CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203551Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 203551	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: None Established/Proper Name: Docetaxel Injection Concentrate Dosage Form: Intravenous Solution Concentrate for Infusion Strengths: 20 mg/1 mL, 80 mg/4 mL, 140 mg/7 mL		
Applicant: Actavis, Inc.		
Date of Receipt: March 14, 2012		
PDUFA Goal Date: April 14, 2013	Action Goal Date (if different):	
Proposed Indication(s): Docetaxel injection concentrate is a microtubule inhibitor indicated for: • **Breast Cancer (BC):** single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC • **Non-Small Cell Lung Cancer (NSCLC):** single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC • **Hormone Refractory Prostate Cancer (HRPC):** with prednisone in androgen independent (hormone refractory) metastatic prostate cancer • **Gastric Adenocarcinoma (GC):** with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction • **Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN):** with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN		

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® Injection NDA 020449	Clinical, Non-Clinical

*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)

ONDQA granted Actavis' request for a waiver from the in vivo bioequivalence study requirements based on a comparison of the proposed drug to the listed drug relied-upon, Taxotere.

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®	020449	Yes

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 application provides a change in formulation from 40 mg/mL Taxotere® to 20 mg/mL docetaxel concentrate for solution for infusion.

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): *NDAs 201195, 22312, 22234, 201525, 22524*

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): 5698582, 5714512, 5750561

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):

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

Patent number(s):	Expiry date(s):
5698582	January 3, 2013
5714512	January 3, 2013
5750561	January 3, 2013

☐ 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.*

☐ 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):
(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):

(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 ☐

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

Label, Labeling and Packaging Review

Date:	February 13, 2013
Reviewer:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Docetaxel Injection Concentrate 20 mg/mL, 80 mg/4 mL, and 140 mg/7 mL
Application Type/Number:	NDA 203551
Applicant:	Actavis Pharmaceuticals
OSE RCM #:	2012-1087-1

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1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling of Docetaxel Injection Concentrate 20 mg/mL, 80 mg/4 mL, and 140 mg/7 mL (NDA 203551) submitted in response to the Division of Medication Error Prevention and Analysis' comments in the November 23, 2012 OSE Review 2012-1087.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

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

- Container Label submitted February 8, 2013 (Appendix A)
- Carton Labeling submitted February 8, 2013 (Appendix B)
- Insert Labeling submitted February 8, 2013

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Docetaxel Injection in OSE Review 2012-1087, and we looked at the review to ensure all our recommendations were implemented.

3 CONCLUSION

DMEPA finds the Applicant's revisions to the labels and labeling acceptable.
If you have questions or need clarifications, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

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

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

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/s/

JAMES H SCHLICK
02/13/2013

TODD D BRIDGES
02/13/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion

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

Memorandum

Date: December 12, 2012

To: Rajesh Venugopal, MPH, MBA – Regulatory Project Manager
Division of Oncology Products 1 (DOP 1)
Office of Hematology and Oncology Products

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

Subject: DCDP comments on draft Patient Product Labeling (PPI)
Docetaxel Injection Concentrate (docetaxel)
NDA 203551

As requested in your consult dated April 27, 2012, DCDP has reviewed the draft PPI for docetaxel. This is a new 505(b)(2) application with Taxotere (NDA 020449) as the reference listed drug (RLD).

Comments on the proposed package insert (PI) were provided on November 26, 2012. DCDP's comments are based on the proposed, marked-up, substantially complete version of the PI sent to OPDP on November 15, 2012, and the Division of Medical Policy Program's (DMPP) review of the proposed PPI dated December 11, 2012.

DCDP agrees with DMPP's comments and recommendations, and has the following additional comments below. Please note we have used DMPP's clean version of the proposed PPI provided as a Word document to DOP 1 and DCDP on December 11, 2012.

Thank you for your consult.

