CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201525Orig1s000

OTHER REVIEW(S)

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 **# 201525** BLA#	NDA Supplement #:S- BLA STN # **N/A**	Efficacy Supplement Type SE- **N/A**
Proprietary Name: N/A Established/Proper Name: **Docetaxel Injection** Dosage Form: **Injection** Strengths: **10mg/mL (20mg/2mL, 80mg/8mL, 160mg/16mL)**		
Applicant: **Sandoz Inc.** Agent for Applicant (if applicable): **N/A**		
Date of Application: **09/16/2010** Date of Receipt: **09/17/2010** Date clock started after UN: N/A		
PDUFA Goal Date: **07/17/2011**	Action Goal Date (if different):	
Filing Date: **10/27/2011**	Date of Filing Meeting: : **10/27/2011**	
Chemical Classification: (1,2,3 etc.) (original NDAs only) **1**		
Proposed indication(s)/Proposed change(s): 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 for metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable locally advanced or metastatic untreated NSCLC. Hormone Refractory Prostrate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer. Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated 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		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***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? ☐ **N/A** ***If yes, contact the Office of Combination***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system	

Products (OCP) and copy them on all Inter-Center consults	☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): **N/A**	
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**			
Are all classification properties [e.g., orphan drug, OTC, 505(b)(2)] entered into tracking system? ***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.				**N/A**
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				**N/A**
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)]?** ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		**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.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	**X**			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
N020449	Taxotere	M-61	05/13/2013
N020449	Taxotere	PED	11/13/2013
N020449	Taxotere	PED	03/28/2011

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

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		**X**		
If another product has orphan exclusivity, is the product			**X**	

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 (HFD-007)***				
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.***			**X**	
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: ☒ legible ☒ English (or translated into English) ☒ pagination	**X**			**Attachments are in PDF and not eCTD format. Not a fileability issue.**

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

☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
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, <u>both</u> the applicant and the 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**			
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**		Actual copies submitted
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	**X**			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	**X**			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for***	**X**			

Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) 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**	

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**		
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?	**X**			Waiver not required since this is a 505(b)(2) application.

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

If no, request in 74-day letter				
If a request for full waiver/partial waiver/deferral is included, does the application contain the **certification**(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	**X**			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a **pediatric Written Request**? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]			**X**	
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		**X**		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		**X**		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☒ Other (specify) **Draft Label**			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***		**X**		
Is the PI submitted in PLR format?[4]	**X**			
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**			**X**	

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

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

submitted, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?				**Pending filing decision**
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)?				**Pending filing decision**
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: CMC Micro***		**X**		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
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): June 26, 2008** ***If yes, distribute minutes before filing meeting***		**X**		**Meeting cancelled. Draft reviewer comments issued.**

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: October 27, 2010

BLA/NDA/Supp #: NDA 201525

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: **Docetaxel Injection**

DOSAGE FORM/STRENGTH: Injection/10mg/mL (20mg/2mL, 80mg/8mL, 160mg/16mL)

APPLICANT: Sandoz Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

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 for metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable locally advanced or metastatic untreated NSCLC. Hormone Refractory Prostrate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer. Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated 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.

BACKGROUND: In accordance with section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, Sandoz Inc. hereby submits an original NDA for Docetaxel Injection 10mg/mL in the following presentations: 20mg/2 mL, 80 mg/8mL and 160 mg/16mL. The reference listed drug (RLD) used for the basis for this 505(b)(2) NDA submission is Taxotere® (docetaxel) Injection Concentrate, NDA 020449 by Sanofi-Aventis.
Pre-NDA Meeting was requested and responses from the FDA were sent on June 26, 2008.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	J.Mwidau	**Y**
	CPMS/TL:	F.Cross	**Y**
Cross-Discipline Team Leader (CDTL)	S. Pope		**Y**
Clinical	Reviewer:	Q. Ryan/K. Snyder	**Y/Y**
	TL:	Cortazar	Y

Social Scientist Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Pharmacology	Reviewer:	J. Fourie Zirkelbach	**Y**
	TL/DDD:	Q. Liu/B. Booth	**N/Y**
Biostatistics	Reviewer:	L. Jun Zhang	**Y**
	TL:	S. Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	S. Khasar	**Y**
	TL:	L. Verbois	**Y**
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	S. Lin	**Y**
	TL:	H. Sarker	**Y**
Quality Microbiology *(for sterile products)*	Reviewer:	B. Riley	N
	TL:	J. McVey	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		

OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers CMC Micro			
Other attendees Dr. Murgo Angelica Dorantes	DDD Biopharmaceutics TL		**Y** **Y**

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 **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ 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 **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS	☒ Not Applicable

Comments:	☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ 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 & Biopharmaceutics) **Comments**: Biowaiver is a review issue	☐ 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**: Review issue	☐ 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

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **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: Anthony Murgo, MD, Acting Division Deputy Director

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. ☐ 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 and chemical classifications and other properties [e.g., orphan drug, OTC, 505(b)(2)], are entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct 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 (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	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.

