviewed by CMC, Clinical, Clinical Pharmacology and Pharmacology and Toxicology; DMEPA and DDMAC.

## Review

The submitted draft package insert, identified as PI of September 9, 2010 was compared to the RLD NDA 020449 (b) (4), which was approved on August 2, 2010.

The attached final agreed upon Package Insert, Carton and Container labeling are the agreed upon labeling between the FDA and the Applicant, and it incorporates all FDA revisions to the labeling during this review cycle.

*{See appended electronic signature page}*

Modupe Fagbami
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

*{See appended electronic signature page}*

Frank Cross, Jr.
Chief, Project Management Staff

Attachment:

Finalized Package Insert
Carton and Container labeling:

58 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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MODUPE O FAGBAMI
03/08/2011

FRANK H CROSS
03/08/2011

SANDI L VERBOIS
03/08/2011

Division of Drug Marketing, Advertising, and Communications

# Internal Consult

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

To: Modupe Fagbami, 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: February 10, 2011

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

NDA 022234

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In response to your consult request via email on February 9, 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 |
|---|---|---|
| • 14.2 Adjuvant Treatment of Breast Cancer, 14.3 Non-Small Cell Lung Cancer, 14.4 Hormone Refractory Prostate Cancer | Kaplan-Meier Curves | • The prominence of the Kaplan-Meier curves for these sections is inadequate to allow healthcare professionals to review this efficacy information. DDMAC recommends that the sponsor increase the prominence of these curves. |



Reference ID: 2925482

| Section | Statement from draft | Comment |
|---|---|---|
| • 14.3 Non-Small Cell Lung Cancer, Table 11 | Footnote for Docetaxel %1-year Survival 95% CI results in TAX320 study | • The * footnote for these results references the incorrect information. This footnote should indicate that these results represent $p \leq 0.05$. DDMAC recommends revising this footnote to reference the correct information. |
| • 14.3 Non-Small Cell Lung Cancer, Table 13 | Footnotes for Endpoint Median Time to Progression (95% CI) | • The dagger footnote for this endpoint references the incorrect information. This footnote should be changed to a "b" to indicate that this endpoint was based on Kaplan-Meier estimates. Additionally, the "b" footnote should be changed to an "a" to indicate that this endpoint was adjusted for multiple comparisons. DDMAC recommends revising these footnotes to reference the correct information. |

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/s/

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ADAM GEORGE
02/10/2011

**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: | January 28, 2011 |
| To: | Robert Justice, MD, Director<br>Division of Drug Oncology Products |
| Through: | Kristina A. Toliver, PharmD, Team Leader<br>Carol A. Holquist, RPh, Director<br>Division of Medication Error Prevention and Analysis (DMEPA) |
| From: | Loretta Holmes, BSN, PharmD, Safety Evaluator<br>Division of Medication Error Prevention and Analysis (DMEPA) |
| Subject: | Label and Labeling Review |
| Drug Name: | Docetaxel Injection<br>20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL |
| Application Type/Number: | NDA 022234 |
| Applicant: | Hospira, Inc. |
| OSE RCM #: | 2010-2332 |

# Contents

## 1 INTRODUCTION

This review evaluates the revised container labels and carton labeling submitted by the Applicant on November 23, 2010 and the insert labeling and Dear Health Care Professional letter submitted by the Applicant on September 23, 2010 for Docetaxel Injection, NDA 022234, 20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL.

## 2 REGULATORY HISTORY

This application received tentative approval letters dated August 11, 2008 and December 11, 2009. According to the Applicant, the following changes were made to the application since the product was tentatively approved: (b) (4) labeling (containers, carton, and insert), and Dear Health Care Professional (DHCP) letter. According to the Applicant, the container labels and carton labeling previously submitted and tentatively approved have been revised based upon formatting/graphical modifications requested in July 2010 during Agency review of Hospira's Topecan Injection (NDA 200582). Additionally, there are two manufacturing facilities for Hospira's Docetaxel Injection; one in Australia and one in India. The Applicant initially provided two sets of container labels and carton labeling. One set has information pertaining to the Australia manufacturing site and the other to the India manufacturing site.

In a labeling meeting held by DDOP on November 18, 2010, we communicated our safety concerns with this product. The review team communicated these safety concerns to the Applicant in a teleconference held on November 23, 2010. At that time, the Applicant stated they had proactively revised the container labels and carton labeling that were submitted on September 23, 2010 in response to safety concerns raised in the November 18, 2010 ISMP Medication Safety Alert newsletter. These revised labels and labeling were submitted to the Agency for our review on November 23, 2010. We note the revised container labels and carton labeling have the India manufacturing site information.

## 3 METHODS AND MATERIALS

DMEPA uses Failure Mode and Effects Analysis (FMEA) to evaluate container labels, carton and insert labeling. This review summarizes our evaluation of the container labels, carton labeling and insert labeling submitted by the Applicant on November 23, 2010 and the Dear Health Care Professional (DHCP) letter submitted on September 23, 2010 (see Appendices C, D, and E).

- Container Labels and Carton Labeling (20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL)
- Insert Labeling (no image)
- Dear Health Care Professional Letter

## 4 DISCUSSION

There are currently two Docetaxel products in the marketplace (Taxotere 1-vial and 2-vial). The older Taxotere 2-vial product is available in a 40 mg/mL concentration which requires an intermediate dilution step with a supplied diluent to render a 10 mg/mL concentration prior to addition of the drug to the infusion solution. However, the recently approved Taxotere 1-vial product is available in a 20 mg/mL concentration which does not require an intermediate dilution step; the drug can be withdrawn from the vial and added directly to the infusion solution. Similar to the Taxotere 1-vial product, Hospira's proposed Docetaxel Injection 10 mg/mL product requires only one dilution step.

Although Hospira's Docetaxel Injection may offer convenience and speed up the drug preparation process, DMEPA has concerns that it could get confused with the currently marketed Taxotere 1-vial and 2-vial products as well as recently approved and forthcoming 1-vial and 2-vial Docetaxel. This potential confusion is due to the differences between the concentrations and preparation of these products. The Taxotere 2-vial product was approved in 1996 and has been in the marketplace for sometime as the only available Docetaxel product. Although there have been postmarketing medication errors caused by confusion with the labels, labeling, and preparation steps which required label and labeling revisions to address the issues, practitioners have become familiar with its concentration and the preparation steps. Thus, healthcare practitioners will likely find it difficult to sort out the different Docetaxel products, the different concentrations, and preparation steps when introduced into the marketplace which may result in new types of errors.

Also of concern is the fact that Hospira's Docetaxel does not have a proprietary name. Thus, practitioners may get confused because there will not be a direct association between a proprietary name and the product characteristics. The potential exists for Hospira's Docetaxel Injection to get confused with either the Taxotere 1-vial or 2-vial formulations since the established name does not indicate to practitioners whether the product requires a one-step or two-step dilution process.

In summary, we anticipate confusion will occur during the procurement, order entry, and drug preparation steps of the medication use process with the use of this product. In order to help mitigate the potential for medication errors to occur, DMEPA has provided recommendations for revisions to the container labels, carton labeling, insert labeling, and Dear Health Care Professional letter submitted by the Applicant.