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/s/

MICHELLE L SAFARIK
12/12/2012

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Medical Policy Initiatives

Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	December 11, 2012
To:	Robert Justice, MD Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nathan Caulk, MS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	Docetaxel Injection Concentrate
Dosage Form and Route:	Intravenous Infusion (IV)
Application Type/Number:	NDA 203-551
Applicant:	Actavis Inc.

1 INTRODUCTION

On March 14, 2012, Actavis Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 203-551 for Docetaxel Injection Concentrate, Intravenous Infusion. The Reference Listed Drug (RLD) is TAXOTERE (docetaxel) Injection Concentrate, Intravenous Infusion NDA 20-449. The proposed indication for Docetaxel Injection Concentrate is for the treatment of:

- Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC non-small cell lung cancer
- Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC
- Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer
- Gastric Adenocacinoma (GC): with cisplatin and fluorouracil for untreated, adnvaced GC, including the gastroesophageal junction
- Squamous Cell Carinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN

On October 16, 2012, the Division of Oncology Products 1 (DOP1) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for Docetaxel Injection Concentrate.

This review is written in response to a request by DOP1 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for Docetaxel Injection Concentrate.

2 MATERIAL REVIEWED

- Draft Docetaxel Injection Concentrate, Intravenous Infusion (IV) PPI received on March 14, 2012, and received by DMPP on October 16, 2012.
- Draft Docetaxel Injection Concentrate, Intravenous Infusion (IV) Prescribing Information (PI) received on March 14, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on November 27, 2012.
- Approved TAXOTERE (docetaxel) Injection Concentrate, Intravenous Infusion (IV) comparator labeling dated December 15, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication*

Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
12/11/2012

BARBARA A FULLER
12/11/2012

LASHAWN M GRIFFITHS
12/11/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

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

Memorandum

Date: November 26, 2012

To: Rajesh Venugopal, Regulatory Project Manager
Division of Oncology Products 1 (DOP1)

From: Gina McKnight-Smith, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

CC: Karen Rulli, Professional Review Team II Leader, DPDP

Subject: Comments on draft labeling (Package Insert) for Docetaxel Injection Concentrate Intravenous Infusion (IV)
NDA 203551

In response to your consult request dated April 27, 2012, we have reviewed the draft Package Insert (PI) for Docetaxel Injection Concentrate Intravenous Infusion (IV).

DPDP has taken into consideration the reference label drug (RLD) for Taxotere (docetaxel) Injection Concentrate, Intravenous Infusion (IV). DPDP used the version of the Docetaxel Injection Concentrate Intravenous Infusion (IV) PI sent via email link to OPDP by Rajesh Venugopal on November 15, 2012.

Section	Statement from draft	Comment
FULL PRESCRIBING INFORMATION: CONTENTS, Section 8 USE IN SPECIFIC POPULATIONS	**8 USE IN SPECIFIC POPULATIONS** 8.1 Pregnancy 8.3 Nursing Mothers 8.5 Geriatric Use 8.6 Hepatic Impairment	In the RLD, section "8.4 Pediatric Use" is included. Unless there is a specific reason for this section title to be omitted, OPDP recommends that the label for NDA 203551 match the RLD.
8 USE IN SPECIFIC POPULATIONS,	--	ODPD suggests adding Section 8.4 for consistency with the RLD. Please see suggested language

Section	Statement from draft	Comment
Section 8.4		below: **8.4 Pediatric Use** The safety and effectiveness of docetaxel in pediatric patients have not been established.

Thank you for the opportunity to consult on the proposed labeling.

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/s/

GINA P MCKNIGHT-SMITH
11/26/2012

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

Label, Labeling and Packaging Review

Date:	November 23, 2012
Reviewer:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Team Leader	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Associate Director	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Docetaxel Injection Concentrate 20 mg/mL, 80 mg/4 mL, and 140 mg/7 mL
Application Type/Number:	NDA 203551
Applicant:	Actavis, Inc.
OSE RCM #:	2012-1087

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1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling of Docetaxel Injection Concentrate 20 mg/mL, 80 mg/4 mL, and 140 mg/7 mL (NDA 203551) submitted on March 14, 2012 for a new one-vial formulation.

