

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207953Orig1s000**

**OTHER REVIEW(S)**

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

**PATIENT LABELING REVIEW**

Date: September 30, 2015

To: Patricia Keegan, M.D.  
Director  
**Division of Oncology Products 2 (DOP2)**

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: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Nazia Fatima, Pharm.D., MBA  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): YONDELIS (trabectedin)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: NDA 207953

Applicant: Janssen Products, LP

## 1 INTRODUCTION

On November 24, 2014, Janssen Products, LP submitted for the Agency's review an original New Drug Application (NDA) 207953 for YONDELIS (trabectedin) for injection. The proposed indication for YONDELIS (trabectedin) for injection is for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma, who have received [REDACTED] (b) (4) prior anthracycline-containing regimen.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on January 30, 2015 and January 20, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for YONDELIS (trabectedin) for injection.

## 2 MATERIAL REVIEWED

- Draft YONDELIS (trabectedin) for injection PPI received on November 24, 2014 and revised on July 31, 2015, and received by DMPP and OPDP on July 31, 2015.
- Draft YONDELIS (trabectedin) for injection Prescribing Information (PI) received on November 24, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 17, 2015.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> 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 Arial font, size 10.

In our collaborative 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 is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP 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.

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

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

/s/  
-----

SHARON R MILLS  
09/30/2015

NAZIA FATIMA  
09/30/2015

BARBARA A FULLER  
09/30/2015

LASHAWN M GRIFFITHS  
09/30/2015

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

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

**Memorandum**

**Date:** 09/29/2015

**To:** Anuja Patel, MPH  
Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products

**From:** Nazia Fatima, Pharm.D, MBA, RAC  
Regulatory Review Officer  
Office of Prescription Drug Promotion

**Subject:** Yondelis<sup>®</sup> (trabectedin) for injection  
NDA 207953

Office of Prescription Drug Promotion Comments on proposed  
labeling (PI)

---

Office of Prescription Drug Promotion (OPDP) has reviewed the package insert (PI) for trabectedin as requested in consult from Division of Oncology Products 2 (DOP2) dated January 20, 2015.

OPDP's review of the proposed PI is based on the substantially completed draft labeling titled, "draft-labeling-text-tracked-changes-word" sent via electronic mail on September 24, 2015 to OPDP from DOP2 (Anuja Patel). OPDP's comments are provided directly on the marked-up version of the label attached below. OPDP has reviewed the carton/container labeling sent via electronic mail on September 18, 2015 to OPDP from DOP2 (Anuja Patel) and has no comments at this time. Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed Patient Package Insert (PPI) will be provided under a separate cover and are based on the draft labeling titled, "FDA Response to Jansen labeling received 7.31.15 including proposed language for Section 5 and 6" sent via electronic mail on September 17, 2015 to OPDP from DOP2 (Anuja Patel).

If you have any questions please feel free to contact me, Nazia Fatima at 240-402-5041 or at [Nazia.Fatima@fda.hhs.gov](mailto:Nazia.Fatima@fda.hhs.gov). Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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

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

/s/  
-----

NAZIA FATIMA  
09/29/2015

---

## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

---

**Date of This Memorandum:** September 11, 2015  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 207953  
**Product Name and Strength:** Yondelis (trabectedin) for Injection, 1 mg/vial  
**Submission Date:** September 4, 2015  
**Applicant/Sponsor Name:** Janssen Products, LP  
**OSE RCM #:** 2014-2474-2  
**DMEPA Primary Reviewer:** Otto L. Townsend, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

---

#### 1 PURPOSE OF MEMORANDUM

DOP2 requested that we review the revised container label and carton labeling for Yondelis (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

#### 2 CONCLUSION

The revised container label and carton labeling for Yondelis is acceptable from a medication error perspective.

---

<sup>1</sup> Townsend, O. Label and Labeling Review for Yondelis (NDA 207953). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 MAR 27. 44 p. OSE RCM No.: 2014-2474.

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

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

/s/  
-----

OTTO L TOWNSEND  
09/11/2015

CHI-MING TU  
09/11/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**CLINICAL INSPECTION SUMMARY**

**DATE:** May 19, 2015

**TO:** Anuja Patel, Regulatory Health Project Manager  
Amy Barone, M.D., Medical Reviewer (Efficacy)  
Dow-Chung Chi, M.D., Medical Reviewer (Safety)  
Division of Oncology Products 2

**FROM:** Lauren Iacono-Connors, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**THROUGH:** Susan Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 207953

**APPLICANT:** Janssen Research & Development, LLC

**DRUG:** Trabectedin (Yondelis®)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Priority

**INDICATION(S):** (b) (4)

CONSULTATION REQUEST DATE:	January 27, 2015
INSPECTION SUMMARY GOAL DATE:	April 26, 2015 (Revised: May 15, 2015)
DIVISION ACTION GOAL DATE:	May 29, 2015 (Revised: TBD)
PDUFA DATE:	July 24, 2015 (Revised: October 24, 2015)

## I. BACKGROUND:

Janssen Research & Development, LLC [Janssen] seeks approval to market trabectedin (b) (4)



Trabectedin is a tris, tetrahydroisoquinoline alkaloid agent, a novel marine antineoplastic alkaloid that has been approved in the European Union and other countries outside the United States for the treatment of soft tissue sarcoma (STS) and ovarian cancer.

The key study supporting this application is Study ET743-SAR-3007. This is a randomized, open-label, active-controlled, parallel-group, multicenter study comparing the safety and efficacy of trabectedin with dacarbazine among adults (15 years of age and older at the time of screening) with unresectable, locally advanced or metastatic L-sarcoma, who were previously treated (in any order) with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and one additional cytotoxic chemotherapy regimen.

Approximately 570 subjects were to be randomized. Eligible subjects were to be randomly assigned to either the trabectedin or dacarbazine treatment groups in a 2:1 ratio. At the time of the clinical cut-off date, September 16, 2013, for the interim analysis a total of 518 subjects had been randomized (345 subjects into the trabectedin arm and 173 subjects into the dacarbazine arm). Survival status was monitored throughout the study and was used to calculate Overall Survival (OS, primary efficacy endpoint). Investigator assessment of response data was used in analyses of Progression Free Survival (PFS, secondary endpoint), Time to Progression (TTP), Objective Response Rate (ORR), and duration of response (DR).

The study was conducted at 85 clinical centers in four countries; the United States of America (75 sites); Australia (4 sites), Brazil (4 sites), and New Zealand (2 sites). The study was conducted under IND 50286.

Three clinical sites were chosen for inspection: Site 001033 (Dr. Scott Schuetze, Ann Arbor, Michigan), Site 001028 (Dr. Shreyaskumar Patel, Houston, Texas) and Site 001001 (Dr. George Demetri, Boston, Massachusetts) based on enrollment of large numbers of study subjects. The study sponsor, Janssen, was also inspected.

**II. RESULTS (by Site):**

<b>Name of CI or Sponsor/CRO, Location</b>	<b>Protocol #, Site #, and # of Subjects</b>	<b>Inspection Date</b>	<b>Final Classification</b>
<b>CI#1:</b> Schuetze, Scott University of Michigan C342 Med Inn Building, SPC 5848 1500 E. Medical Center Drive Ann Arbor, MI 48109	Protocol: ET743-SAR-3007  Site Number: 001033  Number of Subjects: 24	March 9-20, 2015	Pending  Interim classification: VAI
<b>CI#2:</b> Patel, Shreyaskumar The University of Texas – M.D. Anderson Cancer Center 1515 Holcombe Boulevard - Unit 450 Houston, TX 77030	Protocol: ET743-SAR-3007  Site Number: 001028  Number of Subjects: 40	March 23- April 2, 2015	Pending  Interim classification: VAI
<b>CI#3:</b> Demetri, George (Study Coordinating Investigator)  Brigham and Womens Hospital 75 Francis St., Boston, MA 02115  Dana Farber Cancer Institute (DFCI) 450 Brookline Ave., D1212 Boston, MA, 02115  Massachusetts General Hospital 55 Fruit St., Boston, MA 02114	Protocol: ET743-SAR-3007  Site Number: 001001  Number of Subjects: 30	March 30- April 2, 2015	NAI
<b>Sponsor:</b> Janssen Research & Development, LLC 920 Route 202 Raritan, NJ 08869	Protocol: ET743-SAR-3007  Site Numbers: 001033, 001028, 001001, 001008 and 001013	March 16-26, 2015	Pending  Interim classification: VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