## 5 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, carton labeling, insert labeling, and DHCP letter can be improved to minimize the potential for medication errors.

Our comments concerning the DHCP letter submitted by the Applicant on September 23, 2010 were forwarded to the Applicant on November 29, 2010 (see Appendix A).

We communicated our container label and carton labeling recommendations to the Division in a labeling meeting held on December 14, 2010. DMEPA and the Division came to a consensus at that time and on December 20, 2010, our finalized recommendations were emailed to the Division for dissemination to the Applicant (see Appendix B).

In response to our recommendations, the Applicant submitted revised container labels and carton on December 24, 2010 (see Appendices F and G). A revised DHCP letter was also submitted at this time (see Appendix H). DMEPA evaluated these revised labels and labeling and find them acceptable.

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.

## APPENDICES

**Appendix A:** DMEPA comments concerning the Dear Health Care Professional Letter submitted by the Applicant on September 23, 2010. The Division forwarded these comments to the Applicant on November 29, 2010.

1. The preposition "to" was omitted from the last sentence of the letter. Revise the last sentence of the letter to read: "If you need further information related **to** this product, please visit our website..."

2. Revise the beginning portion of the letter as follows. **[DMEPA's revisions to the actual letter are in red print and underlined.]**

   Hospira, Inc. is writing to inform you that the product concentration and preparation procedures for Hospira's Docetaxel Injection is different than those required for other marketed docetaxel injection products. This important information can help avoid errors when compounding Docetaxel Injection made by Hospira and other manufacturers.

   Hospira's Docetaxel Injection is a formulation that may be directly injected into the infusion container without an intermediate dilution step. This differs from the Taxotere® 2-vial product and other Docetaxel drugs, which are concentrated formulations, require mixing with a special diluent before injection into the infusion container.

   Hospira's Docetaxel Injection is available in a 10 mg/mL concentration and the following strengths: 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL.
   This 10 mg/mL concentration also differs from the Taxotere® 1-vial product which is a 20 mg/mL concentration. Therefore, it is important to check the concentration and follow the preparation instructions carefully before using Docetaxel products.

   Follow the Hospira Docetaxel Injection drug preparation instructions as described under the product Full Prescribing Information:

**Appendix B:** DMEPA Label and Labeling Comments, emailed to the Division on December 20, 2010.

**COMMENTS TO THE DIVISION**

Insert Labeling

1. The abbreviations "IV" and 'BID" are used within the insert labeling to represent "intravenous" and "twice daily", respectively. As part of a national campaign to decrease the use of dangerous abbreviations, the FDA agreed to not use such abbreviations in the approved labeling of products. Therefore, we have the following recommendations. Delete the abbreviation "IV" found in several areas of the Highlights of Prescribing Information section and in the Patient Information section of the insert. Replace the abbreviation "BID" (found in section 2.6 Premedication Regimen) with the text "twice daily"

2. The terms (b) (4) and (b) (4) are used throughout the insert to describe the 20 mg/2 mL vial and (80 mg/8 mL and 160 mg/16 mL) vials, respectively. Replace the text (b) (4) with "single use vial" and the text (b) (4) with "multi-use vial".

**COMMENTS TO THE APPLICANT**

A. General Comment

The abbreviation "IV" is used on the principal display panel in the route of administration and on the side panel on the carton in the Directions for Use. As part of a national campaign to decrease the use of dangerous abbreviations, the FDA agreed to not use such abbreviations in the approved labeling of products. Therefore, we recommend "IV" be replaced with the text "Intravenous".

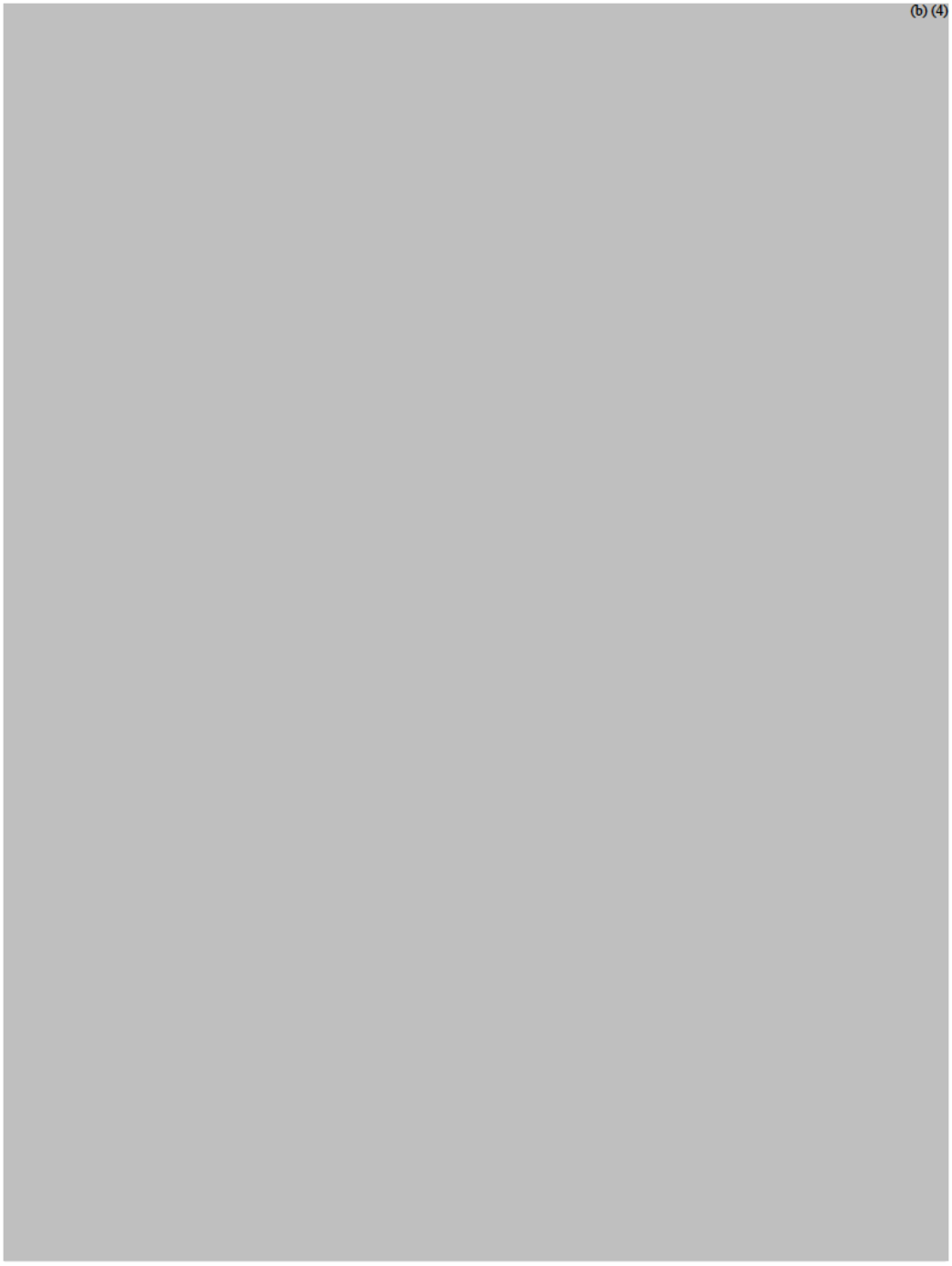
B. Container Labels

1. The concentration of this product differs from the currently approved Taxotere 1-vial product. In order to highlight this difference, place and box the following statement prominently on the principal display panel below the route of administration, "Ready to add to infusion solution. Check concentration prior to preparation. See package insert for complete instructions".
2. Expand the color block (which encloses the established name) to include the total drug content statement.
3. In order to make room on the 20 mg/2 mL label for the information requested in B-1 above, we recommend deleting the (b) (4) and (b) (4) statements. Additionally, relocate the "Caution: Cytotoxic agent" statement to the side panel.
4. 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.