1.1 BACKGROUND ON DOCETAXEL PRODUCTS

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

On August 2, 2010, a new one-vial formulation of Taxotere was approved by the FDA. This one-vial formulation does not require a two step dilution process, and the drug can be withdrawn from the vial and added directly to the infusion solution. However, whereas the two-vial formulation yielded a concentration of 10 mg/mL before being added to the infusion solution, the new one-vial formulation was approved with a concentration of 20 mg/mL. Additionally, On April 20, 2012 a new one-vial formulation with a concentration of 20 mg/mL marketed by Accord was also approved by the FDA.

On March 8, 2011, a 505(b)(2) application for Docetaxel Injection from Hospira was approved by the FDA. On June 29, 2011, another 505 (b)(2) application for Docetaxel Injection from Sandoz was approved by the FDA. The Docetaxel Injection products by Hospira and Sandoz are also one-vial formulations like the one-vial formulation of Taxotere. An important difference between these two products as compared to the one-vial Taxotere formulation by Sanofi Aventis and Accord is their concentration. Taxotere and Accord's one-vial formulation is available in a concentration of 20 mg/mL, whereas Hospira and Sandoz's one-vial formulations are available in a concentration of 10 mg/mL. (b)(4) Since approval, we have received complaints concerning this disparity in concentrations.

Although Sanofi Aventis intends to discontinue the two-vial Taxotere formulation now that a one-vial Taxotere formulation has been introduced to the market, an additional product like the two-vial Taxotere was approved by the FDA. This NDA application, submitted by Accord Healthcare, was approved on June 8, 2011, as a 505 (b)(2) application. Accord Healthcare's Docetaxel Injection is a two-vial formulation that yields a 10 mg/mL concentration after the initial reconstitution step, the same as the two-vial Taxotere by Sanofi Aventis. The FDA also approved on January 11, 2012, a two-vial formulation by Apotex, like the two-vial Taxotere by Sanofi Aventis and Accord. Lastly, the FDA approved a 505 (b)(2) application, submitted by Sun Pharma Global as a

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powder for injection, which differentiates it from all the other approved and pending Docetaxel products. Appendix A summarizes the approved and pending Docetaxel Injection products.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 14, 2012 NDA submission.

- Active Ingredient: Docetaxel
- Indication of Use: 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.
- Route of Administration: Intravenous Infusion
- Dosage Form: Solution for Infusion
- Strength: 20 mg/mL
- Dose and Frequency: See Appendix B
- How Supplied: 20 mg/mL, 80 mg/4 mL, and 140 mg/7 mL
- Storage: Store between 2ºC to 25ºC
- Container and Closure System: Container closure system consist of either 5 mL, 8 mL or 11 mL sterile (b)(4) colorless glass vials, closed with (b)(4) rubber stoppers and sealed with aluminum seals with (b)(4) caps.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (AERS) database for Docetaxel medication error reports. We also reviewed the Docetaxel labels and labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the AERS database using the strategy listed in Table 1. The time frame covered is from February 9, 2012, the date of the last docetaxel AERS search in OSE Review # 2012-203.

Table 1: AERS Search Strategy	
Date	February 9, 2012 to August 2, 2012
Drug Names	Active Ingredient: Docetaxel Trade Name: Taxotere Verbatim Term: "Taxot%", "Doce%"
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The AERS database search identified 11 reports, respectively. Each report was reviewed for relevancy and duplication. After individual review, 8 reports were not included in the final analysis for the following reasons:

- Adverse events related to Docetaxel that did not include a medication error.