**1. CI#1: Dr. Scott Schuetze (Site 001033)**

- a. What was inspected:** The site screened 28 subjects, and 26 subjects were enrolled. At the time of the inspection 22 subjects had completed the study. The study records of all 28 subjects were audited. Areas covered during the inspection include principal investigator oversight, conduct of the study, study recruitment, informed consent, Form FDA 1572/investigator agreements, financial disclosure compliance, subject screening and enrollment, clinical monitoring, source documents, drug accountability, review of the eCRF, safety and primary efficacy endpoint data, IRB correspondence and approval, and correspondence between the sponsor and site.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint of overall survival was verifiable. Subjects that did not withdraw consent to be followed were followed per protocol until death. The secondary endpoint of time to progression was also verifiable as long as the subject remained on study treatment, and was not removed from study treatment due to toxicity. There was no evidence of under-reporting AEs or SAEs. AEs, SAEs, and protocol deviations were reported to both the sponsor and the IRB for this investigational site. Records were maintained in an orderly fashion with all study activity identified by treatment cycle. No major deficiencies were noted during this inspection. A Form FDA 483 was issued citing 1 minor inspectional observation for failure to follow the investigational plan.

**Observation 1.** An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

Subjects 40, 62, 180, and 183 were enrolled into clinical study ET743-SAR-3007 and were randomized to study medication prior to the Clinical Investigator or Sub-Investigator completing the subject eligibility confirmation process.

*OSI Reviewer Notes: Based upon the site 001033 inspectional findings, the four subjects cited in the Form FDA 483 were randomized prior to the site responsible staff (in this case either the CI or sub-investigators) reviewing and signing off on the screening results, such as screening labs. In all cases the FDA field investigator confirmed that each subject did in fact satisfy all entry criteria. This inspection observation should not affect study data generated by this site. Dr. Schuetze understood the observation and promised corrective actions to mitigate this study-specific procedural deviation moving forward both during the inspection and in his written response, dated April 6, 2015.*

- c. Assessment of data integrity:** The data for Dr. Schuetze's site, associated with Study ET743-SAR-3007 submitted to the Agency in support of NDA 207953, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

**2. CI#2: Dr. Shreyaskumar Patel (Site 001028)**

- a. What was inspected:** The site screened forty subjects, and forty subjects were enrolled. Thirty eight subjects were treated with study drug. Study records of thirteen subjects were audited. The record audit included comparison of source documentation to eCRFs and data listings submitted to NDA 207953, focusing on protocol compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The primary efficacy endpoints, as determined by the investigator, were verified. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no major discrepancies. There were instances of protocol deviations and record keeping deficiencies. A Form FDA 483 Inspectional Observations was issued citing two inspection observations.

**Observation 1.** An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

1. The sponsor's subject screening log and subject identification and enrollment log for Study Protocol ET743-SAR-3007 were not completed in that you failed to include the reasons for screen failures, specifically for Subjects 402, and 173, along with your authorized signature.
2. a CRF was not assigned for Subject 173; however, this subject had an AE for thrombosis in the inferior vena cava that was found at screening; after the patient signed the consent form.
3. Subjects 149, 163, 174, 224, 460, 548, 567, and 597, who were in the dacarbazine treatment group, were pre-treated with dexamethasone 10mg intravenously prior to infusion of dacarbazine. However, the use of dexamethasone was not recorded on the site's medication record for research protocol or on these subjects' CRFs as concomitant medication/therapy.

4. Protocol ET743-SAR-3007 specifies that subjects in the Trabectedin group must be pre-treated with 20 mg of dexamethasone intravenously 30 minutes prior to each infusion of study drug. However, pre-treatment with dexamethasone within the 30 minute timeframe was not always done. For example,
  - a. Subject 611 did not receive dexamethasone within 30 minutes of trabectedin treatment at cycles 1-4;
    - i. Cycle 1 (August 23, 2013). According to this subject's eCRF, Dexamethasone was infused at 16:45, yet the Trabectedin start time for administration was not until 18:00; 45 minutes out of window.
    - ii. Cycle 2 (September 13, 2013). According to this subject's eCRF, Dexamethasone was infused at 17:25, yet the Trabectedin start time for administration was not until 18:25; 30 minutes out of window.
    - iii. Cycle 3 (October 4, 2013). According to this subject's eCRF, Dexamethasone was infused at 11:15, yet the Trabectedin start time for administration was not until 12:30; 45 minutes out of window.
    - iv. Cycle 4 (October 25, 2013). According to this subject's eCRF, Dexamethasone was infused at 14:40, yet the Trabectedin start time for administration was not until 15:35; 25 minutes out of window.
  - b. Subject 85 did not receive dexamethasone within 30 minutes of infusion of study drug on May 9, 2012 (Cycle 5). According to this subject's eCRF, Dexamethasone was infused at 11:55, yet the Trabectedin start time for administration was not until 13:55; 90 minutes out of window.
  - c. Subject 139 did not receive dexamethasone with 30 minutes of infusion of study drug on April 19, 2012 (Cycle 1). According to this subject's eCRF, Dexamethasone was infused at 20:45, yet the Trabectedin start time for administration was not until 21:00; 45 minutes out of window.

**Observation 2.** Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically,

1. The site did not assess and capture all adverse events on AE forms for the following subjects in Study ET743-SAR-3007.
  - a. Subject 106 is missing AE information for elevation of cardiac enzymes, hypertension, shortness of breath, cough, and wheezing.

*OSI reviewer notes: In Dr. Patel's written response dated April 20, 2015, he stated that he agreed with the inspection observation but explained that the*

*protocol specifies that, “All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., Cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). In this instance Dr. Patel felt that the symptoms of shortness of breath, coughing, and wheezing, were all signs and symptoms due to a common etiology of acute renal failure, and as such were reported as acute kidney injury. He provided the AE form for Subject 106, dated April 17, 2012, as evidence.*

*Further, this subject’s elevated cardiac enzymes were initially noted on April 18, 2012. Dr. Patel felt that the cardiac enzyme elevation was considered to be secondary to rhabdomyolysis, and this was noted in the clinic notes dated April 19, 2012 (provided with Dr. Patel’s written response). Rhabdomyolysis was reported on the subject’s AE form with a start date of April 17, 2012, because Dr. Patel felt that the acute renal failure was likely due to rhabdomyolysis.*

*The AE form showing report of rhabdomyolysis was provided with Dr. Patel’s written response. The acute renal failure and rhabdomyolysis were properly reported as serious adverse events.*

- b. Subject 600 is missing AE information for fatigue and headache.

*OSI reviewer notes: Dr. Patel stated in his written response that this subject’s AEs were recorded however he acknowledges that the start dates for these AEs were earlier than that documented after he reviewed the clinic notes. Briefly, the AE section of the Subject’s eCRF listed fatigue and headaches recorded with start dates of October 8, 2013, and October 14, 2013, respectively. A review of this subject’s clinic notes (provided with the written response from Dr. Patel), the subject reported feeling mildly fatigued on September 10, 2013. Dr. Patel acknowledged that the start date for fatigue as recorded on the AE form should have been September 10, 2013, instead of October 8, 2013. Also, the start date for headaches should have been recorded as October 13, 2013, not October 14, 2013, based upon the clinic notes (provided with the written response from Dr. Patel).*

2. The site did not record all concomitant medications on the AE record/CRFs for the following ET743-SAR 3007 study subjects:
  - a. The eCRF for Subject 581 is missing administration of vancomycin on 7/25/13;
  - b. The eCRF for Subject 600 is missing administration of Neupogen on 8/14/13; and
  - c. The eCRF for Subject 47 is missing marijuana usage.

