

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**761038Orig1s001**

*Trade Name:* LARTRUVO

*Generic or Proper Name:* olaratumab

*Sponsor:* Eli Lilly and Company

*Approval Date:* July 10, 2017

*Indication:* Lartruvo is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery. This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 761038Orig1s001

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**761038Orig1s001**

**APPROVAL LETTER**



**APPROVAL LETTER**

BLA 761038/1

Eli Lilly and Company  
Attention: Lisa Wenzler, Ph.D.  
Research Advisor, CMC Regulatory, Global Regulatory Affairs-US  
Lilly Corporate Center  
Drop Code 2543  
Indianapolis, IN 46285

Dear Dr. Wenzler:

Please refer to your Supplemental Biologics License Application (sBLA) dated January 13, 2017 and received January 13, 2017, submitted under section 351(a) of the Public Health Service Act for Lartruvo™ (Olaratumab) for Injection, 500 mg/50 mL.

This “Changes Being Effected in 30 days” supplemental biological application proposes to introduce a new vial presentation of 190 mg/19 mL for Lartruvo (Olaratumab) drug product.

We have completed our review of this supplemental biologics application. This supplement is approved.

This information will be included in your biologics license application file.

If you have any questions, call Kelly Ballard, Regulatory Business Process Manager, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

David Frucht, Ph.D.  
Director  
Division of Biotechnology Review and Research II  
Office of Biotechnology Products  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



David  
Frucht

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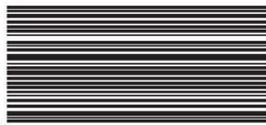


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**LABELING**



**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use LARTRUVO safely and effectively. See full prescribing information for LARTRUVO.

LARTRUVO (olaratumab) injection, for intravenous use  
Initial U.S. Approval: 2016

**INDICATIONS AND USAGE**

LARTRUVO™ is a platelet-derived growth factor receptor alpha (PDGFR- $\alpha$ ) blocking antibody indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery. (1)  
This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial. (14)

**DOSE AND ADMINISTRATION**

- Administer LARTRUVO at 15 mg/kg as an intravenous infusion over 60 minutes on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity. (2.1)
- For the first 5 cycles, LARTRUVO is administered with doxorubicin. (2.1)
- Premedicate with diphenhydramine and dexamethasone intravenously, prior to LARTRUVO on Day 1 of cycle 1. (2.2)
- For intravenous infusion only. Do not administer as an intravenous push or bolus. (2.4)

**DOSE FORMS AND STRENGTHS**

Injection: 500 mg/50 mL (10 mg/mL) or 190 mg/19 mL (10 mg/mL) solution in a single-dose vial (3)

**CONTRAINDICATIONS**

None. (4)

**WARNINGS AND PRECAUTIONS**

- Infusion-Related Reactions:** Monitor for signs and symptoms during and following infusion. Discontinue LARTRUVO for Grade 3 or 4 infusion-related reactions. (2.2, 2.3, 5.1)
- Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of potential risk to the fetus and to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose. (5.2, 5.1, 5.3)

**ADVERSE REACTIONS**

The most common ( $\geq 20\%$ ) adverse reactions of LARTRUVO plus doxorubicin are nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neuropathy, and headache. (6.1)  
The most common ( $\geq 20\%$ ) laboratory abnormalities were lymphopenia, neutropenia, thrombocytopenia, hyperglycemia, elevated aPTT, hypokalemia, and hypophosphatemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**USE IN SPECIFIC POPULATIONS**

Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2017

**FULL PRESCRIBING INFORMATION: CONTENTS\***

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761038Orig1s001**

**CHEMISTRY REVIEW(S)**



## Memorandum of Review:

<b>STN:</b>	761038
<b>Subject:</b>	CBE-30, introduction of a new presentation for drug product
<b>Date:</b>	1/13/2017
<b>Review/Revision Date:</b>	5/23/2017
<b>Primary Reviewer:</b>	Chikako Torigoe, PhD
<b>Secondary Reviewer:</b>	William Hallett, PhD
<b>Assigned RPM:</b>	Kelly Ballard
<b>Applicant:</b>	Eli Lilly and Company
<b>Product:</b>	Olaratumab
<b>Indication:</b>	Soft-tissue sarcoma
<b>Filing Action Date:</b>	3/14/2017
<b>Action Due Date:</b>	7/13/2017

### I. Summary Basis of Recommendation:

- a. **Recommendation:** I recommend the approval of this supplement.
  