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on August 2, 2012 for additional cases and actions concerning Docetaxel. The PubMed search consisted of the search terms "docetaxel" and "medication error". The following ISMP newsletters were searched using the term "docetaxel":

- ISMP Acute Care Newsletter
- ISMP Community Edition
- ISMP Nursing Edition
- ISMP Canada Safety Bulletin

The search did not yield additional cases.

2.3 LABELS AND LABELING

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

- Container Labels submitted March 14, 2012 (Appendix D)
- Carton Labeling submitted March 14, 2012 (Appendix E)
- Insert Labeling submitted June 6, 2012

2.4 PREVIOUS REVIEWS

We read through our three previous docetaxel label and labeling reviews (listed below). Examination of these reviews did not identify any medication error cases that were pertininet to this review.

- OSE RCM# 2012-203, Docetaxel Injection Concentrate (Accord) Label and Labeling Review, April 4, 2012
- OSE RCM# 2011-2624, Docetaxel Injection (Sandoz) Label and Labeling Review, December 21, 2011
- OSE RCM# 2010-2465, Docetaxel Injection (Sandoz) Label and Labeling Review, April 5, 2011

3 MEDICATION ERROR RISK ASSESSMENT

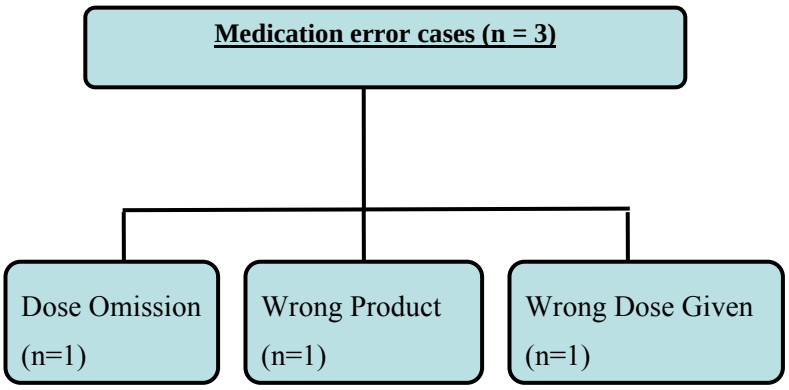
The following sections describe the results of our AERS search and the risk assessment of the Docetaxel product design as well as the associated labels and labeling.

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

3.1 AERS MEDICATION ERROR CASES

Following exclusions as described in section 2.1, 3 Docetaxel medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]. Figure 1 provides a stratification of the number of cases included in the review by type of error.

Figure 1: Docetaxel medication errors (n = 3) categorized by type of error



- Dose Omission (n=1)

This case (ISR# 8228392) involved a possible dose omission with docetaxel. The nurse reported that cetuximab and docetaxel were given in combination only at every third treatment. The reporter did not state the correct chemotherapy regimen. Therefore, we are unable to determine if the regimen was given incorrectly. The outcome of the event was not reported.

- Wrong Product (n=1)

This case (ISR # 8507742) involved the use of a new concentration of docetaxel stocked in the pharmacy. The pharmacy system that calculates active medication volumes for intravenous infusion labels was not updated to reflect the new concentration. As a result, the pharmacy label incorrectly stated the volume of docetaxel required for the dose. The error was caught by the technician before the dose was given to the patient.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

- Wrong Dose Given (n=1)

This case (ISR# 8406899) involved an under dose of the patient due to the site inadvertently recalculating the patients weight. The physician treating the patient reported that no adverse outcome occurred due to the under dose.

The present reported cases do not indicate that the label or labeling of currently marketed Docetaxel products require additional changes from a regulatory perspective.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

3.2.1 PROPOSED PRODUCT STRENGTHS AND CONCENTRATION

The proposed Docetaxel Injection Concentrate product includes the same total vial strengths of the one-vial RLD, Taxotere (20 mg/mL and 80 mg/4 mL) as well as the same concentration (20 mg/mL). However, the Applicant is also proposing the addition of a 140 mg/7 mL presentation. The dosages for the indications for Docetaxel Injection Concentrate support a 140 mg presentation, in accordance with the package insert which states the largest dose administered to a patient is 100 mg/m^2.