*OSI reviewer notes: Dr. Patel provided a comprehensive written response to these inspection observations dated April 20, 2015. Briefly, he concurs with the observations and provided a robust corrective action plan that includes correction of study subject records as appropriate, development of standard operating procedures and planned periodic training for all study staff that should mitigate GCP compliance deviations moving forward.*

*Albeit these observations are GCP violations, they should not importantly impact overall study data generated by this site. Based upon the FDA field investigators preliminary communication and the written response from Dr. Patel, subjects were well managed and were not at undue risk during the conduct of the study at this site.*

- c. Assessment of data integrity:** Notwithstanding the inspection observations noted, the data for Dr. Patel' site, associated with Study ET743-SAR-3007 submitted to the Agency in support of NDA 207953, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- 3. CI#3: Dr. George Demetri (Site 001001):** Dana Farber Cancer Institute (DFCI) is considered the Lead Site for subjects enrolled at DFCI and Massachusetts General Hospital (MGH); subjects were not enrolled at Brigham and Women's Hospital.

- a. What was inspected:** The site screened thirty six subjects, thirty two subjects were enrolled, and thirty received investigational product. All subject study records were audited for informed consent, overall response and primary efficacy endpoint. Half of the subjects enrolled were audited for eligibility and protocol adherence. The record audit included comparison of source documentation to eCRFs and data listings submitted to the original NDA 207953, focusing on protocol compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary efficacy endpoint data were verified. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no major discrepancies. Investigational drug accountability records were sufficient to reconcile the quantity received, dispensed, and destroyed/returned. A Form FDA 483 was not issued.

- c. Assessment of data integrity:** The data for Dr. Demetri's site, associated with Study ET743-SAR-3007 submitted to the Agency in support of NDA 207953, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

#### **4. Sponsor: Janssen Research & Development, LLC**

- a. What was inspected:** The inspection focused on study Sites 001033, 001028 and 001001, and two additional randomly selected study Sites 001008 and 001013. The inspection included but was not limited to assessment of adverse events/serious adverse events reporting, and of the retrospective audit of a subset (60%) of subjects' tumor response by radiographic PFS (rPFS) as determined by blinded, independent radiologists in accordance with an Independent Review Charter. The primary efficacy endpoint of overall survival was also confirmed for the five study sites audited. The study oversight program included an Independent Data Monitoring Committee functioning under Charter. IDMC meeting minutes and suitability of IDMC members were reviewed. Principal Investigator site qualification (financial disclosure, IRB, and curriculum vitae), study specific training for investigators and monitors, Form FDA 1572 and investigator agreements and monitoring reports and sponsor actions as a result of monitoring reports were assessed. Finally, investigational product chain of custody and product quality, from bulk source to clinical study sites, was reviewed and the process verified.

- b. General observations/commentary:** Records and procedures were clear, and generally well organized. The sponsor maintained adequate oversight over the study. Monitoring appeared to be adequate. AEs were audited from the eCRF and compared with the datalistings submitted to the application based upon the interim analysis data cut-off date of September 16, 2013. There was evidence of under-reporting AEs/SAEs by the sponsor in the original application. For example, Subject 288 (Site 001013) had a number of AEs recorded in the eCRF and included in the datalistings submitted to the application. Datalistings show an SAE of esophageal pain on January 17, 2013, and anorexia (b) (6) with hospitalization, thrush, and failure to thrive. Hospitalization occurred (b) (6). An AE of fever was also captured during this timeframe. However, Subject 288 had numerous AEs recorded in the eCRF that occurred (b) (6) but are not included in the datalistings submitted in the application. Examples include the following: Grade 3 anemia, Esophageal Tracheal Fistula, Esophageal perforation, and gram positive bacteremia, and lower back pain. In addition, Subject 288 was hospitalized (b) (6) (Hospitalized for (b) (6) days).

None of these AEs/SAEs were submitted to the application. When queried, the firm indicated that this was likely due to late data point entries into the eCRF for this subject.

A Review of site-specific monitoring reports revealed, specifically for Site 001013, that there was a significant lag between the times a study AE occurred and the time that the AE data were entered into the eCRF by study site staff. The monitor found and recorded in their monitoring visit reports that the site was falling behind on data entry and as such eCRFs were not “current”. This was deficiency was noted during numerous monitoring interim visits. The monitor repeatedly requested that the site catch up on data entry. In some cases, in particular Site 001013, these data entry deficiencies resulted in missing safety information at the time of the IA data cut off September 16, 2013. As such, these safety events did not make it into the original Application submission.

The primary efficacy endpoint data were verifiable; specifically, subject eCRFs were compared with datalistings submitted to the application. No discrepancies were noted. Compliance with the study protocol, the sponsor’s own SOPs and relevant regulatory requirements appeared to be adequate. No study sites were closed due to non-compliance. Monitoring reports showed the monitors informed the study sites of any issues and provided re-training where necessary. A Form FDA 483 was issued citing two inspection observations.

**Observation 1.** Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND.

Specifically, for one out of five clinical sites reviewed, Principal Investigator failed to update the electronic case report form within 10 days of the subject's visit as required by investigator agreement.

For example, Subject 288, adverse events were not entered into the eCRF within 10 days of the subject's visit.

Furthermore, the adverse events were not included in the interim analysis of safety and efficacy data included in the Clinical Study Report submitted to the application for marketing approval of the investigational product.

*OSI reviewer notes: The eCRF for Subject 288, and the corresponding datalistings submitted to the original application (NDA 207953), show that the subject had numerous SAEs and corresponding hospitalization that occurred (b) (6). However, a number of SAEs recorded in the eCRF for Subject 288 that occurred (b) (6) were not included in the datalistings submitted in the application. Examples include the following AEs: Grade 3 anemia (start date (b) (6)), Esophageal Tracheal Fistula*

(start date, (b) (6)), Esophageal perforation (start date (b) (6)), gram positive bacteremia (start date, (b) (6)), and lower back pain (start date, (b) (6)). Yet, none of these AEs/SAEs were included in the application. Subject 288 next study visit was February 26, 2013 when the subject's study treatment was discontinued.

Review of the audit trail for the AE entries into the eCRF for Subject 288 revealed that while the AEs occurred during the timeframe specified above, the AEs were not entered into the eCRF until July 2014. Specifically, Grade 3 anemia (start date (b) (6)) was not entered into the eCRF until February 24, 2014, Esophageal Tracheal Fistula (start date, (b) (6)) was not entered into the eCRF until January 28, 2014, Esophageal perforation (start date (b) (6)) was not entered into the eCRF until January 7, 2014, gram positive bacteremia (start date, (b) (6)) was not entered into the eCRF until January 8, 2014, and lower back pain (start date, (b) (6)) was not entered into the eCRF until January 28, 2014.

When queried during the inspection, the firm indicated that this was likely due to late data point entries into the eCRF for this subject. However, this lag between the adverse event start occurrence and the date that the site entered the information into the eCRF was not in compliance with the protocol and in this specific instance also resulted in SAEs that occurred prior to the interim analysis cut-off date not being included in the safety datasets submitted to the FDA for their marketing application. Review of the Site 001013 clinical monitoring reports found that it was clear that the site was falling behind in data entry. Therefore, the firm was aware of the site study performance deficiency prior to the interim analysis data cut-off date.

During the inspection Janssen informed that a prespecified 4-month safety update was planned to be submitted to NDA 207953 on March 24, 2015, based upon a new safety data cut-off date of July 10, 2014. Janssen stated that the update would remedy the missing safety information for this site.

During the inspection the FDA auditors reviewed the safety data set updates for the 4-month safety update planned for submission to the application on or about March 24th, 2015, for the 5 Sites audited during this inspection. With only a minor exception the new safety dataset accurately reflects all AEs reported in eCRFs that occurred prior to the new cut-off date of July 10, 2014. Therefore, the updated safety data appear reliable based upon available information for the five sites audited.