- b. **Justification:** The formulation for the proposed olaratumab Injection 190 mg/19 mL dosage form is identical to the formulation for the currently approved olaratumab Injection 500 mg/50 mL dosage form. No changes are introduced to the materials of the container closure system. The proposed changes to the manufacturing process are considered low risk. The provided data adequately support the analytical comparability between the 190 mg/19 mL and the 500 mg/50 mL dosage forms. The processing time limits are appropriately determined from the product quality perspective. The shipping process is adequately validated for the 190 mg/19 mL dosage form.

### II. Language for Action Letter: This “Changes Being Effectuated in 30 days” supplemental biological application proposes to introduce a new vial presentation of 190 mg/19 mL for Lartruvo (olaratumab) drug product.

We have completed our review of this supplemental biologics application. This supplement is approved.

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William  
Hallett

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761038Orig1s001**

**MICROBIOLOGY/VIROLOGY REVIEW(S)**

Center for Drug Evaluation and Research  
Office of Pharmaceutical Quality  
Office of Process and Facilities  
Division of Microbiology Assessment  
WO Building 22  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** February 10, 2017  
**To:** Administrative File, **STN** 761038/1  
**From:** Aimee Cunningham, Ph.D., Reviewer, CDER/OPQ/OPF/DMA/ Branch IV  
**Endorsement:** Natalia Pripuzova, Ph.D., Reviewer, CDER/OPQ/OPF/DMA/Branch IV  
**Subject:** CBE-30: New Vial Presentation of 190 mg/19 mL (FEI: 1819470)  
**US License:** 1891  
**Applicant:** Eli Lilly and Co.  
**Facility:** Lilly Corporate Center, Indianapolis, IN, 46285, USA (FEI: 1819470)  
**Product:** LARTRUVO™ (Olaratumab)  
**Dosage:** 10 mg/mL, solution for intravenous infusion (190 mg/19 mL)  
**Indication:** Advanced Soft Tissue Carcinoma  
**Due date:** 07/13/2017

**Recommendation on Approvability** – The supplement (CBE-30) was reviewed from a drug product quality microbiology control perspective and is recommended for approval.

**Summary:** In this submission, Eli Lilly is seeking the approval of a new vial presentation (190 mg/19 mL) of Olaratumab. The BLA currently is approved for a 500 mg/50 mL vial presentation.

**Product Quality Microbiology Information Reviewed**

Submission Type	Sequence number	Sequence date
Original CBE-30 submission	0104	13-January-17
Response to IR	0117	8-February-17

**Drug Product Review**

**Module 3.2**

**P.1 Description and Composition of the Drug Product**

Olaratumab injection solution for i.v. infusion is a sterile solution at 10 mg/mL intended for single use. The DP composition has not changed, but is now being presented at 190 mg/19 mL in addition to the previously approved 500 mg/50 mL. The unit formula for each presentation is below:

The post-approval stability commitment has not changed from the previous BLA, and remains one lot annually from each approved vial presentation. With the addition of the 20 mL vial presentation, Lilly commits to test at least two lots annually.

SATISFACTORY

### **P.8.3 Stability Data**

Stability data was provided for three commercial batches of 20 mL vials which were stored at 2-8°C. These batches were acceptable for endotoxin, sterility, and container closure integrity.

SATISFACTORY

### **CGMP Status**

The assessment of manufacturing facilities is documented in panorama.

### **Conclusion**

- I. The supplement was reviewed from a product quality microbiology perspective and is recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by OBP.
- III. No inspection follow-up items were identified.

AIMEE CUNNINGHAM  
(REVIEWER)  
02/10/2017

NATALIA PRIPUZOVA  
(SECONDARY REVIEWER)  
02/10/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

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**OTHER REVIEW(S)**



**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**761038Orig1s001**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



BLA 761038/1

## INFORMATION REQUEST

Eli Lilly and Company  
Attention: Lisa Wenzler, Ph.D.  
Research Advisor, CMC Regulatory, Global Regulatory Affairs-US  
Lilly Corporate Center  
Drop Code 2543  
Indianapolis, IN 46285

Dear Dr. Wenzler:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received January 13, 2017, submitted under section 351(a) of the Public Health Service Act for Lartruvo™ (Olaratumab).