3.2.2 PRODUCT DIFFERENTIATION

Due to the availability of multiple formulations in varying concentrations that require differing instructions for drug preparation, the potential for confusion among docetaxel 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

Additionally, the use of properly placed and well differentiated statements on the container and carton labeling may help to minimize the potential for confusion between strengths from the same company or between companies.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling are unacceptable. The strength presentation needs to be revised to improve readability, thereby decreasing the possibility of confusion between the 10 mg/mL and the 20 mg/mL docetaxel products. Additionally, the statement "For Intravenous Infusion Only" should be added to the principal display panel to help differentiate the proposed product from other two-vial formulations. DMEPA also recommends removing certain statements as well as moving other

statements to ensure the most important information is on the principal display panel to help minimize potential errors.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Label

1. Container Label for the 20 mg, 80 mg and 140 mg Vial

a. As proposed, the principal display panel (PDP) occupies approximately two-thirds of the label. A PDP that covers a large horizontal area requires practitioners to rotate the container in order to read the most important information. Redesign the label format so that the established name, product strength, route of administration, and the warning statement "Ready to add…" appear on a PDP that requires no or minimal rotation of the label for a practitioner to read this important information. If space permits, the statement "Single Use Vial" could also appear on the PDP.

b. We note that there are two bar code formats on the label. The bar code at the bottom of the PDP appears unnecessary since the NDC bar code is displayed on the side panel. If this bar code is not beneficial for practioners in the United States, then we recommend removal of this bar code or decrease the size and relocate the bar code to the side panel.

c. Decrease the prominence of the statement "Single Use Vial" to minimize distraction with the strength presentation. The statement should appear with a prominence similar to its appearance on the carton labeling. If space is limited on the PDP, then this statement may appear on the side panel.

d. To make room for additional statements to the principal display panel, delete the statement "Sterile, Nonpyrogenic, Preservative-free" since it is also stated on the carton.

e. Because the labels are small, remove the ingredients per mL information per 21 CFR 201.10 (h)(2)(i). The ingredient information will be located on the carton labeling to comply with this regulation. This will help minimize distraction from the strength and warning statements discussed in the following recommendations A.1.f-h.

f. Change the statement "Ready to add infusion solution" by including the word "to" in the statement to read "Ready to add to infusion solution".

g. Add the statement "For Intravenous Infusion Only" to the principal display panel immediately above the statement "Ready to add to infusion solution".

h. To make room for additional statements on the principal display panel, revise the Usual Dosage and Administration statement to read "See package insert for complete instructions", and relocate to the side panel.

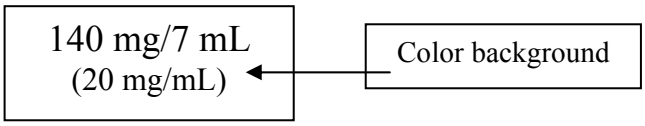
i. Consider changing the statements "Ready to add to infusion solution" to a different font color to improve readability, yet still optimizing the readability of the total drug content and concentration per mL statement on the principal display panel.

j. Change "Batch" to "Lot" where the expiration date and lot number will be printed.

2. Container Label for 80 mg and 140 mg Vial

a. Relocate the concentration per mL statement "20 mg/mL" on the 80 mg/4 mL and 140 mg/7 mL presentations to just below the total drug content in all places that it appears. Additionally, place the total drug content and "20 mg/mL" statement in the same box with the same color background. Ensure the font size of the per mL concentration is smaller than the font size of the total drug content. Refer to the Unites States Pharmacopeia General Chapter <1> Injections for additional guidance, if needed.