C. Carton Labeling

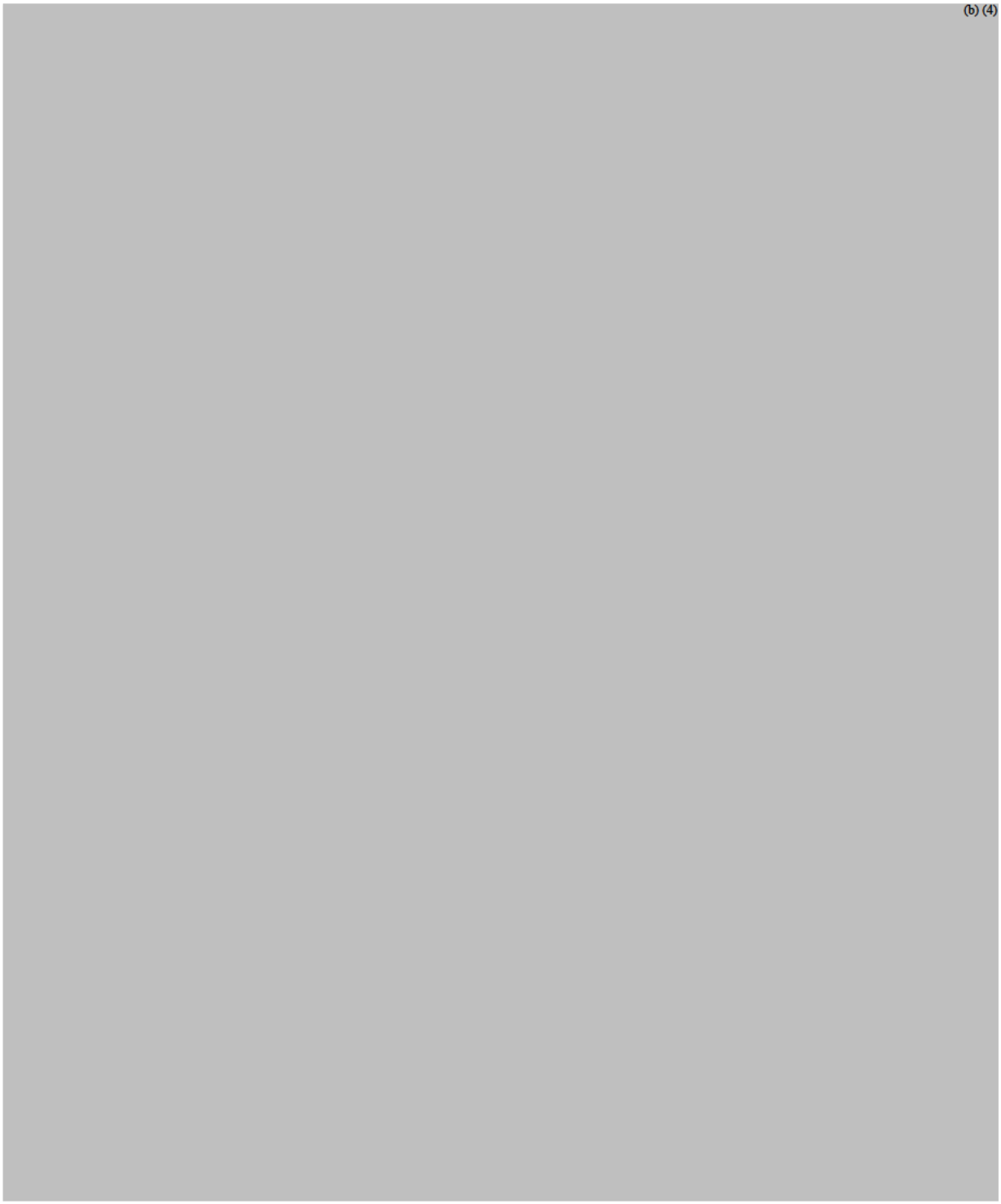
1. Add a banner to the principal display panel with the following statement: "New concentration and preparation". Please note this statement must be removed after six months.
2. The 20 mg and 160 mg strengths are both presented in (b) (4) color blocks that don't make the total drug content stand out. Ensure these strengths are well differentiated from one another and from the 80 mg strength.
3. The red color block at the top portion of the carton labeling contains the drug concentration "10 mg/mL". Practitioners may misinterpret this statement as the total drug content, especially on the 20 mg/2 mL strength. Therefore, we recommend you also include the total drug content in the color block [e.g., 20 mg/2 mL (10 mg/mL), 80 mg/8 mL (10 mg/mL), or 160 mg/16 mL (10 mg/mL)], as appropriate.
4. The top portion of the label (above the established name) appears cluttered. Delete the statement (b) (4) and relocate the "Rx only" statement to one of the side panels.
5. Expand the color block (which encloses the established name) to include the total drug content statement.
6. Increase the size of the statement "Ready to add to infusion solution" on the principal display panel in order to make it more prominent.
7. Relocate the statement "Warning: Keep out of reach of children" to one of the side panels. In the position where the warning statement is currently located, place the statement "Caution: Cytotoxic Agent" and use a black font color.
8. The statement "Caution: Cytotoxic Agent" is in the red color block at the bottom portion of the carton labeling. Delete this statement from this area and relocate it as described in comment C-7, above. Place the following statement in the red color block at the bottom of the carton labeling: "Check concentration prior to preparation. See package insert for complete instructions".
9. Delete the section (b) (4) from the side panel. The instructions in that section are not complete so we prefer healthcare practitioners read the insert for full directions for use.
10. Under the section (b) (4), delete the first sentence (the sentence begins with the words (b) (4)). Additionally, change the (b) (4) heading to "Usual Dosage" since the actual dosage and administration instructions are not provided here.

