



BLA 761102

BLA APPROVAL

Servier Pharmaceuticals LLC
Attention: Denisa Weinstein, MSc, RAC
Associate Director, Global Regulatory Affairs
501 Boylston Street, Floor 10
Boston, MA 02116

Dear Ms. Weinstein:

Please refer to your Biologics License Application (BLA) dated December 22, 2017, received December 22, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for ASPARLAS (calaspargase pegol-mknl); 3,750 units/5 mL (750 units/mL).

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2125 to Servier Pharmaceuticals LLC, Boston, MA, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product ASPARLAS (calaspargase pegol-mknl). ASPARLAS is indicated for use as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia in pediatric and young adult patients age 1 month to 21 years.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture [REDACTED] (b) (4) calaspargase pegol-mknl drug substance (SC-PEG L-asparaginase) at [REDACTED] (b) (4). The final formulated drug product will be manufactured, filled, labeled, and packaged at [REDACTED] (b) (4). You may label your product with the proprietary name, ASPARLAS, market it in 3750 units/5 mL, Injection in single-dose vials.

DATING PERIOD

The dating period for ASPARLAS shall be 36 months from the date of manufacture when stored at 2 – 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 [REDACTED] (b) (4) [REDACTED] when stored at [REDACTED] (b) (4) [REDACTED].

FDA LOT RELEASE

You are not currently required to submit samples of future lots of ASPARLAS to the Center for Drug Evaluation and Research (CDER) for release by 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 ASPARLAS, 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 AND 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 Prescribing Information). 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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on December 17, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2017, Revision 4)*. For administrative purposes, designate this submission “**Final Printed**”

Carton and Container Labeling for approved BLA 761102.” Approval of this submission by FDA is not required before the labeling is used.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that your request for a rare pediatric disease priority review voucher has been denied. You did not qualify for the voucher because the application was not deemed eligible for a priority review.

ADVISORY COMMITTEE

Your application for ASPARLAS was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment, with the timetable you submitted on December 19, 2018, which states that you will conduct these studies according to the following schedule:

PMC 3550-1 To develop and validate screening and confirmatory assays for the evaluation of anti-calaspargase antibodies. Develop an assay to determine whether any anti-calaspargase antibodies are anti-PEG. The Sponsor will submit final reports in accordance with 21 CFR 601.12.

Final Report Submission: 01/2019

PMC 3550-2

To reanalyze the remaining immunogenicity samples from Study DFCI 11-001 to determine the incidence of anti-calaspargase pegol and anti-PEG antibodies using the ADA validated assays from PMC 3550-1. For any newly confirmed positive samples, the neutralizing capacity of the anti-calaspargase antibodies will be evaluated with the validated integrated binding ADA/serum asparaginase activity

assays. The Sponsor will submit the final study report in accordance with 21 CFR 601.12.

Final Report Submission: 12/2019

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

We remind you of your postmarketing commitments, with the timetables you submitted on December 19, 2018, which state that you will conduct these studies according to the following schedules:

PMC 3550-3 Complete the qualification of bioburden and endotoxin test methods using two additional batches of [REDACTED] (b) (4) drug substance and submit the information and summary data in accordance with 21 CFR 601.12.

Final Report Submission: 01/2019

PMC 3550-4 Validate the maximum crimping parameter using a container closure integrity test capable of detecting ≤ 20 μm breaches and submit the validation data in accordance with 21 CFR 601.12.

Final Report Submission: 04/2019

PMC 3550-5 Complete the qualification of endotoxin test method for the DP release sample using one additional calaspargase pegol-mknl DP lot and submit the endotoxin method qualification data in accordance with 21 CFR 601.12.

Final Report Submission: 01/2019

PMC 3550-6 To perform a leachables study to evaluate leachables from the container closure system of calaspargase pegol-mknl drug product and assess the potential impact of leachables on product quality at the end of shelf-life. The analysis will be performed using one drug product lot and/or a representative sample (e.g. formulation buffer) analyzed at the end of shelf life. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Characterization of the potential impact on product quality will be assessed using adequate analytical methods. Complete data and the risk evaluation for the potential impact of leachables on product safety and quality will be submitted in accordance with 21 CFR 601.12.

Final Report Submission: 06/2022

PMC 3550-7 To perform a shipping validation study under real time shipping conditions (i.e. temperature, mode of transport, shipping duration, and shipping containers and packing representative of the minimum and maximum load) using a representative commercial calaspargase pegol-mknl drug product lot in the final commercial container closure and packaging systems to evaluate the ability of the shipping containers to maintain the recommended temperature and to evaluate the impact of shipping from the manufacturing sites(s) to the distribution sites(s) on the physical integrity and product quality of calaspargase pegol-mknl drug product. The shipping validation data will be submitted in accordance with 21 CFR 601.12.

Final Report Submission: 07/2020

PMC 3550-8 To perform a shipping validation study under real time shipping conditions (i.e. temperature, mode of transport, shipping duration, and shipping containers and packing representative of the minimum and maximum load) using a representative commercial (b) (4) lot in the final commercial container closure and packaging systems to evaluate the ability of the shipping containers to maintain the recommended temperature and to evaluate the impact of shipping on the quality of (b) (4). The shipping validation data will be submitted in accordance with 21 CFR 601.12.

Final Report Submission: 07/2020

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 summary 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

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 Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

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

As required under 21 CFR 601.12(f)(4), 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>.

REPORTING REQUIREMENTS

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

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 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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.

If you have any questions, call Wanda Nguyen, Regulatory Project Manager, at (301) 796-2808.

Sincerely,

{See appended electronic signature page}

Amy McKee, MD
Acting Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling
Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMY E MCKEE
12/20/2018