For example:



B. Carton Labeling

1. Add the statement "Contains 1 mL", Contains 4 mL", and "Contains 7 mL" to the appropriate vial carton.

2. Place the total drug content per vial and the strength per mL "20 mg/mL" statement in the same box with the same color background in each place that it occurs on the carton. Ensure the font size of the per mL concentration is smaller than the font size of the total drug content. See the example in A.2.a for guidance.

3. See A.1.f and A.1.j above and make the appropriate changes to the carton.

4. Revise the bolded concentration statement "**(20 mg/mL)**" that is located in the box on the side panel with the instructions "Withdraw the required amount of docetaxel…" to a red font color in bold type.

5. Change the statement "Single Use Vial" to read "Single Use Vial: Discard Unused Portion." Move this statement to the display on the side panel.

C. Insert Labeling

1. How Supplied/Storage and Handling – Section 16.1

a. Add the strength per mL statement "(20 mg/mL)" immediately after the statement "80 mg/4 mL".

b. Change the statement "140 mg/ mL" to 140 mg/7 mL". The number "7" is missing. Additionally, add the strength per mL statement "(20 mg/mL)" immediately after the statement "140 mg/7 mL".

If you have questions or need clarifications, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

REFERENCES

OSE RCM: 2011-2624. Docetaxel (Sandoz) Label and Labeling Review, December 21, 2011.

OSE RCM: 2009-122. Taxotere (Docetaxel) Label and Labeling Review, January 8, 2010.

OSE RCM: 2011-201. Taxotere (Docetaxel) Label and Labeling Review, February 24, 2011.

OSE RCM: 2011-282. Docetaxel (Accord) Label and Labeling Review, April 5, 2011.

OSE RCM: 2012-203. Docetaxel (Accord) Label and Labeling Review, April 4, 2012

APPENDICES

APPENDIX A: TABLE OF DOCETAXEL PRODUCTS

NDA	Applicant	Formulation	Concentration	Status
20449/S-054 Taxotere	Sanofi-Aventis	1 vial	20 mg/mL	Approved on 5/14/96
20449 Taxotere	Sanofi-Aventis	2 vial	10 mg/mL after initial dilution	Approved on 08/2/10
201195	Accord Healthcare	2 vial	10 mg/mL after initial dilution	Approved on 06/08/11
201195/S-001	Accord Healthcare	1 vial	20 mg/mL	Approved on 04/20/12
203551	Actavis***	1 vial	20 mg/mL	Pending
022234	Hospira	1 vial	10 mg/mL	Approved on 03/8/11
201525	Sandoz	1 vial	10 mg/mL	Approved on 06/29/11
022534 Docefrez	Sun Pharma Global FZE	Lyopholized powder plus diluent	**20 mg vial** 20 mg/0.8 mL (25 mg/mL) **80 mg vial** 24 mg/mL	Approved on 05/3/11
[redacted]	(b)(4)	[redacted]	[redacted]	[redacted]
022312	Apotex	2 vial	10 mg/mL after initial dilution	Approved on 1/11/12

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

APPENDIX B: DOCETAXEL INDICATIONS AND DOSE

Indication of Use	Dose
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 C. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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

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

/s/

JAMES H SCHLICK
11/21/2012

TODD D BRIDGES
11/21/2012

SCOTT M DALLAS
11/21/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 203551 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Not proposed Established/Proper Name: Docetaxel Injection Concentrate Dosage Form: Intravenous -solution concentrate for infusion Strengths: 20 mg/ 1 mL, 80 mg/4 mL, 140 mg/7 mL		
Applicant: Actavis, Inc. Agent for Applicant (if applicable): Lachman Consultant Services, Inc.		
Date of Application: March 14, 2012 Date of Receipt: March 14, 2012 Date clock started after UN:		
PDUFA Goal Date: January 14, 2013	Action Goal Date (if different):	
Filing Date: (Day60) May 13, 2012	Date of Filing Meeting: April 26, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Breast, non-small cell lung, prostate, gastric adenocarcinoma, head and neck.		