**Appendix C:** Container labels submitted by the Applicant on November 23, 2010 (not to scale)

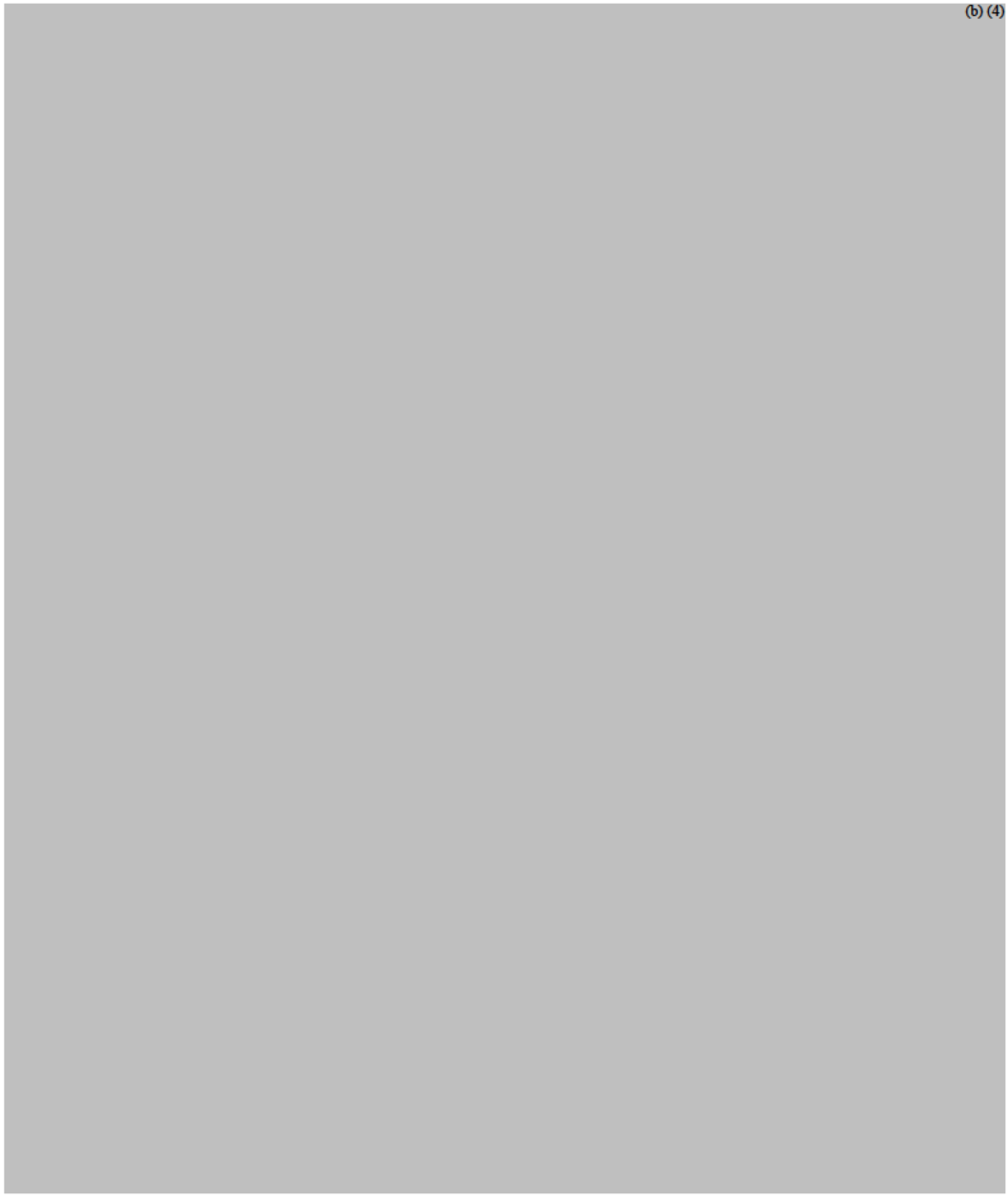



Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

**Appendix E:** Proposed Dear Health Care Professional letter submitted by the Applicant on September 23, 2010



**Appendix F:** Revised container labels submitted by the Applicant on December 24, 2010 (not to scale)




2 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

**Appendix H:** Revised DHCP letter submitted by the Applicant on December 24, 2010

# Important Preparation Information For Docetaxel Injection

Dear Health Care Professional,

Hospira, Inc. is writing to inform you that the product concentration and preparation procedures for Hospira's Docetaxel Injection is different than those required for other marketed Docetaxel Injection products. This important information can help avoid errors when compounding Docetaxel Injection made by Hospira and other manufacturers.

Hospira's Docetaxel Injection is a formulation that may be directly injected into the infusion container without an intermediate dilution step. This differs from the Taxotere® 2-vial product and other Docetaxel products, which are concentrated formulations, require mixing with a special diluent before injection into the infusion container.

Hospira's Docetaxel Injection is available in a 10 mg/mL concentration and the following strengths: 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL. This 10 mg/mL concentration also differs from the Taxotere® 1-vial product which is a 20 mg/mL concentration. Therefore, it is important to check the concentration and follow the preparation instructions carefully before using Docetaxel products.

Follow the Hospira Docetaxel Injection drug preparation instructions as described under the product Full Prescribing Information:

- Aseptically withdraw the required amount of Docetaxel Injection (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.

- Thoroughly mix the infusion by gentle manual rotation.

- As with all parenteral products, Docetaxel Injection should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the Docetaxel Injection or diluted solution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.

**Please consult the current prescribing information for Docetaxel Injection.** If you need further information related to this product, please contact Medical Communications at medcom@hospira.com or 1-800-615-0187.

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/s/

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LORETTA HOLMES
01/28/2011

DENISE P TOYER on behalf of KRISTINA C ARNWINE
01/28/2011

CAROL A HOLQUIST
01/28/2011

# NDA REGULATORY FILING REVIEW
**(Including Memo of Filing Meeting)**

NDA # 22-234 Supplement # Efficacy Supplement Type

Proprietary Name: Docetaxel Injection
Established Name: docetaxel
Strengths: 20 mg/2 mL single-dose vial, 80 mg/8 mL multi-dose vial, 160 mg/16 mL multi-dose vial
Applicant: Hospira, Inc.
Agent for Applicant (if applicable): N/A

Date of Application: 7/9/07
Date of Receipt: 7/11/07; Major CMC Microbiology amendment received on April 28, 2008
Date clock started after UN: N/A
Date of Filing Meeting: 9/6/07
Filing Date: 9/9/07
Action Goal Date (optional): 5/1/08; revised to 8/1/08 User Fee Goal Date: 5/11/08; revised to 8/11/08

Indication(s) requested: This 505(b)(2) NDA is seeking approval of the same indications as the RLD (TAXOTERE® (docetaxel) Injection Concentrate, 20 mg and 80mg.

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

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

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

Type of Original NDA: (b)(1) ☐ (b)(2) X
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

***NOTE:***
*(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S X P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☒(505(b)(2)
Waived (e.g., small business, public health) ☐

***NOTE:*** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES X NO ☐
  If yes, explain: NDA 20-449, 3/22/09 (Gastric CA); 10/17/09 (SCCHN)

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO X
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES X NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES X NO ☐
  **If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES X NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

  1. This application is a paper NDA (Paper CTD format) YES X

  2. This application is an eNDA or combined paper + eNDA YES ☐
     This application is: All electronic ☐ Combined paper + eNDA ☒
     This application is in: NDA format ☐ CTD format ☒

Combined NDA and CTD formats ☐

Does the eNDA, follow the guidance?
(http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES ☐ X

**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**
Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO ☐
- Exclusivity requested? YES _____ Years NO X
  ***NOTE:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES X NO ☐
  **If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

  ***NOTE:*** *Debarment Certification should use wording in FD&C Act 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 . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO X
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO X
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO X

  If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  **(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**
  **NOTE:** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section)Yes X NO☐
- PDUFA and Action Goal dates correct in tracking system? YES X NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. Yes

- List referenced IND numbers: N/A

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) N/A NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) N/A NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) N/A NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

## Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☐ NO X

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: Applicant to submit PLR formatted labeling by 9/21/07.