OSI reviewer, Lauren Iacono-Connors, communicated these preliminary findings regarding the initial and 4-month updated safety dataset integrity concerns to the DOP2 CDTL, Marc Theoret, and the Medical Officer (safety), Dow-Chung Chi, on March 27, 2015. While the preliminary inspectional findings of the Janssen inspection is VAI, OSI recommended that the review

*division may wish to pursue these preliminary findings and the extent of safety data integrity across all study sites with Janssen. Subsequently, a telecom was held between DOP2/OSI and the firm, Janssen, on March 30<sup>th</sup>, 2015, to initiate a resolution to the preliminary inspection observations and the potential impact on the integrity and reliability of the safety datasets in the application. In response to subsequent DOP2 information requests, Janssen submitted application amendments on April 17 and 27, 2015. On May 1, 2015, DOP2 issued a review extension-major amendment letter to Janssen for this application.*

**Observation 2.** Failure to ensure proper monitoring of the study.

Electronic records are used, but they do not meet electronic and human readable copy and audit trail requirements to ensure that they are trustworthy, reliable and generally equivalent to paper records.

Specifically, the electronic monitoring reports are not adequate in that:

1. The audit trail fails to capture changes to the monitoring reports for all sites.
2. The monitoring reports are not generally equivalent to the paper records in that changes cannot be seen or detected in the monitoring report.

*OSI Reviewer Notes: The firm acknowledged the observation during the inspection and committed to assessing internal monitoring visit report procedures to ensure transparency between draft and final MVRs.*

- c. Assessment of data integrity:** Notwithstanding the inspection observations noted above, the data from this sponsor submitted to the Agency associated with Study ET743-SAR-3007 in support of NDA 207953 appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

### **III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

Based on the review of preliminary inspectional findings for Site 001033 (Dr. Scott Schuetze), Site 001028 (Dr. Shreyaskumar Patel), Site 001001 (Dr. George Demetri) and the study sponsor, Janssen Research & Development, LLC, the Study ET743-SAR-3007 data submitted to the Agency in support of NDA 207953 appear reliable based on available information.

With respect to Dr. Schuetze's site, only very minor procedural deficiencies were noted during this inspection. These observations should not importantly impact overall study outcome. With respect to the inspectional findings at Dr. Patel's site, the inspection found only minor record keeping issues. There were several instances noted where adverse events were either not reported to the sponsor or misreported. These AEs found during this inspection represent a small proportion of all AEs reported for this site. These observations appear to be isolated and non-systemic for this site and should not importantly impact overall study outcome for safety.

With respect to the study sponsor Janssen, Subject 288 (Site 001013) had numerous AEs recorded in the eCRF that occurred [REDACTED] (b) (6) [REDACTED] but are not included in the datalistings submitted in the original application. When queried during the inspection, the firm indicated that this was likely due to late data point entries into the eCRF for this subject. A Review of site-specific monitoring reports revealed specifically for Site 001013 that there was significant lag between the time the study AE occurred and the time that data were entered into the eCRF by study site staff. The monitor found and recorded in their monitoring visit reports that the site was falling behind on data entry and as such eCRFs were not "current".

During the inspection the FDA auditors reviewed the safety data set updates for the 4-month safety update planned for submission to the application on or about March 24th, 2015, for the 5 Sites audited during this inspection. With only a minor exception the new safety dataset accurately reflects all AEs reported in eCRFs that occurred prior to the new cut-off date of July 10, 2014. Therefore, the updated safety data appear reliable based upon available information for the five sites audited.

These preliminary inspection observations for Janssen were communicated to DOP2 CDTL Marc Theoret et. al., on March 27, 2015. Subsequently, a telecom was held between DOP2/OSI and the firm, Janssen, on March 30th, 2015, to initiate a resolution to the preliminary inspection observations and the potential impact on the integrity of the safety datasets for all study sites in the application. In response to subsequent DOP2 information requests, Janssen submitted application amendments on April 17 and 27, 2015.

**Note:** Certain observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{ See appended electronic signature page }

Lauren Iacono-Connors, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Susan D. Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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

/s/  
-----

LAUREN C IACONO-CONNORS  
05/19/2015

SUSAN D THOMPSON  
05/26/2015

KASSA AYALEW  
05/26/2015

---

## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

---

**Date of This Memorandum:** May 6, 2015  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 207953  
**Product Name and Strength:** Yondelis (trabectedin) for Injection, 1 mg/vial  
**Submission Date:** November 24, 2014 and February 27, 2015  
**Applicant/Sponsor Name:** Janssen Products, LP  
**OSE RCM #:** 2014-2474-1  
**DMEPA Primary Reviewer:** Otto L. Townsend, PharmD  
**Associate Director:** Lubna Merchant, M.S., PharmD

---

#### 1 PURPOSE OF MEMORANDUM

During labeling meetings for Yondelis (trabectedin) we learned that this product appears to promote (b) (4) growth. To address this risk to patients, the review team plans to recommend the use of a 0.2 micron in-line filter during the 24-hour infusion of Yondelis. This memorandum is written to provide recommendations to further stress the importance of following strict aseptic technique during preparation of Yondelis and to strengthen language requiring the use of an in-line filter during administration of Yondelis. The revisions are in addition to recommendations that we made during a previous label and labeling review.<sup>1</sup>

#### 2 CONCLUSIONS

To address the risk of microbial contamination, the Prescribing Information for Yondelis could be improved to promote the safe use of the product. We recommend the following:

---

<sup>1</sup> Townsend, O. Label and Labeling Review for Yondelis (trabectedin) (NDA 207953). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 MAR 27. 45 p. OSE RCM No.: 2014-2474.

- A. Place greater emphasis on the importance of following strict aseptic technique (b) (4) language below is consistent with instructions in the labeling of Blincyto which shares the same risk of bacterial contamination<sup>2</sup>:

**Aseptic Preparation**

Aseptic technique must be strictly observed when preparing (b) (4) To prevent accidental contamination, prepare (b) (4) according to aseptic standards, including but not limited to:

- Preparation must be done in a USP <797> compliant facility.
- Preparation must be done in an ISO Class 5 laminar flow hood or better.
- The admixing area should have appropriate environmental specifications, confirmed by periodic monitoring.
- Personnel should be appropriately trained in aseptic manipulations and admixing of oncology drugs.
- Gloves and surfaces should be disinfected.

- B. To minimize this risk of contamination, the in-line filter and intravenous tubing should be attached under the aseptic conditions described above. This recommendation is also consistent with instructions in labeling for Blincyto. Therefore, under Section 2.4: Preparation for Administration, change the following statement,

(b) (4)

to

(b) (4)

---

<sup>2</sup> Amgen, Inc. Blincyto (blinatumomab) for injection. 2014 [cited 2015 Apr]. In: DailyMed [Internet]. [2015]. [20 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=38b482a8-960b-4591-9857-5031ecb830aa>

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

/s/  
-----

OTTO L TOWNSEND  
05/06/2015

LUBNA A MERCHANT  
05/06/2015



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

---

Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Review**

**Date:** April 21, 2015

**From:** Carrie Ceresa, Pharm D, MPH  
Clinical Analyst, Maternal Health Team  
Pediatric and Maternal Health Staff

**Through:** Tamara Johnson, M.D., M.S.  
Acting Team Leader, Maternal Health Team  
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Acting Division Director,  
Division of Pediatric and Maternal Health

**To:** The Division of Oncology Products 2 (DOP2)

**Drug:** YONDELIS (trabectedin) for injection

**NDA:** 207953

**Subject:** Maternal Health Labeling Recommendations

**Applicant** Janssen Products

**Materials Reviewed:**

- November 24, 2014, NME NDA– Original Priority submission from Janssen
- August 9, 2009, DPMH (formerly PMHS) review for NDA (b) (4)
- July 31, 2009, Pharmacology/Toxicology DOP1 review for NDA (b) (4)

**Consult Question:** DOP 2 requests assistance to apply the new Pregnancy and Lactation Labeling Rule requirements to the YONDELIS labeling.

## INTRODUCTION

On November 24, 2014, Janssen Products, LP submitted NDA 207953 for YONDELIS (trabectedin) injection

(b) (4)

DOP2 consulted DPMH to review and update the Pregnancy, Lactation, and Females and Males of Reproductive Potential information in the YONDELIS labeling.