We are reviewing your submission and have the following information request. We request a prompt written response by COB April 14, 2017 in order to continue our evaluation of your application.

Provide the following information on the shipping validation studies for olaratumab drug product 190 mg/19 mL dosage form.

- a) In your Drug Product Shipping Validation studies, single values are reported for product quality results. Provide the information on how many vials were selected for the product quality attribute tests and how the results are reported (e.g. averaged, single vial). In addition, provide the information on how the vials were selected for the tests.
- b) High Molecular Weight Species (HMWS) is one of the quality attributes that may be impacted by the shipping stress. Provide the justification for not performing SE-HPLC in the quality attribute tests.
- c) In Table 3.2.P.3.5.3.1.2-1, the data from only one small ISC configuration are provided. Provide the data for both maximum and minimum load configurations.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

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BLA 761038/1

INFORMATION REQUEST

Eli Lilly and Company  
Attention: Lisa Wenzler, Ph.D.  
Research Advisor, CMC Regulatory, Global Regulatory Affairs-US  
Lilly Corporate Center  
Drop Code 2543  
Indianapolis, IN 46285

Dear Dr. Wenzler:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received January 13<sup>th</sup>, 2017, submitted under section 351(a) of the Public Health Service Act for Lartruvo™ (Olaratumab).

We are reviewing your submission and have the following information request. We request a prompt written response by COB February 9<sup>th</sup>, 2017 in order to continue our evaluation of your application.

Please refer to **3.2.P.3.5, Process Validation and Evaluation**, submitted on 13 January 2017, sequence 0104. Please provide the following additional information to support the new 190 mg/19 mL vial presentation:

1. If the filling operation for the 190 mg/19 mL presentation will use [REDACTED] (b) (4), please clarify whether the sterilization validation data provided in the BLA also covers the [REDACTED] (b) (4).
2. Provide the following additional information for the media fills referenced in Tables 3.2.P.3.5.2.4.2-1 and 3.2.P.3.5.2.4.2-2:
  - a. The medium used.
  - b. The total time for the fill and the number of units filled.
  - c. The number of units filled but not incubated. Briefly explain why these units were excluded.
  - d. Compare the media fill conditions to those used for routine production (belt speed, number of personnel and shift changes, duration of fill, number of containers filled, interventions, etc.) and explain how [REDACTED] (b) (4)

3. Regarding the qualification of the vial depyrogenation, please clarify the sub-process parameters used in validation in comparison to production parameters for 10 mL and 50 mL vials used to qualify 20 mL vials.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

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BLA 761038/1

**CBE 30 CMC SUPPLEMENT -  
ACKNOWLEDGEMENT & FILING**

Eli Lilly and Company  
Attention: Lisa Wenzler, Ph.D.  
Research Advisor, CMC Regulatory, Global Regulatory Affairs-US  
Lilly Corporate Center  
Drop Code 2543  
Indianapolis, IN 46285

Dear Dr. Wenzler:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351 of the Public Health Service Act for the following:

<b>BLA SUPPLEMENT NUMBER:</b>	761038/1
<b>PRODUCT NAME:</b>	Lartruvo™ (Olaratumab)
<b>REASON FOR THE SUBMISSION:</b>	Provides for a new vial presentation of 190mg/19mL which includes revisions to the relevant sections of the USPI
<b>DATE OF SUBMISSION:</b>	January 13, 2017
<b>DATE OF RECEIPT:</b>	January 13, 2017

This acknowledgment recognizes that your submission is in the form of a "**Supplement-- Changes Being Effectuated in 30 Days**" as described under 21 CFR 601.12(c). Continued use of the changes is subject to final approval of this supplement.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 14, 2017 in accordance with 21 CFR 601.2(a).

If the application is filed, the goal date will be July 13, 2017.

## **SUBMISSION REQUIREMENTS**

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Biotechnology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

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