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO X

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO X

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  YES ☐ NO X

- Risk Management Plan consulted to OSE/IO? N/A X YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? N/A X YES ☐ NO ☐

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by YES ☐ NO ☐

DNPCE, has the clinical review division been notified?

## Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  N/A X YES ☐ NO ☐

## Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: 9/5/07

NDA #: 22-234

DRUG NAMES: Docetaxel Injection, 10 mg/mL Vials

APPLICANT: Hospira, Inc.

BACKGROUND: NDA submitted on July 9, 2007, for the following indications:

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

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

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

ASSIGNED REVIEWERS (including those not present at filing meeting):

| **Discipline/Organization** | **Reviewer** |
|---|---|
| Medical: | Ryan |
| Secondary Medical: | Ibrahim |
| Statistical: | N/A |
| Pharmacology: | Brower/Leighton |
| Statistical Pharmacology: | |
| Chemistry: | Ocheltree |
| Environmental Assessment (if needed): | |
| Biopharmaceutical: | Abraham/Booth |
| Microbiology, sterility: | |
| Microbiology, clinical (for antimicrobial products only): | |
| DSI: | N/A |
| OPS: | |
| Regulatory Project Management: | Cross |
| Other Consults: | N/A |

Per reviewers, are all parts in English or English translation? YES X NO ☐
If no, explain:

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES NO X
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO X

- 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?

N/A X YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A X FILE ☐ REFUSE TO FILE ☐
STATISTICS N/A FILE REFUSE TO FILE ☐

BIOPHARMACEUTICS N/A FILE X REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO X

PHARMACOLOGY/TOX N/A FILE X REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO X

CHEMISTRY N/A 7FILE X REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES X NO ☐
- Sterile product? YES X NO ☐
  If yes, was microbiology consulted for validation of sterilization?
  YES X NO ☐

ELECTRONIC SUBMISSION:

None

REGULATORY CONCLUSIONS/DEFICIENCIES:
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

☐ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- X Filing issues to be communicated. List (optional):

**ACTION ITEMS:**

1. X Schedule team meetings – how often? ___Monthly, bi weekly in __ _____
2. X Schedule labeling meetings – how often? ___Biweekly (last 6 weeks of 10 month review cycle) All disciplines will be conducting labeling reviews since proposed label will be in PLR format.
3. X Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
4. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
5. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
6. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
7. X Convey document filing issues/no filing issues to applicant by Day 74.

Frank Cross
Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own

studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review**
**Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES X NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): 20-449, Taxotere Injection Concentrate
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO X

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO X

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) 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.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☒

   (***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))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

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

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.* (TAXOTERE® (docetaxel) Injection Concentrate, 20 mg and 80mg).

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES X NO ☐

(***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.)

(TAXOTERE® (docetaxel) Injection Concentrate, 20 mg and 80mg).

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

*(b)* Is the pharmaceutical alternative approved for the same indications for which the 505(b)(2) application is seeking approval? YES X NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES X NO ☐

*If "**Yes**," to (c), proceed to question 7.*

***NOTE:*** *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)?

YES ☐ NO X

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12. Yes

8. Describe the change from the listed drug(s) provided for in 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 capsules to solution"). This application provides for a change as follows:

The major differences between Sanofi-Aventis' Taxotere® and Hospira's product are as follows:

a) The Hospira product can be directly diluted into infusion solutions, as compared to Taxotere®, which must be diluted to a strength of 10 mg/mL prior to addition into infusion solutions.
b) Hospira, Inc. is registering an additional presentation (160 mg/16 mL) that the innovator does not have.

c) Hospira, Inc. is proposing a multi-dose application for the 80 mg/8 mL and 160 mg/16mL presentations as compared to Taxotere® which is supplied as singledose vials.

Although Taxotere® is approved for indications in the treatment of breast cancer, nonsmall cell lung cancer, prostate cancer, squamous cell carcinoma of the head/neck, and gastric/GE junction adenocarcinoma, exclusivity for the head/neck cancer and gastric/GE junction indications does not expire until 2009. Therefore, the Hospira indications in the tentative approval letter will be limited to breast cancer, lung cancer, and prostate cancer.

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO X

10. 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 less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO X

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO X

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES X NO ☐

13. 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.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

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

☐ 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)
Patent number(s): 4814470 - 5/14/2010

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)
Patent number(s): 5438072 - 11/22/2013 5698582 - 7/3/2012 5714512 - 7/3/2012; 5750561 - 7/3/2012

**NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 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):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

**N/A** YES ☐ NO ☐

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO X

**Applicant submitted a request to waive the requirement to conduct a bioequivalence study.**

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☒ NO ☐

If "**Yes**," please list:

| Application No. | Product No. | Exclusivity Code | Exclusivity Expiration |
|---|---|---|---|
| **20-449** | **001** | **I-490** | **3/22/09** |
| **20-449** | **001** | **I-519** | **10/17/09** |

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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.**

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/s/

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Frank Cross
8/11/2008 05:31:42 PM
CSO

**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: | August 4, 2008 |
| To: | Robert Justice, MD, Director<br>Division of Drug Oncology Products (HFD-150) |
| Thru: | Linda Y. Kim-Jung, PharmD, Team Leader<br>Denise P. Toyer, PharmD, Deputy Director<br>Carol A. Holquist, RPh, Director<br>Division of Medication Error Prevention and Analysis (HFD-420) |
| From: | Loretta Holmes, BSN, PharmD, Safety Evaluator<br>Division of Medication Error Prevention and Analysis (HFD-420) |
| Subject: | Division of Medication Error Prevention and Analysis<br>Label and Labeling Review |
| Drug Name: | Docetaxel Injection<br>10 mg/mL (2 mL, 8 mL, and 16 mL vials) |
| Application Type: | NDA 22-234 |
| Applicant: | Hospira, Inc. |
| OSE RCM #: | 2008-410 |

# CONTENTS

## EXECUTIVE SUMMARY

Our Label and Labeling Risk Assessment indicated that the proposed Docetaxel Injection may offer an advantage over the currently marketed Taxotere Injection Concentrate because it does not require two dilution steps. However, these differences may introduce new types of errors. Due to healthcare practitioner's familiarity with Taxotere and the fact that Docetaxel will not use a tradename, it is likely that practitioners may intuitively think that Docetaxel Injection is a generic equivalent of Taxotere.