This review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

## BACKGROUND

### Product Background

Trabectedin is an alkylating drug that is composed of three fused tetrahydroisoquinoline ring systems. Although the exact mechanism is unknown it is believed that trabectedin stimulates the transcription-coupled nucleotide excision repair system to direct the proteasome-dependent degradation of RNA polymerase II. Trabectedin has been shown to be cytotoxic to a variety of tumor cell lines, including those derived from ovarian cancers in cell culture and xenograft experiments.<sup>1</sup>

Alkylating agents work by inhibiting DNA transcription and prohibiting protein synthesis. The most predominant toxicities have been demonstrated to the bone marrow and gastrointestinal tract.<sup>2</sup> Alkylating agents, such as cyclophosphamide and chlorambucil, decrease the rate of cell proliferation, and it is believed that alkylating agents pose a threat to the rapidly dividing cells of the embryo and fetus. In addition, these agents have shown chromosomal alterations in humans and have shown teratogenicity in animal models. Alkylating agents may also have adverse effects on gonadal function (i.e., suppression of ovarian function, oligospermia, azoospermia).<sup>3</sup>

### Pregnancy and Lactation Labeling Rule (PLLR)

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”<sup>4</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and

<sup>1</sup> July 31, 2009, Pharmacology/Toxicology DOP1 review for NDA (b) (4)

<sup>2</sup> Alkylating Agents. National Library of Medicine. [livertox.nih.gov/AlkylatingAgents.htm](http://livertox.nih.gov/AlkylatingAgents.htm). Accessed 13 April 2015.

<sup>3</sup> Glantz, J. (1994). Reproductive Toxicology of Alkylating Agents. *Obstetrical and Gynecological Survey*, 49(10), 709-715.

<sup>4</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>5</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR will officially take effect on June 30, 2015. In the meantime, conversion to the PLLR format is voluntary. The recommendations in this review are consistent with the PLLR format.

## **DISCUSSION**

### **Review of Data**

#### **Pregnancy**

A search of published literature was performed and no data were found reporting the use of YONDELIS in pregnant women. The applicant reported one pregnancy in post-marketing data with trabectedin exposure. A 22 year-old female received trabectedin for treatment of osteosarcoma as a 24-hour infusion every three weeks under compassionate use. The estimated fetal exposure period and gestational age the fetus was first exposed was not available in the submission. Trabectedin was discontinued after four cycles and the pregnancy was terminated at 20 weeks gestation. Fetal pathology was normal upon autopsy.<sup>6</sup>

*Reviewer comment: No trabectedin-associated risk can be determined from this single case report; however, alkylating agents such as trabectedin have shown cytotoxicity and genotoxicity in published literature.*

According to Glantz, et al. 1994, malformations characteristic to alkylating agents involve the central nervous system, vertebra and ribs, urogenital tract, face and limbs. In addition, the severity of the malformation depends strongly on the time and dose of the exposure and inclusion of other chemotherapeutic agents. Moreover, the risk of fetal anomalies is greatly increased when exposure occurs during the first trimester, however, growth retardation has been observed during all trimesters.<sup>3</sup>

In animal reproduction studies conducted in rats and rabbits, trabectedin was not teratogenic at the highest doses tested (0.015 mg/m<sup>2</sup> /day in the rat and 0.024 mg/ m<sup>2</sup> /day in the rabbit) when administered during organogenesis. Because of dose-limiting maternal toxicity, these dosages are approximately 46- to 73-fold lower than the clinical dose of 1.1 mg/m<sup>2</sup> based on body surface area. Maternal body weight and food consumption were decreased in the rat and rabbit. Although maternal toxicity was observed, there were no effects on embryofetal survival or the incidence of malformations in either species.<sup>1</sup> However, animal reproduction studies in other alkylating agents have shown teratogenicity.<sup>3</sup>

---

<sup>5</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

<sup>6</sup> NDA 207953 original submission. Module 2.7.4 Summary of Clinical Safety.

## **Lactation**

The Drugs and Lactation Database (LactMed)<sup>7</sup> was searched for available lactation data with the use of YONDELIS, and no information was located. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

There are no animal data on the use of trabectedin and milk; however, breastfeeding is generally contraindicated in patients exposed to cytotoxic agents such as trabectedin because of the possibility of genotoxicity.<sup>8</sup>

## **Females and Males of Reproductive Potential**

### *Infertility*

There are no human data available regarding the effects of trabectedin on fertility. No fertility or early embryonic development studies were conducted.

### *Contraception*

DPMH recommends an additional 5 drug half-lives for contraception use after completion of treatment because drugs are generally eliminated from the body between 4 and 5 half-lives. However, DOP's general policy is to use 6 drug half-lives for contraception recommendations. The terminal phase half-life of trabectedin is approximately 175 hours; therefore, the drug should be eliminated in approximately six weeks. DOP's policy is to recommend females of reproductive potential use contraception for 2 months after last dose (rounded up from 6 weeks for simplicity). In addition, DOP2 recommends males with female partners use contraception for 5 months (rounding up from 4.5 for simplicity) after the last dose of drug which includes 6 half-lives and 1 spermatogenesis cycle.

*Reviewer comment: Although our recommendations slightly differ from those of DOP2, we understand that this is a long-standing policy and we do not have strong objections to it.*

## **CONCLUSION**

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling were structured to be consistent with the PLLR. Because the applicant has voluntarily complied with the PLLR requirements prior to the June 30, 2015 effective date, language waiving the current labeling requirements should be included in the approval letter. The following approval letter language is suggested.

---

<sup>7</sup> United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

<sup>8</sup> Pistilli, B., Bellettini, G., Giovannetti, E., Codacci-Pisanelli, G., Azim, H., Benedetti, G., et al. (2013). Chemotherapy, targeted agents, antiemetics and growth-factors in human milk: How should we counsel cancer patients about breastfeeding? *Cancer Treatment Reviews*, 39, 207-211.

## “WAIVER OF PREGNANCY, LABOR AND DELIVERY, AND NURSING MOTHERS SUBSECTIONS

We are waiving the current requirements of 21CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), regarding the content and format of labeling for subsections 8.1 Pregnancy, 8.2 Labor and Delivery, and 8.3 Nursing Mothers of prescribing information. Your approved labeling for subsections 8.1, 8.2, and 8.3 reflects the content and format requirements of the Pregnancy and Lactation Labeling Rule (79 FR 72063, December 4, 2014) which implements on June 30, 2015.”

DPMH refers to the NDA action for final labeling. The sponsors draft labeling recommendation can be found in Appendix A.

### DPMH LABELING RECOMMENDATIONS HIGHLIGHTS

#### -----WARNINGS AND PRECAUTIONS-----

- Embryo-Fetal Toxicity: Can cause fetal harm. Advise (b) (4) of potential risk to a fetus and to use effective contraception. ( (b) (4), 8.1, 8.3)

## 5 WARNINGS AND PRECAUTIONS

### (b) (4) Embryo-Fetal Toxicity

Based on its mechanism of action, YONDELIS can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during therapy and for at least 2 months after the last dose of YONDELIS. Advise males with female partners of reproductive potential to use effective contraception during therapy and for at least 5 months after the last dose of YONDELIS[see Use in Specific Populations (8.1, 8.3)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk summary

Based on its mechanism of action, trabectedin can cause fetal harm when administered during pregnancy[see *Clinical Pharmacology (12.1)*]. There are no available data with the use of trabectedin during pregnancy. (b) (4)

(b) (4) Animal reproductive and developmental studies at relevant doses have not been conducted with trabectedin; however, placental transfer of trabectedin was demonstrated in pregnant rats. Advise pregnant woman of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population are unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

## 8.2 Lactation

### Risk Summary

There are no data on the presence of trabectedin in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions from YONDELIS in breastfed infants, advise a nursing woman to discontinue nursing during treatment with YONDELIS.

## 8.3 Females and Males of Reproductive Potential

### Contraception

#### *Females*

Advise female patients of reproductive potential to use effective contraception during and for 2 months after the last dose of YONDELIS [see Use in Specific Populations (8.1)].

#### *Males*

YONDELIS may damage spermatozoa, resulting in possible genetic and fetal abnormalities. Advise males with a female sexual partner of reproductive potential to use effective contraception during and for 5 months after the last dose of YONDELIS [see Nonclinical Toxicology (13.1)].

