



BLA 761036

BLA ACCELERATED APPROVAL

Janssen Biotech, Inc.
c/o Janssen Research and Development, LLC
Attention: Brian Maloney, RPh, MS
Director, Regulatory Affairs
920 Route 202, PO Box 300
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your Biologics License Application (BLA) dated July 9, 2015, received July 9, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Darzalex™ (daratumumab) injection, 100 mg/5 mL and 400 mg/20 mL.

We also refer to our approval letter dated November 16, 2015 which contained the following error: the vial container labeling submitted October 20, 2015 was blank.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain November 16, 2015, the date of the original approval letter.

LICENSING

We have approved your BLA for Darzalex™ (daratumumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Darzalex™ under your existing Department of Health and Human Services U.S. License No. 1864. Darzalex™ is indicated for treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or are double refractory to a proteasome inhibitor and an immunomodulatory agent.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture [REDACTED] (b) (4). You are approved to manufacture daratumumab drug substance at Janssen Biologics, Cork, Ireland. The final formulated 100 mg/5 mL drug product will be manufactured, filled, labeled, and packaged at Cilag A.G., Schaffhausen, Switzerland and the 100 mg/5 mL and 400 mg/20 mL drug product will be manufactured, filled, and labeled at [REDACTED] (b) (4). The 100 mg/5 mL and 400 mg/20 mL drug product may also be

packaged at [REDACTED] (b)(4). You may label your product with the proprietary name Darzalex and will market it in 100 mg/5 mL and 400 mg/20 mL injection in single-dose vials.

DATING PERIOD

The dating period for Darzalex™ shall be 18 months from the date of manufacture when stored at 2°C - 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 18 months from the date of manufacture when stored at (b)(4)°C. The dating period for your [REDACTED] (b)(4) shall be (b)(4) months from the date of manufacture when stored at (b)(4)°C. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Darzalex™ to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Darzalex™, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

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, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, 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, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed.

Container Labels

Use the container labels submitted October 2, 2015 for initial marketing.

Use the container labels submitted October 20, 2015 starting 6 weeks post launch.

Carton Labeling

Use the carton labeling submitted October 20, 2015.

Please submit these labels electronically according to the guidance for industry titled “*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 BLA 761036.**” Approval of this submission by FDA is not required before the labeling is used.

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

ADVISORY COMMITTEE

Your application for daratumumab was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated November 16, 2015. This requirement, along with required completion dates, is listed below.

- | | |
|------------|---|
| PMR 3000-1 | Conduct the analysis and submit the complete final report and data showing clinical efficacy and safety from Trial MMY3003, a “Phase 3, 2-arm, Randomized, Parallel-group Trial of Lenalidomide and |
|------------|---|

Dexamethasone with or without Daratumumab in Patients with Previously-treated Multiple Myeloma.”

Trial Completion (primary endpoint): 04/2017
Final Report Submission: 07/2017

PMR 3000-2 Conduct the analysis and submit the complete final report and data showing clinical efficacy and safety from Trial MMY3004, a “Phase 3, 2-arm, Randomized, Parallel-group Trial of Bortezomib and Dexamethasone with or without Daratumumab in Patients with Previously-treated Multiple Myeloma.”

Trial Completion (primary endpoint): 02/2017
Final Report Submission: 05/2017

Submit clinical protocols to your IND 100638 for this product. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected trial completion and final report submission dates, any changes in plans since the last annual report, and number of patients entered into each trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart E Postmarketing Requirement(s)**.”

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 biologic 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 Federal Food, Drug, and Cosmetic Act (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 identify unexpected serious risks of developing antibodies causing immunogenicity related adverse events, including

hypersensitivity reactions and loss of product efficacy that can lead to increased mortality rate in treated patients; or to assess a signal of a serious risk of treatment emergent adverse events in patients with hepatic impairment treated with the product.

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 these serious risks.

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

- PMR 3000-3 Submit the final report of a study conducted to assess the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 3000-4.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2018

- PMR 3000-4 Conduct a study to validate an assay for binding antibodies to daratumumab to assess the product's potential for immunogenic reactions in treated patients. Submit a validation report for the validated, sensitive, and accurate assay for the detection of binding antibodies to daratumumab, including procedures for the accurate detection of binding antibodies to daratumumab in the presence of daratumumab levels expected in the serum or plasma at the time of patient sampling.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2018

- PMR 3000-5 Conduct a study to validate an assay for neutralizing antibodies to daratumumab to assess the potential for increased adverse outcome from loss of product effect in treated patients. Submit a validation report for the validated, sensitive, and accurate assay for the detection of neutralizing antibodies to daratumumab, including procedures for the accurate detection of neutralizing antibodies to daratumumab in the presence of daratumumab levels that are expected in the serum or plasma at the time of patient sampling.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2015

PMR 3000-6 Collect, analyze, and submit additional safety data from ongoing clinical trials to characterize the safety of daratumumab in patients with baseline hepatic impairment.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	04/2017
Final Report Submission:	07/2017

Submit the protocol(s) to your IND 100638, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. 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 601.70 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 601.70 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 601.70. 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 3000-7 Perform a shipping study to confirm validation of the commercial daratumumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipment samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of daratumumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2016

PMC 3000-8 Provide quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the [REDACTED] (b) (4) [REDACTED] and drug substance long term storage containers.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2016

PMC 3000-9 Re-evaluate [REDACTED] (b) (4) lot release and stability data after at least 30 lots have been manufactured using the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 07/2016
Final Report Submission: 09/2016

PMC 3000-10 Re-evaluate daratumumab drug substance lot release and stability data after at least 30 lots have been manufactured using the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 07/2016
Final Report Submission: 09/2016

PMC 3000-11 Re-evaluate daratumumab drug product lot release and stability data after at least 30 lots have been manufactured using the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 07/2016
Final Report Submission: 09/2016

PMC 3000-12 To determine the maximum hold times for all [REDACTED] (b) (4) [REDACTED] using a surrogate solution that supports microbial growth. Submit results in accordance with 21 CFR 601.12, in the Final Report.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2016

Submit clinical protocols to your IND 100638 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected study completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

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

Alternatively, you may submit promotional materials for accelerated approval products 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>).

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

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, call the Regulatory Project Manager for this application.

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 Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

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
11/16/2015