Our FMEA analysis indicated that the Taxotere labels/labeling provide detailed instructions involving the two step dilution process. Although, DMEPA considered revisions to the Docetaxel labels/labeling to help differentiate them from Taxotere; we noted that the Docetaxel labels/labeling are similar to other intravenous products that require only one dilution step. There is a potential for an increase in errors if we revise the Docetaxel labels/labeling to present information differently than on other intravenous products that require only one dilution step. In our opinion, the most effective means for communicating these differences is to highlight to healthcare practitioners the differences between Docetaxel Injection and Taxotere Injection Concentrate.

Therefore, we recommend the Applicant inform healthcare practitioners about the differences between Docetaxel Injection and Taxotere Injection Concentrate thru its promotional materials. In addition to any information disseminated by the Applicant (e.g., Dear Healthcare Professional letters), DMEPA would be willing to work with the Division to write articles in professional journals such as for the Institute for Safe Medication Practices (ISMP).

DMEPA's comments on the container label, carton and insert labeling are listed in Section 6. However, an internal meeting was held August 8, 2008 involving representatives from DDOP, ONDQA, and OSE where DMEPA's label/labeling issues were discussed. Although, revised labels/labeling were not submitted due to time constraints DDOP, ONDQA, and OSE came to a consensus on the revised labels and labeling.

## 1 BACKGROUND

### 1.1 INTRODUCTION

This review is written in response to a request from the Division of Drug Oncology Products (HFD-150) for a review of the labels and labeling of Docetaxel Injection.

### 1.2 REGULATORY HISTORY

This NDA is a 505(b)(2) application. The reference listed drug is Taxotere (Docetaxel) Injection Concentrate (NDA 20-449). Both products have similar indications of use with dosages that vary according to the indication of use.

One notable difference between these products is that preparation of an intravenous infusion using Taxotere Injection Concentrate requires two steps whereas Docetaxel Injection requires one. DMEPA also notes that upon marketing of Taxotere Injection Concentrate, the Agency received medication error reports concerning drug preparation errors due to the confusing presentation of the active drug concentration and volume, diluent volume, and instructions for preparation. In order to address these issues, the product has undergone several labeling revisions.

### 1.3 PRODUCT INFORMATION

Docetaxel Injection is a microtubule inhibitor indicated for the treatment of breast cancer, non-small cell lung cancer, hormone refractory prostate cancer (b) (4) . Docetaxel Injection has a boxed warning concerning certain precautions, contraindications, and adverse reactions. For dosage information, see Appendix A. Docetaxel Injection is to be administered intravenously over 1 hour every 3 weeks. Contact of Docetaxel Injection 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-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 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 the following sizes: 20 mg/2 mL single-dose vials, 80 mg/8 mL multi-dose vials, and 160 mg/16 mL multi-dose vials.

## 2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis staff conducting a label, labeling, and/or packaging risk assessment (see 2.2 Container, Carton Label, and Insert Label Risk Assessment). The primary focus for the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

### 2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

Because the Division of Medication Error Prevention and Analysis staff analyze reported misuse of drugs, the Division of Medication Error Prevention and Analysis staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The Division of Medication Error Prevention and Analysis uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product, the following was reviewed: package insert labeling submitted by the Applicant on July 9, 2007; and container labels and carton labeling submitted by the Applicant on April 24, 2008 (see Appendix B):

- Container Labels: 20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL
- Carton Labeling: 20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL
- Package Insert Labeling (no image)

Additionally, we compared the container labels and carton labeling of Docetaxel Injection 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, 2008 which covers the period May 4, 2007 through May 13, 2008 (see Appendix C).

- Container Labels: 20 mg/0.5 mL and 80 mg/2 mL
- Carton Labeling: 20 mg/0.5 mL and 80 mg/2 mL

# 3 RESULTS

## 3.1 DOCETAXEL INJECTION AND TAXOTERE INJECTION CONCENTRATE CONTAINER LABEL AND CARTON LABELING COMPARISON

Review of the container labels and carton labeling identified areas of similarities and differences between Docetaxel Injection and Taxotere Injection Concentrate as stated below (also refer to Appendix D).

- The proposed Docetaxel Injection has no tradename.
- The "20 mg" and "80 mg" portions of the total drug content statements overlap for both products. The total drug content statements for Docetaxel Injection are: **20 mg**/2 mL, **80 mg**/8 mL, and 160 mg/16 mL vs. Taxotere Injection Concentrate: **20 mg**/0.5 mL and **80 mg**/2 mL.
- The volume for Taxotere 80 mg is 2 mL whereas the volume for Docetaxel 2 mL represents the 20 mg strength of Docetaxel.
- The route of administration statement for both products overlaps with the wording "For IV Infusion Only".
- The dosage form statement differs between the products (Docetaxel Injection vs. Taxotere Injection Concentrate).
- Docetaxel Injection requires a one step dilution whereas Taxotere Injection Concentrate requires two dilution steps to prepare an intravenous infusion.

- Taxotere Injection Concentrate contains the following cautionary statements in regard to strength "Before Initial Dilution" and "After Final Dilution", whereas Docetaxel Injection does not have these statements.
- Each Taxotere Injection Concentrate carton contains 1 vial of active drug and 1 vial of diluent whereas each Docetaxel Injection carton contains 1 vial of active drug.
- Taxotere, before opening, can be stored at room temperature or in a refrigerator whereas Docetaxel Injection is to be stored at room temperature.

## 3.2 LABEL AND LABELING RISK ASSESSMENT FOR THE PROPOSED DOCETAXEL INJECTION

### 3.2.1 *General Comment For All Labels And Labeling*

Abbreviations such as "IV" and "BID" are used in the labels and labeling.

### 3.2.2 *Container Labels*

The "mg" and "mL" portions of the total drug content is stated in an oblong graphic which uses two different colors for the "XX mg" and "XX mL".

On the 160 mg/16 mL multidose vial, the storage statement "Protect from Light" competes in prominence with the route of administration statement "For IV infusion only".

The storage temperature range is only stated in degrees Celsius.

### 3.2.3 *Carton Labeling*

The "mg" and "mL" portions of the total drug content is stated in an oblong graphic which uses two different colors for the "XX mg" and "XX mL".

In relation to other important information such as the established name, total drug content, and route of administration statement, the "Rx only" statement is too prominent.

The instructions for the [redacted] (b) (4) stated on the side panels contain some duplicative information regarding preparation for this product.

### 3.2.4 *Package Insert Labeling*

Some dosage ranges are expressed such that the unit of measure does not follow the first number (e.g., "60-100 mg/$m^2$").

# 4 DISCUSSION

## 4.1 DOCETAXEL INJECTION AND TAXOTERE INJECTION CONCENTRATE CONTAINER LABEL AND CARTON LABELING COMPARISON

The proposed Docetaxel formulation may offer an advantage over the currently marketed Taxotere Injection Concentrate because it does not require two dilution steps. However, this very difference can introduce a new type of error. Due to healthcare practitioner familiarity with Taxotere and the fact that the proposed product will not use a tradename, it is likely that practitioners may intuitively think that Docetaxel Injection is a generic equivalent of Taxotere.

Our analysis involved a comparison of the labels and labeling of Docetaxel to Taxotere. In fact although there are similarities, there are obvious differences between the two products.