#### *Infertility*

YONDELIS may result in decreased fertility in males and females [see Nonclinical Toxicology (13.1)].

## 17 PATIENT COUNSELING INFORMATION

(b) (4)

## APPENDIX A - Janssen Labeling Recommendations

### 5<sup>(b)</sup><sub>(4)</sub> Embryofetal Toxicity

(b) (4)

(b) (4)

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

(b) (4)

### **8.2 Lactation**

#### Risk Summary

(b) (4)

### **8.3 Females and Males of Reproductive Potential**

#### Contraception

(b) (4)

Infertility

[REDACTED]

(b) (4)

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

/s/  
-----

CARRIE M CERESA  
04/21/2015

TAMARA N JOHNSON  
04/22/2015

LYNNE P YAO  
04/22/2015

---

**LABEL AND LABELING REVIEW**

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

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

---

**Date of This Review:** March 27, 2015  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 207953  
**Product Name and Strength:** Yondelis (trabectedin) for Injection, 1mg/vial  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Janssen Products, LP  
**Submission Date:** November 24, 2014 and February 27, 2015  
**OSE RCM #:** 2014-2474  
**DMEPA Primary Reviewer:** Otto L. Townsend, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

---

## 1 REASON FOR REVIEW

Janssen submitted proposed container label, carton labeling, and Prescribing Information (PI) with the original NDA. As part of the NDA review, we are assessing the submitted materials for areas of vulnerability that could lead to medication errors.

## 2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified the following areas of vulnerability that could lead to medication errors:

- The container label and carton labeling contain a prominent graphic that competes with the proprietary name and has the potential to be confused as part of the proprietary name.
- The container label and carton labeling do not appropriately designate the dosage form and product strength.
- Passive voice is used on carton labeling.
- To read important safety information on the container label, the user must rotate the vial.
- Sections 2 and 16 of the Prescribing Information (PI) could be improved.

## 4 CONCLUSION & RECOMMENDATIONS

The proposed container label, carton labeling, and PI can be improved to increase readability and prominence of important information, to promote the safe use of the product, and to clarify information.

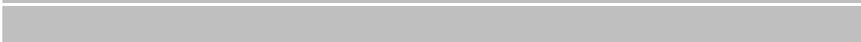
#### 4.1 RECOMMENDATIONS FOR THE DIVISION

- A. Please see Appendix H for our recommendations related to Sections 2 and 16 of the PI. We have added recommendations as comments to the version of the PI with Applicant's tracked changes that was submitted on February 27, 2015 in response to the Filing Communication issued by DOP2 on February 5, 2015.
  
- B. We note that this proposed product is supplied as a sterile lyophilized powder. We defer to CMC for determination of the appropriate dosage form (e.g. for Injection).

#### 4.2 RECOMMENDATIONS FOR THE JANSSEN

We recommend the following be implemented prior to approval of this NDA:

##### A. CARTON LABELING

1.  (b) (4)  
 The graphic  (b) (4)  
  
 looks like the letter, "Y,"  (b) (4)  
 We recommend deletion of this interfering graphic, or that it be decreased in its size and be relocated.
  
2. Since the proposed product is a dry powder, express the strength in terms of the total amount of drug per vial as follows:<sup>1</sup>  
XX mg/vial or XX mg per vial
  
3. Current labeling on the principal display panel (PDP) contains the following  (b) (4)  
  
 Change the statement to, "Reconstitute before further dilution." and relocate this statement such that it is immediately before the statement, "For Intravenous Infusion Only".

---

<sup>1</sup> Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

## B. CONTAINER LABEL

1. See comment A.1.
2. See comment A.2.
3. To better organize information on the container label and to limit the need to rotate the vial when reading important safety information, consider the following:
  - a) Change the orientation of the statements, “Cytotoxic. Store unopened vials in a refrigerator at...” (b) (4) to vertical and relocate above (to the left of) the barcode.
  - b) Relocate the manufacturer statements and logo (b) (4) to the right side of the label such that it appears between the barcode and the space reserved for the lot number and expiration date. This format is similar to the format on the back panel of the carton labeling.
  - c) Relocate the cautionary statements, (b) (4) and “Discard any unused portion” (b) (4) to the lower portion of the PDP.

For example (please note this example is provided to clarify recommendations 3.a to 3.c, but does not reflect all of our recommendations):



**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Yondelis (trabectedin) that Janssen submitted on November 24, 2014.

<b>Table 2. Relevant Product Information for Yondelis</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	trabectedin
<b>Indication</b>	(b) (4)
<b>Route of Administration</b>	Intravenous infusion
<b>Dosage Form</b>	For Injection
<b>Strength</b>	1 mg/vial
<b>Dose and Frequency</b>	1.5 mg/m <sup>2</sup> body surface area as a 24-hour intravenous infusion, every 3 weeks
<b>How Supplied</b>	1 mg of trabectedin, as a sterile lyophilized white powder in a 25 mL glass vial
<b>Storage</b>	2°C to 8°C (36°F to 46°F)

## **APPENDIX C. PREVIOUS DMEPA REVIEWS**

### **C.1 Methods**

We searched the L:/ drive on February 9, 2015 using the terms, “trabectedin” to identify reviews previously performed by DMEPA.

### **C.2 Results**

Our search did not identify any previous labeling reviews.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with postmarket medication error data, we reviewed the following Yondelis labels and labeling submitted by Janssen on November 24, 2014.

- Container label
- Carton labeling
- Prescribing Information

### **G.2 Label and Labeling Images**

#### Container Label



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

---

<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/  
-----

OTTO L TOWNSEND  
03/27/2015

CHI-MING TU  
03/27/2015



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 3, 2015

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Anuja Patel, RPM  
DOP2

Subject: QT-IRT Consult to NDA 207953

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/20/2015 regarding your labeling consultation for trabectedin. The QT-IRT received and reviewed the following materials:

- Your consult
- QT-IRT's previous review for Study ET743-OVC-1001-OLE under IND 50286 (1/27/2012)
- Proposed YONDELIS (trabectedin) label

## QT-IRT Comments for DOP2

The following is the sponsor's proposed labeling language related to QT.

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

(b) (4)

(b) (4)

*QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.*

## **12.2. Pharmacodynamics**

### **Cardiac Electrophysiology**

(b) (4)

Thank you for requesting our input into the development of this product under NDA 207953. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cdcrpqt@fda.hhs.gov](mailto:cdcrpqt@fda.hhs.gov)

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

/s/  
-----

JIANG LIU  
03/03/2015

NORMAN L STOCKBRIDGE  
03/03/2015

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

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

**Application:** NDA 207953

**Application Type:** New NDA (NME)

**Name of Drug/Dosage Form:** YONDELIS (trabectedin)

**Applicant:** Janssen Products, LP

**Receipt Date:** November 24, 2014

**Goal Date:** July 24, 2015

## 1. Regulatory History and Applicant's Main Proposals

Trabectedin, an antineoplastic agent, was granted marketing authorization (MA) under "exceptional circumstances" by the EMA in 2007 for the treatment of patients with STS who have progressed after both anthracycline and ifosamide treatment or for whom these treatments are unsuitable, under Study ET743-STIS-201 which FDA considered to be exploratory given limitations in design and conduct. As of July 10, 2014, trabectedin is approved for the treatment of STS in 75 countries.

(b) (4)

The current NDA submission, NDA 207953, proposes the following indication:

(b) (4)

This NDA contains multiple study reports that were previously provided in NDA (b) (4)

## 2. Review of the Prescribing Information

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

## Selected Requirements of Prescribing Information

### 3. Conclusions/Recommendations

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

In addition, the following labeling issues were identified:

1. Use either underlining or italics (but not both) for subheadings and headings. Use a consistent approach (e.g., italics for subheadings and underlining for headings) throughout the labeling.

#### GENERAL COMMENT:

For recently published guidances and final rule, refer to the FDA website titled PLR Requirements for Prescribing Information found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

All SRPI format deficiencies of the PI and other labeling issues and comments identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by **February 27, 2015**. The resubmitted PI will be used for further labeling review.

