CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761116Orig1s000

Trade Name:	Elzonris Injection, 1,000 mcg in 1 mL solution
Generic or Established:	Tagraxofusp-erzs
Sponsor:	Stemline Therapeutics, Inc.
Approval Date:	December 21, 2018
Indication:	For the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	**X**
Non-Clinical Review(s)	**X**
Statistical Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761116

BLA APPROVAL

Stemline Therapeutics, Inc.
Attention: Deborah Norby
Vice President, Regulatory Affairs
750 Lexington Avenue, 11th Floor
New York, NY 10022

Dear Ms. Norby:

Please refer to your Biologics License Application (BLA) dated June 21, 2018, received June 21, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Elzonris (tagraxofusp-erzs) injection, 1,000 mcg in 1 mL solution.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2088 to Stemline Therapeutics, Inc., New York, NY, 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 Elzonris (tagraxofusp-erzs). Elzonris is indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture tagraxofusp-erzs drug substance at (b) (4)
The final formulated drug product will be manufactured and filled at (b) (4)
. The final formulated drug product will be labeled and packaged at (b) (4). You may label your product with the proprietary name, Elzonris, and market it at 1,000 mcg in 1 mL strength in single-dose vials, injection.

DATING PERIOD

The dating period for Elzonris shall be 36 months from the date of manufacture when stored at (b) (4) °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 (b) (4) from the date of manufacture when stored at (b) (4)

We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug substance under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Elzonris 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 Elzonris, 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 14, 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 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761116**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Elzonris was not referred to an FDA advisory committee, because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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 NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 3551-1 Perform a study to evaluate the impact of the removal of (b) (4) If the data support removal of (b) (4) a plan for the removal of (b) (4) from the tagraxofusp-erzs manufacturing process will be provided. The plan should include an evaluation of consistency of the (b) (4) process and comparability of tagraxofusp-erzs manufactured with and without (b) (4). The final study report will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on December 12, 2018 states that you will conduct this study according to the following schedule:

Final Report Submission: March 2020

PMC 3551-2 Conduct (b) (4) bioburden and endotoxin test method qualification using two additional drug substance batches. The final qualification report will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on December 12, 2018 states that you will conduct this study according to the following schedule:

Final Report Submission: September 2019

PMC 3551-3 Perform a drug substance and drug product shipping study using the proposed commercial shipping lanes and modes of transportation to evaluate the impact of shipping on product quality. The study conditions should represent the worst case for tagraxofusp-erzs shipping and should evaluate product quality post-shipment using validated methods with pre-defined acceptance criteria. The shipping qualification report will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on December 12, 2018 states that you will conduct this study according to the following schedule:

Final Report Submission: September 2019

PMC 3551-4 Conduct (b) (4) bioburden test method qualification using one additional batch of tagraxofusp-erzs drug product. The qualification report will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on December 13, 2018 states that you will conduct this study according to the following schedule:

Final Report Submission: March 2019

PMC 3551-5 Implement (b) (4) sterile filtration of tagraxofusp-erzs drug product (b) (4). The qualification report will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on December 13, 2018 states that you will conduct this study according to the following schedule:

Final Report Submission: March 2019

Submit clinical protocols to your IND 114513 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 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.

We remind you of our 12/13/2018 request to submit for a period of 10 years from the U.S. approval date, all cases of delayed engraftment or graft failure reported after allogeneic hematopoietic stem cell transplantation in patients previously treated with Elzonris (tagraxofusp-erzs) as 15-day alert reports, and to provide detailed analyses of events of delayed engraftment or graft failure reported from clinical study and postmarketing reports in your periodic safety reports (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 600.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval of Elzonris (tagraxofusp-erzs) as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of delayed engraftment or graft failure reported with Elzonris (tagraxofusp-erzs) should also be provided in the periodic safety report.

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

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 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 Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

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
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/

RICHARD PAZDUR
12/21/2018