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/s/

JAMILA MWIDAU
05/25/2011

FRANK H CROSS
05/31/2011

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

Date:	May 27, 2011
Application Type/Number:	NDA 201525
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Irene Z. Chan, PharmD, BCPS, Team Leader Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Memorandum
Drug Name and Strength:	Docetaxel Injection 20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL
Applicant:	Sandoz Inc.
OSE RCM #:	2010-2465

This memorandum evaluates the revised container labels and carton labeling received on May 24, 2011 for Sandoz's Docetaxel Injection in response to a request from the Division of Drug Oncology Products (see Appendices A and B). DMEPA finds the revised container labels and carton labeling acceptable. We have no additional comments at this time.

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

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/s/

LORETTA HOLMES
05/27/2011

IRENE Z CHAN
05/27/2011

CAROL A HOLQUIST
05/27/2011

Division of Drug Marketing, Advertisement, and Communications

Internal Consult

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

To: Jamila Mwidau, Project Manager, Division of Drug Oncology Products, (DDOP)

From: Nisha Patel, Regulatory Review Officer
Zarna Patel, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications, (DDMAC)

CC: Karen Rulli, Group II Leader, DDMAC
Amy Toscano, Group IV Leader, DDMAC

Date: April 14, 2011

Re: Comments on draft labeling (Package Insert), including patient labeling (Patient Package Insert) for Docetaxel Injection
NDA 201525

In response to your consult dated November 18, 2010, we have reviewed the draft Package Insert (PI) and Patient Package Insert (PPI) for Docetaxel, and offer the following comments. We have also taken in to consideration the labeling for Taxotere (docetaxel) Injection. DDMAC has made these comments using the version updated by FDA on April 1, 2011.

Please note that our comments have been made directly on the labeling (PI and PPI).

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/s/

NISHA J PATEL
04/14/2011

ZARNA PATEL
04/14/2011

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

Date:	April 5, 2011
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Irene Z. Chan, PharmD, BCPS, Team Leader Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name:	Docetaxel Injection 20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL
Application Type/Number:	NDA 201525
Applicant:	Sandoz Inc.
OSE RCM #:	2010-2465

1 INTRODUCTION

This review evaluates the labels and labeling for Sandoz's Docetaxel Injection submitted on September 16, 2010 for areas of vulnerability that could lead to medication errors. This review is written in response to a request from the Division of Drug Oncology Products.

1.1 REGULATORY HISTORY

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

1.2 BACKGROUND ON DOCETAXEL PRODUCTS

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

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

On March 8, 2011, a 505(b)(2) application for Docetaxel Injection, manufactured by Hospira, was approved by the FDA. The Docetaxel Injection by Hospira is also a one-vial formulation like the one-vial formulation of Taxotere. An important difference between these two products is their concentration. Taxotere's one-vial formulation is available in a concentration of 20 mg/mL, whereas Hospira's one-vial formulation of docetaxel is available in a concentration of 10 mg/mL. The reference listed drug for Hospira's product is Taxotere. Since approval, we have received complaints concerning this disparity in concentrations.

Sanofi Aventis intends to discontinue the two-vial Taxotere formulation now that a one-vial Taxotere formulation has been introduced to the market. Although the two-vial Taxotere will be discontinued, there are currently two 505(b)(2) applications pending approval, including this one, which propose a two-vial formulation of docetaxel. These two-vial formulations will yield a 10 mg/mL concentration after the initial reconstitution step which is the same as two-vial Taxotere. There is also one 505(b)(2) application pending approval that proposes a powder for injection, which differentiates it from all the other approved and pending docetaxel products.

1.3 PRODUCT INFORMATION FOR SANDOZ'S DOCETAXEL INJECTION

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

Docetaxel Injection is a one-vial formulation available in a 10 mg/mL concentration. The appropriate amount is withdrawn from the vial and can be added directly to the infusion solution.

Docetaxel Injection will be available in the following strengths: 20 mg/2 mL, 80 mg/8 mL, and 160 mg/6 mL.

This product has different excipients as compared to the RLD. Additionally, this product is ready to use whereas the RLD is provided as an active drug solution with a separate diluent that must be mixed together before it can be used to prepare the infusion solution.

2 METHODS AND MATERIALS

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

2.1 AERS SELECTION OF CASES

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

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

2.2 ISMP MEDICATION ERROR REPORT

The article "Dosing error with the new Taxotere concentration" in the March 24, 2011 issue of ISMP Medication Safety Alert[1] was reviewed

2.3 LABEL AND LABELING RISK ASSESSMENT

DMEPA uses Failure Mode and Effects Analysis (FMEA) to evaluate container labels and carton and insert labeling. This review summarizes our evaluation of the container labels, carton and insert labeling submitted by the Applicant on September 16, 2010 (see Appendices D and E).