---

## Appendix

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

---

## Highlights

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

### HIGHLIGHTS GENERAL FORMAT

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

***Comment:*** *No comments.*

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

***Comment:*** *There was no boxed warning in the proposed labeling.*

## Selected Requirements of Prescribing Information

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.  
***Comment:*** *No comments.*
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.  
***Comment:*** *No comments.*
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.  
***Comment:*** *No comments.*
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.  
***Comment:*** *No comments.*
- YES** 7. Section headings must be presented in the following order in HL:

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

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

***Comment:*** *Contraindications should be moved to next column and kept with bullet listings. No boxed warning in the proposed labeling. This is a new label yet to be approved, recent major changes are not applicable.*

### HIGHLIGHTS DETAILS

#### Highlights Heading

## Selected Requirements of Prescribing Information

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.  
**Comment:** *No comments.*

### Highlights Limitation Statement

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

### Product Title in Highlights

- YES** 10. Product title must be **bolded**.  
**Comment:** *No comments.*

### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.  
**Comment:** *No comments.*

### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.  
**Comment:** *No boxed warning is proposed.*

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.  
**Comment:** *No comments.*

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.  
**Comment:** *No comments.*

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).  
**Comment:** *No comments.*

### Recent Major Changes (RMC) in Highlights

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

## Selected Requirements of Prescribing Information

**Comment:** *No comments.*

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

**Comment:** *No comments.*

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

**Comment:** *No comments.*

### Indications and Usage in Highlights

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

**Comment:** *The established pharmacologic class(EPC) appears to be broad, and will be reviewed and potentially revised during labeling negotiations.*

### Dosage Forms and Strengths in Highlights

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

**Comment:** *Only one dosage form is proposed.*

### Contraindications in Highlights

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

**Comment:** *No comments.*

### Adverse Reactions in Highlights

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

**Comment:** *No comments.*

### Patient Counseling Information Statement in Highlights

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

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

## Selected Requirements of Prescribing Information

- “See 17 for PATIENT COUNSELING INFORMATION”

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

- “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling”
- “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”
  - **Comment:** *Minor modification is needed here, the proposed labeling is missing the highlighted hyphen: “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling”*

### Revision Date in Highlights

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

**Comment:** *No comments.*

---

## Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.

**Comment:** *No comments.*

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

**Comment:** *No comments.*

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

**Comment:** *No comments.*

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

**Comment:** *No comments.*

- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

**Comment:** *Not all are in title case, Please refer to edits in the TOC of the PI for 7.4 Plasma Protein Binding*

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

**Comment:** *No comments.*

- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the

## Selected Requirements of Prescribing Information

following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”

***Comment:*** No comments.

### Full Prescribing Information (FPI)

---

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

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

***Comment:*** No comments.

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

## Selected Requirements of Prescribing Information

**Comment:** *No comments.*

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

**Comment:** *No comments.*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

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

**Comment:** *No comments.*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

**Comment:** *No comments.*

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

**Comment:** *No comments.*

#### CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

**Comment:** *There are Contraindication listed for this product.*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

**Comment:** *Minor modification is needed here. The proposed labeling currently reads “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 <sup>(b) (4)</sup> clinical trials of another drug and may not reflect the rates observed in practice.” Please replace highlighted word with “in the.”*

*Please refer to FDA Guidance for Industry- Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.*

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

## Selected Requirements of Prescribing Information

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

**Comment:**

(b) (4)

### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:** No comments.

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

**Comment:** No comments.

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

**WARNING: [SUBJECT OF WARNING]**

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

[text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

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

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

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/  
-----

ANUJA PATEL  
02/05/2015

MONICA L HUGHES  
02/06/2015

## 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 # 207953 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: N/A (NME) <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Yondelis Established/Proper Name: trabectedin Dosage Form: powder for reconstitution, intravenous Strengths: 1 mg		
Applicant: Janssen Products, LP Agent for Applicant (if applicable): Janssen Research & Development, LLC		
Date of Application: November 24, 2014 Date of Receipt: November 24, 2014 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: July 24, 2015		Action Goal Date (if different):
Filing Date: January 23, 2015		Date of Filing Meeting: January 8, 2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/ <span style="float: right;">(b) (4)</span>		
<span style="float: right;">(b) (4)</span>		
Type of Original NDA: AND (if applicable)		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Type of NDA Supplement: If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> <li>• <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i></li> <li>• <i>The product is a Qualified Infectious Disease Product (QIDP)</i></li> <li>• <i>A Tropical Disease Priority Review Voucher was submitted</i></li> <li>• <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i></li> </ul>	
Resubmission after withdrawal? <input checked="" type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> 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): IND <sup>(b) (4)</sup> and IND 050286

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Submitted request to change to "trabectedin" on 1.20.15

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>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.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>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.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). <b>If yes</b> , answer the bulleted questions below:							
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				<input type="checkbox"/>	<input type="checkbox"/>		N/A
• 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)].				<input type="checkbox"/>	<input type="checkbox"/>		N/A
• 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)]?				<input type="checkbox"/>	<input type="checkbox"/>		N/A
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>							
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>				<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If yes</b> , please list below:							
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration				
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 may block the approval but not the submission of a 505(b)(2) application.</i>							
<b>Exclusivity</b>				<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?				<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>							
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?				<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , # years requested: Applicant is requesting [redacted] (b) (4) [redacted] 7 years Orphan Drug exclusivity for the use of trabectedin for treatment of soft							

tissue sarcoma.  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes, did the applicant:</b> (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)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission, does it follow the eCTD guidance?</b> <sup>1</sup> <b>If not, explain (e.g., waiver granted).</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information</b> (NDAs/NDA efficacy supplements only)	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>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].</i>  <i>Note: Debarment Certification should use wording in FD&amp;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..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>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)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The electronic submission contains a Field Copy Certification statement indicating that Applicant has informed their local FDA District Office that the NDA is planned for submission November 25, 2014
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		This application is exempt from PREA as it has orphan designation for soft tissue sarcoma (designation # 04-1936) dated September 30, 2004
<p><b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b></p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b></p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><b><u>BPCA:</u></b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Proprietary name request was submitted December 16, 2014. RPM confirmed that submission is coded in DARRTS correctly.
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	A copy of the most recent EU Risk Management Plan was submitted on December 16, 2014, at the request of DRISK reviewer.
<input type="checkbox"/> <b>Not applicable</b>				

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>Prescription Labeling</b>				
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI)- *Patient Information sheet is included <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult submitted January 20, 2015 for PI, PPI, and carton and immediate container labels
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult submitted January 20, 2015 for PPI, PI and EU Risk Management Plan that was submitted under the NDA
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult submitted January 20, 2015 for PPI and PI
<b>OTC Labeling</b>				
Check all types of labeling submitted.	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		N/A
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> <i>QT Consult sent 1.20.15</i> <i>Patient Labeling sent to OMP 1.20.15</i> <i>OSI Consult under review by clinical as of 1.23.15</i> <i>Micro Consult submitted by Rabiya Laiq (OPQ) via Panorama</i> <i>Facility/OMPQ Consult submitted by Rabiya Laiq (OPQ) via Panorama</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) <b>Date(s):</b> October 21, 2010; Meeting Minutes Issued November 30, 2010 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Discussed design of Phase 3 Study ET743-SAR-3007
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s) <b>Date(s):</b> October 17, 2014; Meeting Minutes issued November 16, 2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** January 8, 2015

**BACKGROUND:** Trabectedin, an antineoplastic agent, was granted marketing authorization (MA) under “exceptional circumstances” by the EMA in 2007 for the treatment of patients with STS who have progressed after both anthracycline and ifosamide treatment or for whom these treatments are unsuitable, under Study ET743-ST5-201 which FDA considered to be exploratory give limitations in design and conduct. As of July 10, 2014, trabectedin is approved for the treatment of STS in 75 countries.