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

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

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

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

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

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
020449	Taxotere	PED	November 13, 2013
020449	Taxotere	M-61	May 13, 2013

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X			

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

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

authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in 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…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***		X		Submitted electronically

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			X	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		

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

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***		X		Request for waiver of Pediatric studies were included, however this 505b2 did not trigger PREA therefore not necessary.
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

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

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

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

End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 27, 2012

BLA/NDA/Supp #: NDA 203551

PROPRIETARY NAME: none proposed

ESTABLISHED/PROPER NAME: Docetaxel Injection Concentrate

DOSAGE FORM/STRENGTH: Intravenous -solution concentrate for infusion
20 mg/ 1 mL, 80 mg/4 mL, 140 mg/7 mL

APPLICANT: Actavis, Inc.
US Agent: Lachman Consultant Services, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Breast Cancer, Non-Small Cell Lung Cancer, hormone refractory Prostate Cancer, Gastric Adenocarcinoma, Squamous Cell Carcinoma of the Head and Neck Cancer.

BACKGROUND: Lachman Consultant Services, Inc., the Agent for Actavis, Inc., submitted a new 505(b)(2) NDA 203551 for Docetaxel on March 14, 2012. The referenced listed NDA is NDA 020449 for Taxotere® (docetaxel) Injection Concentrate. NDA 203551 differs from the reference listed drug, Taxotere by the inactive ingredients. Actavis, Inc. did not have any INDs associated with this 505(b)(2) NDA.

Background on patents and exclusivity exist for the reference listed drug Taxotere® and they affect the package insert label subsection 8.4 Pediatric Use.

Patent data (numbers 5698582 and 5714512 and 5750561) expiration dates: July 3, 2012
Patent data (numbers 5698582*PED and 5714512*PED and 5750561*PED) expiration dates: July 3, 2012

Exclusivity data leading to revisions to the labeling based on data submitted in response to pediatric written request – expiration date: May 13, 2013
and Exclusivity data -(PED) expiration date: November 13, 2013

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Skarupa	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Sarah Pope Miksinski		N
Clinical	Reviewer:	Paul Kluetz	Y

	TL:	Ellen Maher	Y
Social Scientist Review (*for OTC products*)	Reviewer:	NA	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	NA	
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	NA	
	TL:		
Clinical Pharmacology Comment: no Clin Pharm Information to review, no changes to the label	Reviewer:	Jeanne Fourie Zirkelbach	No
	TL:	Qi Liu	No
BioPharm	Reviewer:	Elsbeth Chikhale	Yes
	TL:	Ali Al Hakim	No
Biostatistics	Reviewer:	NA	
	TL:		
Nonclinical (Pharmacology/Toxicology)-Filable	Reviewer:	Wei Chen	Yes
	TL:	Anne Pilaro	Yes
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	NA	
	TL:		
Product Quality (CMC) Filable	Reviewer:	Haripada Sarker	Yes
	TL/BC	Sarah Pope Miksinski, Ph.D.	No
	RPM:	Debbie Mesmer	Yes
Quality Microbiology *(for sterile products)*	Reviewer:	Steven P. Donald, M.S.	No
	TL:	Bryan Riley, Ph.D.	No
CMC Labeling Review	Reviewer:		
	TL:		

Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers: OSE representative	Frances Fahnbulleh		No
Other attendees			

FILING MEETING DISCUSSION:

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

Comments: No clinical module to review. While the Applicant requested Pediatric Waiver, this 505b2 application does not trigger PREA, and request for Pediatric Waiver was not necessary.	☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: NonClinical-no labeling changes	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: Report from Haripada Sarker, consult to EA officer is not yet done until reviewers verify data in the DMF; there may not need to consult EA officer. What the reviewers verify will be in their review.	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☒ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Robert Justice, MD

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. PLR formatting issues will be placed in the letter so that the revised label will be resubmitted and ready for labeling meetings. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by

	Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

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 OND ADRA or OND IO.