Specifically, the Taxotere labels/labeling provide detailed instructions involving the two step dilution process. DMEPA notes that this two step dilution process is not typical since preparing an intravenous infusion using a solution that must be diluted usually requires only one step.

Our focus was on preventing practitioners from intuitively diluting Docetaxel using the Taxotere two step dilution methods. We initially focused on differentiating the Docetaxel labels/labeling and not changing the Taxotere label/labeling since Taxotere has undergone numerous labeling revisions in response to confusion with the labels/labeling. In assessing whether any changes to the Docetaxel labels/labeling were needed, the FMEA determined that the Docetaxel labels look similar to other intravenous products that require one dilution step (e.g., withdrawing the required drug dose from a vial and diluting the dose in a minibag of solution). By changing the Docetaxel labels/labeling we would be presenting information differently on the Docetaxel labels/labeling than other intravenous products that require only one dilution step.

In light of this analysis, the FMEA determined that there is a potential for an increase in errors if we revise the Docetaxel labels/labeling. In our opinion, the most effective means for communicating these differences is to highlight to healthcare practitioners about the differences between Docetaxel Injection and Taxotere Injection Concentrate.

### 4.2 DOCETAXEL INJECTION LABEL AND LABELING

Our Label and Labeling Risk Assessment identified areas where the layout and presentation of information, such as the total drug content statement, route of administration and dosing instructions need to be improved to provide better clarity.

The total drug content statement on the container label and carton labeling is presented in an oblong graphic with the "mg" and "mL" portions blocked by a different color. We acknowledge that this presentation is a trade dress used by the applicant, Hospira. However, in our opinion, the use of a much darker color for the net quantity (e.g., black for 2 mL and light peach for the XX mg), detracts attention away from the "mg" portion. Thus, at a glance, one sees the net quantity and not the entire drug content statement. DMEPA notes that Taxotere is available in a 2 mL vial size and bringing more attention to the net quantity (2 mL) may cause confirmation bias that both products are essentially the same ( e.g., 80 mg/**2 mL** Taxotere vs. 20 mg/**2 mL** Docetaxel Injection) when in fact the 2 mL volumes represent different strengths.

We also note that enhancing the prominence of the route of administration may better alert practitioners to the fact that this product is more conventional or typical in that it does not require more than one dilution step when preparing an infusion. Relocating the Rx symbol away from the mid portion of the principal display panel on the carton labeling would allow for the "For IV infusion only" statement to follow directly beneath the product strength, giving it a better prominence. Likewise, relocating or reducing the size of the "Protect from Light" wording (on the 16 mL multidose vial container label) would increase the prominence of the "For IV infusion only" statement.

We also found duplicate information on the carton labeling under (b) (4) and the (b) (4). (b) (4) Presenting this information under one heading (e.g., Dosage and Administration) would makes it easier for healthcare practitioners to get all the information in one place.

Our analysis also identified the use of abbreviations and omissions of the unit of measures throughout the label/labeling. Abbreviations such as "IV" and "BID" are used in the labels and labeling which can be source of confusion and misinterpretation of information. DMEPA notes

that in order to address safety concerns with the use of error-prone medical abbreviations, the FDA in conjunction with the Institute for Safe Medication Practices (ISMP), launched a nationwide health professional educational campaign in 2006 aimed at reducing the number of common but preventable sources of medication errors caused by the use of error-prone medical abbreviations. As part of this campaign, the Agency agreed not to approve the use of such abbreviations in labels and labeling. Also, we noted the use of numerical dosage ranges in which the first number does not contain the unit of measure (e.g., "60-100 $mg/m^2$"). Including the unit of measure with the numerical value may help to prevent ambiguity and misinterpretation.

Finally, the storage temperature range on the container labels is only stated in degrees Celsius whereas the carton states the range in both degrees Celsius and Fahrenheit. Since healthcare practitioners in the U.S. are more familiar with the temperature in degrees Fahrenheit, having this additional information readily available helps to ensure that the product will get stored under the correct conditions should the vial get separated from the carton. Also, this will ensure that the information is consistently presented on the labels and labeling.

# 5 CONCLUSIONS

In our opinion, the familiarity with Taxotere and the fact Docetaxel will not have a tradename may cause practitioners to intuitively think that Docetaxel Injection is a generic equivalent of Taxotere. However, FMEA determined that the Docetaxel labels/labeling are similar to other intravenous products that only require one dilution step and that there may be a potential for other types of medication errors if we revise the Docetaxel labels/labeling. Therefore, the most effective means for communicating these product differences is to highlight to healthcare practitioners about the differences between Docetaxel and Taxotere Injection Concentrate.

Additionally, our Label and Labeling Risk Assessment identified several areas where the layout and presentation of information such as the statement of strength, route of administration and dosing instructions can be improved to provide better clarity or prominence. In an internal meeting held August 8, 2008 involving representatives from DDOP, ONDQA, and OSE that DMEPA's label/labeling issues contained in this review were discussed. Although, revised labels/labeling were not submitted due to time constraints DDOP, ONDQA, and OSE came to a consensus on the revised labels and labeling.

# 6 RECOMMENDATIONS

## 6.1 COMMENTS TO THE DIVISION

The Division of Medication Error Prevention and Analysis believes the Label and Labeling risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6.2 that aim at reducing the risk of medication errors.

In addition to any information disseminated by the Applicant, DMEPA would be willing to work with the Division to write newsletters and or alerts for the Institute for Safe Medication Practices' (ISMP) newsletters and in professional journals such as for the Hematology/Oncology Pharmacy Association (HOPA) in order to better inform healthcare practitioners of the different docetaxel products.

The Division of Medication Error Prevention and Analysis would appreciate feedback of the final outcome of this consult. 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 correspondence to the applicant pertaining to this issue. If you have further questions or need clarification, please contact Sandra Griffith, OSE Project Manager, at 301-796-2445.

## 6.2 COMMENTS TO THE APPLICANT

### 6.2.1 *Labels and Labeling*

A. Product Design

Although the proposed Docetaxel Injection offers the advantage of requiring only one dilution step, we anticipate errors in product preparation because healthcare practitioners have become accustomed to the two step dilution process required for Taxotere. We would like healthcare practitioners and pharmacy technicians to be made aware of this major difference between Docetaxel Injection and the currently marketed Taxotere.

Therefore, at the time of product launch, DMEPA recommends that the applicant inform healthcare practitioners about the differences in the preparation of the proposed Docetaxel Injection which has one dilution step versus other docetaxel products which require two dilution steps (e.g., Dear Healthcare Professional letter).

B. General Comment

Replace the abbreviations used in the labels and labeling with the corresponding words spelled out in their entirety (e.g., intravenous, twice daily, etc.).

C. Container Labels

1. Present both the total drug content and concentration per mL in a single color block to ensure equal prominence to both the "XX mg" and "XX mL". The total drug content should be revised to read "XX mg/XX mL" or "XX mg per mL". For example:

| | | |
|---|---|---|
| 80 mg/8 mL<br>(10 mg/mL) | or | 80 mg per 8 mL<br>(10 mg/mL) |

2. Decrease the size of the "Protect from Light" statement on the 160 mg/16 mL multidose vial.
3. State the storage temperature range in degrees Fahrenheit (in addition to the degrees Celsius which is already present).

