



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207953

NDA APPROVAL

Janssen Products, L.P.
Attention: Barbara Kolb, Senior Director, Global Regulatory Affairs, Janssen Research and
Development
Janssen Research & Development, LLC
920 U.S. Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Kolb:

Please refer to your New Drug Application (NDA) dated November 24, 2014, received November 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Yondelis (trabectedin), for injection, for intravenous use, 1 mg sterile lyophilized powder.

We also refer to our approval letter dated October 23, 2015 which contained the following error: the final analysis plan for post marketing requirements 2964-1 should be submitted to IND 050286, the vial container labeling contained a watermark, and the vial container labeling was blank.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain October 23, 2015, the date of the original approval letter.

We acknowledge receipt of your amendment(s) dated November 24, 2014; December 11, 2014; December 16, 2014 (2); December 18, 2015; January 21, 2015; January 23, 2015; January 27, 2015 (2); January 28, 2015; January 30, 2015; February 2, 2015; February 18, 2015; February 27, 2015; March 5, 2015; March 13, 2015; March 19, 2015; March 24, 2015; March 26, 2015; March 27, 2015; April 17, 2015; April 27, 2015; April 30, 2015; May 8, 2015; May 15, 2015; June 1, 2015; June 2, 2015; June 11, 2015; June 16, 2015; July 31, 2015; August 5, 2015; August 7, 2015; August 12, 2015; August 25, 2015; September 4, 2015; September 18, 2015; September 21, 2015; September 23, 2015; September 28, 2015; September 30, 2015; October 2, 2015; October 14, 2015; October 15, 2015; October 18, 2015; October 20, 2015; and October 22, 2015.

This new drug application provides for the use of Yondelis (trabectedin) sterile lyophilized powder for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert and the patient package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on September 18, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 207953.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

DATING PERIOD

The shelf life for Yondelis shall be 36 months when stored at 2°C to 8°C (36°F to 46 °F).

ADVISORY COMMITTEE

Your application for Yondelis was not referred to an FDA advisory committee because

- the safety profile is acceptable for the proposed indication; and
- the application did not raise significant safety or efficacy issues that were unexpected for this indication.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of cardiac dysfunction with Yondelis (trabectedin), and to assess a signal of a serious risk of impaired hepatic function on the pharmacokinetics of Yondelis (trabectedin).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of cardiac dysfunction with Yondelis and to assess a signal of a serious risk of increased trabectedin toxicities due to altered pharmacokinetics of Yondelis in patients with impaired hepatic function.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2964-1 Submit integrated safety analyses and supporting data from an adequate number of clinical trial(s) to characterize the risk of cardiomyopathy and its sequelae in patients receiving trabectedin; to identify risk factors for development of these sequelae; and to support labeling instructions for dose modification and monitoring. The design of the trial should include a patient population with previous exposure to anthracyclines and have sufficient cardiac monitoring to achieve these objectives.

The timetable you submitted on September 30, 2015, states that you will conduct this trial according to the following schedule:

Final Analysis Plan Submission: March 2016
Trial Completion (Cardiac Sub Study): July 2018
Final Report (Cardiac Analysis) Submission: November 2018

Submit the final analysis plan to your IND 050286 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”, “Required Postmarketing Final Report Under 505(o)”, “Required Postmarketing Correspondence Under 505(o)”**.

2964-2 Submit the final report of the completed clinical pharmacokinetic trial to determine the pharmacokinetics of Yondelis (trabectedin) in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

The timetable you submitted on September 28, 2015, states that you will conduct this trial according to the following schedule:

Final Report Submission: January 28, 2016

Submit the Final Study Report to this NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”, “Required Postmarketing Final Report Under 505(o)”, “Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>.

For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application within two weeks of receipt of this communication.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Ms. Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
10/23/2015