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

/s/

LISA M SKARUPA
05/09/2012

Modified Regulatory Project Manager
PLR FORMAT LABELING REVIEW

Application: NDA 203551
Name of Drug: Docetaxel Injection Concentrate 20 mg/ml
Applicant: Actavis, Inc.
Labeling Reviewed: **Submission Date: March 14, 2012**
Receipt Date: March 14, 2012

The following label is the proposed docetaxel injection in the newly submitted 505b2 NDA 203551 (submitted March 14, 2012 and noted as "Revised 01/2012"). Based on revised date January 2012, the proposed label was originally compared to the last approved in December 2011 (NDA 20449 Supplement 065). Since that review, I have modified the labeling review to use the one vial label which was approved September 7, 2011, Supplement 064 (label 'Revised 09/2011').

This addendum, only holds the Applicant Actavis' proposed labeling (package insert with patient labeling, noted as 'Revised 01/2012') which was compared to the Reference Listed Drug Label –NDA 20449- Supplement 064, the one vial formulation (label 'Revised 09/2011').

The red fonts are the changes made to the Reference Listed Drug Label (NDA 20449) and would be reviewed during the labeling meetings for this newly submitted 505b2.

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

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

/s/

LISA M SKARUPA
05/02/2012

ALICE KACUBA
05/02/2012

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 203551
Name of Drug: Docetaxel Injection Concentrate 20 mg/ml
Applicant: Actavis, Inc.

Labeling Reviewed

Submission Date: March 14, 2012
Receipt Date: March 14, 2012

Background and Summary Description

Lachman Consultant Services, Inc., the Agent for Actavis, Inc., submitted a new 505(b)(2) NDA 203551 for Docetaxel on March 14, 2012. The referenced listed NDA is NDA 020449 for Taxotere® (docetaxel) Injection Concentrate. NDA 203551 differs from the reference listed drug, Taxotere by the inactive ingredients. Actavis, Inc. did not have any INDs associated with this 505(b)(2) NDA.

Background on patents and exclusivity exist for the reference listed drug Taxotere® and they affect the package insert label subsection 8.4 Pediatric Use.

Patent data (numbers 5698582 and 5714512 and 5750561) expiration dates: July 3, 2012
Patent data (numbers 5698582*PED and 5714512*PED and 5750561*PED) expiration dates: July 3, 2012

Exclusivity data leading to revisions to the labeling based on data submitted in response to pediatric written request – expiration date: May 13, 2013
and Exclusivity data -(PED) expiration date: November 13, 2013

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with an "X" in the checkbox next to the labeling requirement.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The Applicant will be requested to resubmit labeling that addresses all identified labeling deficiencies by two weeks of the date signed. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager Date

Chief, Project Management Staff Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, **only identified deficiencies should be checked**.

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

- **Product Title**
  - ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded.**
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☒ Must have the verbatim statement "***See full prescribing information for complete boxed warning.***" If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary. Applicant need only a period before the last quotation mark.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**

☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**
  - ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
  - ☐ All contraindications listed in the FPI must also be listed in HL.
  - ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
  - ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**
  - ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
  - ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**
  - ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**

- **Revision Date**
  - ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☒ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read: Applicant needs to add subsection 8.4 Pediatric Use

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.
  - ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."
  - ☒ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

Applicant has to just update this language from the old language in subsection 6.2.

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

- **Use in Specific Populations**
  - ☒ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

    Applicant did not have Subsection 8.4 Pediatric Use.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "See FDA-approved patient labeling (Medication Guide)"
    - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information)"

    Applicant needs to add words "(Patient Information)"
    - "See FDA-approved patient labeling (Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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

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

/s/

LISA M SKARUPA
04/27/2012

ALICE KACUBA
04/30/2012