D. Carton Labeling

1. Present both the total drug content and concentration per mL in a single color block. The total drug content should be revised to read "XX mg/XX mL" or "XX mg per mL". For example:

| | | |
|---|---|---|
| 80 mg/8 mL<br>(10 mg/mL) | or | 80 mg per 8 mL<br>(10 mg/mL) |

2. Relocate the "Rx" symbol away from the mid section of the principal display panel to allow for more prominence for the route of administration statement.

3. Move the information in the [redacted] (b) (4) section to the [redacted] (b) (4) section so that the information in both sections is under one heading, [redacted] (b) (4).

E. Package Insert Labeling

Ensure that the unit of measure follows the first numerical value when expressing dosage ranges (e.g., "60 mg -100 mg/$m^2$" or "60 mg to 100 mg/$m^2$").

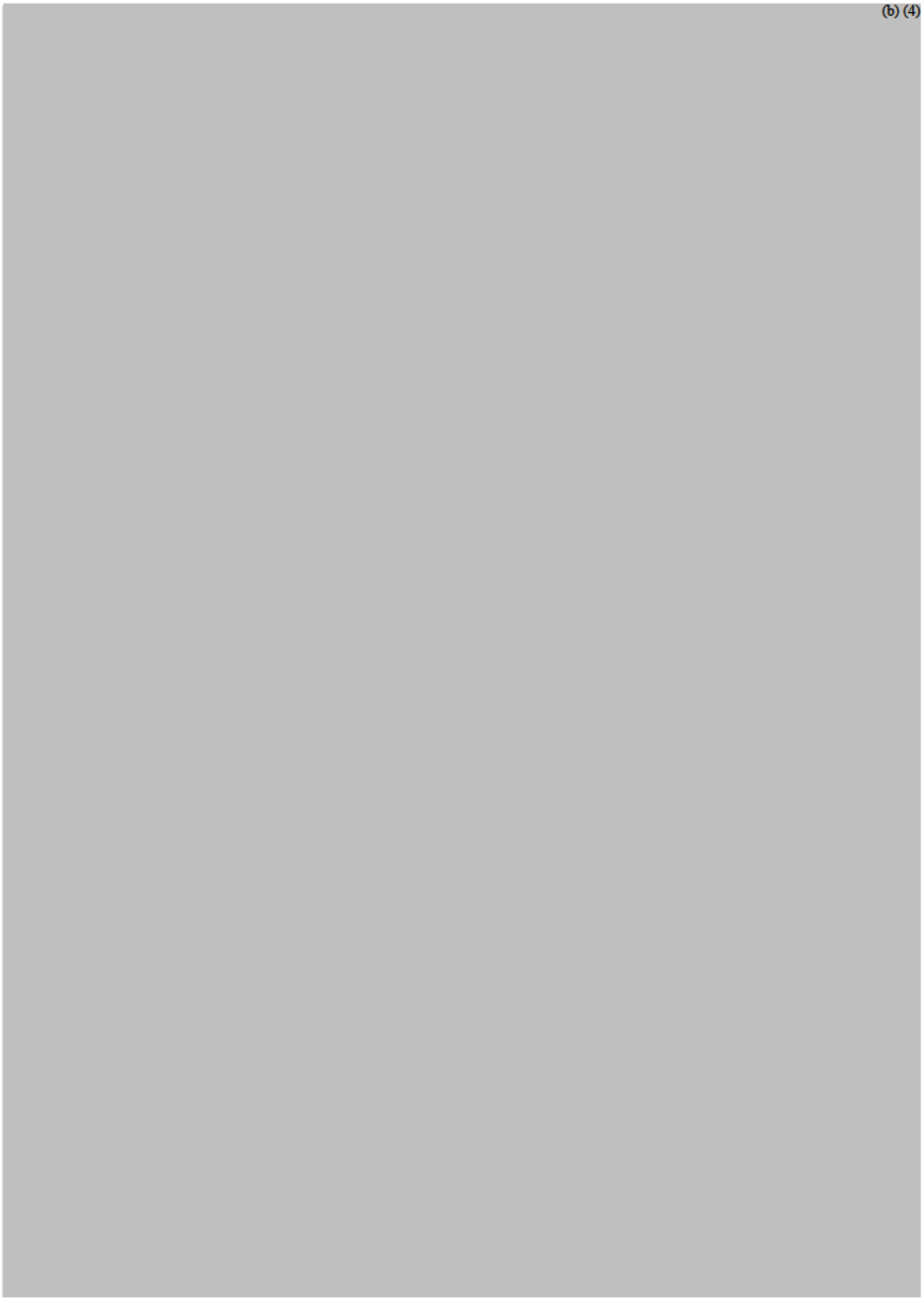
## Appendix A:

### Docetaxel Injection Indications and Dosage

| 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 |
| [redacted] (b) (4) | |
| **Premedication Regimen** | Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice a day) for 3 days starting 1 day before administration.<br>Hormone refractory prostate cancer: oral dexamethasone 8 mg, at 12, 3, and 1 hours before treatment |

**Appendix B:**

**Docetaxel Injection Container Labels (not to scale)**

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**Appendix D:**

**Comparative Analysis of Carton Labeling of Docetaxel Injection and Taxotere Injection Concentrate (20 mg strength used for comparison)**

| | Taxotere Injection Concentrate | Docetaxel Injection |
|---|---|---|
| Tradename | TAXOTERE® | None |
| Established Name | *docetaxel* | Docetaxel |
| Dosage Form Statement | Injection Concentrate | Injection |
| Statement of Strength (Total Drug Content) | 20 mg/0.5 mL<br>80 mg/2 mL | 20 mg/2 mL<br>80 mg/8 mL<br>160 mg/16 mL |
| Statement of Strength Cautionary Statement | [redacted] (b) (4) | |
| Route of Administration | | |
| Number of Dilution Steps Required | | |
| Packaging Configuration | | |
| Storage Temperature | | |
| Overall Side-By-Side Comparison (Principal Display Panel) | | |
| Container Labels | | |

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/s/
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Loretta Holmes
8/8/2008 02:46:44 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/8/2008 02:56:42 PM
DRUG SAFETY OFFICE REVIEWER

# MEMORANDUM

**To:** **Frank Cross**
**Division of Drug Oncology Products**

**From:** **Iris Masucci, PharmD, BCPS**
**Division of Drug Marketing, Advertising, and Communications**
**for the Study Endpoints and Label Development (SEALD) Team, OND**

**Date:** **April 15, 2008**

**Re:** **Comments on draft labeling for docetaxel injection**
**NDA 22-234**

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We have reviewed the proposed label for docetaxel (FDA version dated 4/2/08) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

Attached is a marked up version of the proposed label.

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/s/
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Iris Masucci
4/17/2008 01:50:52 PM
DDMAC REVIEWER

Laurie Burke
4/18/2008 04:22:39 PM
INTERDISCIPLINARY