[Redacted] (b) (4)

The current NDA submission, NDA 207953, is proposed [Redacted] (b) (4)

[Redacted] (b) (4)

A pre-NDA (Type B) clinical meeting was held October 17, 2014, between FDA and Janssen to discuss the format and content of NDA 207953 based on progression-free survival (PFS), overall response rate (ORR) and duration of response results from Study ET743-SAR-3007 entitled, “A Randomized Controlled Study of Yondelis (trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma.” FDA Meeting Minutes were issued on November 16, 2014.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Anuja Patel	Y
	CPMS/TL:	Monica Hughes	N
Cross-Discipline Team Leader (CDTL)	Marc Theoret		Y
Division Director/Deputy	Patricia Keegan		Y
Office Director/Deputy	Richard Padzur		Y
Clinical	Reviewer:	Jennie Chang	Y

		Dow-Chung Chi	Y
	TL:	Marc Theoret	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:		
Clinical Pharmacology	Reviewer:	Sriram Subramaniam	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Huanyu Chen	Y
	TL:	Kun He	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dubravka Kufrin	Y
	TL:	Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) ( <i>for protein/peptide products only</i> )	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	DS: Charles Jewell DP: William Adams	Y N
	TL:		
Biopharmaceutics	Reviewer:	Okpo Eradiri	N
	TL:		
Quality Microbiology	Reviewer:	Erika Pfeiler	Y
	TL:		
CMC Labeling Review	Reviewer:		

	TL:		
Facility Review/Inspection	Reviewer:	Robert Wittorf	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Otto Townshend	Y
	TL:	Alice Chi- Ming Tu	N
OSE/DRISK (REMS)	Reviewer:	Mona Patel	Y
	TL:	Naomi Redd	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers/disciplines	Reviewer:		Y
	TL:		N
Other attendees	Olen Stephens, OPQ Application Team Lead		Y
	Rabiya Laiq, OPQ Regulatory Business Process Manager (RBPM)		Y
	Frances Fahnbulleh, OSE RPM		Y
	Nazia Fatima, OPDP Reviewer		Y

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
--	--

<p>between the proposed product and the referenced product(s)/published literature?</p> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p><b>CLINICAL</b></p> <p>Comments: Labeling Comments to be provided in the Day 74 letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>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</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: <ul style="list-style-type: none"> <li><b>the clinical study design was acceptable</b></li> <li><b>the application did not raise significant safety or efficacy issues</b></li> </ul>
<ul style="list-style-type: none"> <li>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?</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (protein/peptide products only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> CMC Amendment was received on January 23, 2015, in response to an information request. The amendment is under review and if further comments need to be sent to the Applicant they will be sent in the 74-day letter.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>New Molecular Entity (NDAs only)</b></p>	

<ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b> submitted by OPQ via Panorama</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b><u>Quality Microbiology</u></b></p> <ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization?</li> </ul> <p><b>Comments:</b> Consult submitted by OPQ via Panorama</p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b> Consult submitted by OPQ via Panorama. DOP 2 requested that inspection be completed by Mid April 2015 per filing meeting discussion.</p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter

<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>None</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Richard Pazdur</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): March 19, 2015</p> <p><b>Comments:</b> The following agreements were made during the filing meeting:</p> <ul style="list-style-type: none"> <li>• CMC will issue Information Requests for their disciplines (Micro, Biopharmaceuticals, Drug Substance, and Drug Product). OPQ Application Team Lead will confirm that any outgoing CMC information requests have been cleared by discipline team leaders.</li> <li>• OPQ Regulatory Business Process Manager (RBPM) will CC OND RPM on any outgoing CMC information requests to Applicant.</li> <li>• CMC summary filing review of the application, will be uploaded in Panorama by OPQ Application Team Lead.</li> <li>• DOP 2 requested that CMC Manufacturing Inspection (b) (4) (FEI# (b) (4)) be</li> </ul>	

expedited and completed (b) (4) OMPQ agreed to forward the request to ORA district office.	
<ul style="list-style-type: none"> <li>Please see attached milestone dates as generated by Panorama</li> </ul>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	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, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>notify sponsor in writing by day 60 (see CST for choices)</li> <li>notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA's completed: September 2014

## OND Project Tasks

#	Task	Assigned To	Task Pln Comp	Status
<b>Parent: Filing Activities(7)</b>				
62	Issue Acknowledgement Letter		12/8/14	
63	Complete Site Identification with OSI		1/1/15	
67	Filing/Planning Meeting	Anuja Patel	1/8/15	
69	Clinical (Medical) Filing Checklist		1/22/15	
71	Non-Clinical Filing Checklist		1/22/15	
72	Clinical Microbiology Filing Checklist		1/22/15	
73	RPM Filing Checklist		1/22/15	
<b>Parent: Final Filing Activities(4)</b>				
83	ATTACH EXPEDITED REVIEW TEMPLATE TO THIS TASK (IF APPLICABLE)		12/8/14	
84	<b>ATTACH REVIEW TEMPLATE TO THIS TASK</b>		7/24/15	
155	Issue Priority Designation/Filing Determination Letter		1/23/15	
156	Issue Filing 74-Day Letter		2/6/15	
<b>Parent: Team Meetings, Mid-Cycle Meeting, Mid-Cycle Communication Meeting(4)</b>				
90	REMS Determination Meeting		2/22/15	
91	Mid-Cycle Meeting		2/24/15	
93	Team Labeling Meeting		3/2/15	
94	Mid-Cycle Communication Meeting		3/9/15	
<b>Parent: Clinical (Medical) Review(2)</b>				
99	Clinical (Medical) Primary Review, Including Secondary Review Sign-Off		4/26/15	
100	Clinical (Medical) Secondary Review (If Necessary)		4/29/15	
<b>Parent: Non-Clinical Review(2)</b>				
105	Non-Clinical Primary Review, Including Secondary Review Sign-Off		4/26/15	
106	Non-Clinical Secondary Review (If Necessary)		4/29/15	

#	Task	Assigned To	Task Pln Comp	Status
<b>Parent: Clinical Microbiology Review (2)</b>				
108	Clinical Microbiology Primary Review, Including Secondary Review Sign-Off		4/26/15	
109	Clinical Microbiology Secondary Review (If Necessary)		4/29/15	
<b>Parent: Discipline Review Letters(1)</b>				
126	Issue Discipline Review Letters		4/29/15	
<b>Parent: Final Labeling and PMR/PMC(7)</b>				
128	Send Substantially Complete Labeling to OPDP		4/15/15	
129	Send Substantially Complete Labeling to Patient Labeling (DMPP)		4/15/15	
130	Send Labeling to Applicant		4/28/15	
131	Send PMR/PMC to Applicant		4/28/15	
132	Patient Labeling Review		4/28/15	
133	OPDP Review		4/28/15	
134	Begin Labeling/PMR/PMC Discussions with Applicant		5/5/15	
<b>Parent: Late Cycle Meeting Occurs If Advisory Committee Meeting Is Needed(3)</b>				
136	Pre-Meeting for Late Cycle Meeting (LCM)		4/27/15	
137	Send LCM Briefing Package to Sponsor		5/6/15	
138	LCM		5/14/15	
<b>Parent: Advisory Committee Meeting (When Needed)(1)</b>				
140	Advisory Committee Meeting		5/25/15	
<b>Parent: Late Cycle Meeting Occurs If Advisory Committee Meeting Is Not Needed(3)</b>				
142	Pre-Meeting for Late Cycle Meeting (LCM)		4/27/15	
143	Send LCM Briefing Package to Applicant		5/14/15	
144	LCM		5/25/15	
<b>Parent: CDTL Memo(1)</b>				
146	CDTL Review		6/29/15	
<b>Parent: Action Phase(7)</b>				
148	Incorporate OSI Clinical Inspection Summary Review		5/25/15	

#	Task	Assigned To	Task Pln Comp	Status
149	Wrap-Up Meeting		6/20/15	
150	PeRC Meeting		6/26/15	
151	Division Director Review		7/14/15	
152	Office Director Review		7/24/15	
153	Obtain OC Clearance of Confirmatory TB-EER (BLAs Only)		7/24/15	
154	Action Letter		7/24/15	

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

/s/  
-----

ANUJA PATEL  
01/23/2015

MONICA L HUGHES  
01/23/2015