- Container Labels: 20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL

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

- Carton Labeling: 20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL
- Insert Labeling: No image

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

3 RESULTS AND DISCUSSION

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

3.1 FDA ADVERSE EVENTS REPORTING SYSTEM (AERS) CASES

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

Potential Error (n=2)

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

Improper Dose or Wrong Technique (n=1)

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

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

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

based on previous recommendations implemented for other docetaxel products to minimize the risk of confusion.

3.2 ISMP MEDICATION ERROR REPORT

ISMP published a report dated March 24, 2011, that described a medication error in which a patient on Taxotere received twice the intended dose 100 mg/m^2 rather than the reduced dose of 50 mg/m^2. This error occurred soon after an ambulatory cancer center pharmacy began to transition from the two-vial Taxotere which yields a concentration of 10 mg/mL after initial dilution to the new one-vial Taxotere which has a 20 mg/mL concentration. The physician ordered 50 mg/m^2 and although the dose administered was 100 mg/m^2 which is within safe dosing limits, the patient suffered febrile neutropenia which necessitated hospitalization. There are a number of factors that could lead to such an error including long-time familiarity with the two-vial Taxotere formulation, confirmation bias, delays in updating computer software to reflect the new concentration, stocking of both products concurrently, calculating the dose based on the 10 mg/mL concentration but using the 20 mg/mL concentration to prepare the infusion, and lack of knowledge regarding the new concentration of Taxotere.

3.3 LABEL AND LABELING RISK ASSESSMENT

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

- The color scheme used for strength differentiation overlaps with that of one-vial Taxotere.
- There is a lack of statements that highlight and caution healthcare providers about the product concentration.
- The established name lacks prominence.
- The company logo is too prominent.

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

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

This product has a concentration of 10 mg/mL whereas one-vial Taxotere has a concentration of 20 mg/mL which is a potential source of confusion.

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

4 CONCLUSION AND RECOMMENDATIONS

Our evaluation identified areas where information on the container labels and carton labeling can be improved to minimize the potential for medication errors. Section 4.1 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

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

4.1 COMMENTS TO THE APPLICANT

A. General Comments for all Container Labels and Carton Labeling

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

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

    The colors you propose for strength differentiation of the 20 mg and 80 mg strengths are similar to those utilized for the currently marketed one-vial Taxotere. This may lead to confusion since Docetaxel Injection and one-vial Taxotere differ in concentration (10 mg/mL vs. 20 mg/mL). Another potential source of confusion is the fact that the red color for Docetaxel Injection 20 mg/2 mL is similar to that of one-vial Taxotere 80 mg/4 mL and the green color for Docetaxel Injection 80 mg/8 mL is similar to that of one-vial Taxotere 20 mg/mL. Therefore, not only could the concentrations get confused but the strengths could get confused as well which could lead to wrong dose errors. Thus, we request you choose colors for strength differentiation that do not overlap with the currently marketed one-vial Taxotere.

2. Revise the statement "For Intravenous (b) (4) Only" to read: "For Intravenous Infusion Only"

3. Add the following statements to the principal display panel: "Ready to add to infusion solution" and "Check concentration prior to preparation. See package insert for complete instructions".

4. The Sandoz name logo is too prominent on the labels and labeling. Minimize or delete the Sandoz name logo.

B. Container Labels

The established name lacks prominence. Increase the prominence of the established name.

C. Carton Labeling

1. Add a statement to the principal display panel that reads: "Check concentration prior to preparation. See package insert for complete instructions."
2. Add the concentration to the top of the principal display panel (e.g., 20 mg/2 mL (10 mg/mL), 80 mg/8 mL (10 mg/mL), or 160 mg/16 mL (10 mg/mL). See the approved Hospira one-vial Docetaxel Injection.
3. Add a banner to the top of the principal display panel that states the following: "New Concentration and Preparation". Please note this statement must be removed after six months.

APPENDICES

Appendix A: Docetaxel Injection Indications of Use and Dosage Information

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

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

Report	ISR Number
1	5316842
2	5338548
3	5403737
4	5455743
5	5490684
6	5581415
7	5621594
8	5684161
9	5744074
10	5788965
11	6082771
12	6134156
13	6221946
14	6392206
15	6607952
16	6611878
17	6673107
18	7033529
19	7092480
20	7153486
21	7206114
22	7206129
23	7206142
24	7235796
25	7241888
26	7270819
27	7355206

Appendix C: Excluded AERS Search Results

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

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

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/s/

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

IRENE Z CHAN
04/05/2011

CAROL A HOLQUIST
04/06/2011