



BLA 761312

BLA APPROVAL

Citius Pharmaceuticals, Inc.
Attention: Catherine Kessler
Executive Vice President, Regulatory Affairs
11 Commerce Drive, First Floor
Cranford, NJ 07016

Dear Ms. Kessler:

Please refer to your biologics license application (BLA) dated and received September 28, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Lymphir (denileukin diftitox-cxdl) for injection.

We acknowledge receipt of your resubmission dated February 13, 2024, which constituted a complete response to our July 28, 2023, action letter.

We are issuing Department of Health and Human Services U.S. License No. 2290 to Citius Pharmaceuticals, Inc., Cranford, NJ, 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 Lymphir (denileukin diftitox-cxdl). Lymphir is indicated for the treatment of adult patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture denileukin diftitox drug substance

(b) (4) The final formulated drug product will be manufactured and filled (b) (4)

(b) (4). The final formulated drug product will be labeled, and packaged (b) (4)

(b) (4) You may label your product with the proprietary name, Lymphir, and market it as a 300 mcg lyophilized cake in a single-dose vial, for injection.

DATING PERIOD

The dating period for Lymphir shall be 60 months from the date of manufacture when stored at 2°C to 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 (b) (4) months from the date of manufacture when stored at (b) (4) °C.

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocol(s) 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 Lymphir 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 Lymphir, or in the manufacturing facilities, will require the submission of information to your BLA 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.

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.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information).

¹ See <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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* (October 2009).²

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 enclosed carton and container labeling, specifically container labeling submitted on February 13, 2024, and carton labeling submitted on June 25, 2024, 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 *SPL Standard for Content of Labeling Technical Qs & As*. For administrative purposes, designate this submission **“Final Printed Carton and Container Labeling for approved BLA 761312.”** Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for denileukin diftotox-cxdl was not referred to an FDA advisory committee because it did not raise significant efficacy or safety concerns for the proposed indication.

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 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.

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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 visual impairment.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of visual impairment.

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

- 4670-1 Conduct a clinical study to further characterize the known serious risk of visual impairment including risk factors, manifestations, and outcomes in patients with cutaneous T-cell lymphoma (CTCL) treated with denileukin diftitox-cxdI. The visual impairment monitoring procedures in this study should include, but should not be limited to, visual acuity, slit lamp examination, dilated fundusoscopic examination, and optical coherence tomography. The study will ascertain for and closely monitor any potential risk factors associated with visual impairment. Evaluate patients with CTCL treated with denileukin diftitox-cxdI and provide data on at least 50 patients with visual impairment that occurred on denileukin diftitox-cxdI treatment.

The timetable you submitted on July 16, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	05/2025
Trial Completion:	05/2028
Final Report Submission:	09/2028

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

Submit clinical protocol(s) to your IND 110489 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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(a)(1) 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(a)(1) 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:

- 4670-2 Update the process control strategy for E7777 DS to include (b) (4) (b) (4) and provide method validation data for each sample from three independent DS batches.

The timetable you submitted on July 23, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2026

- 4670-3 Provide qualification data from three DS batches for the bioburden test using 10 mL sample volumes (b) (4) and update the BLA with the revised bioburden alert and action limits to reflect the 10 mL sample.

The timetable you submitted on July 23, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2026

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/subjects 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. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁴

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.⁵ Information and Instructions for completing the form can be found at FDA.gov.⁶

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 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 at 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:

⁴ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

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

If you have any questions, contact Ashlee Bow, Regulatory Project Manager, at 301-796-6716 or email ashlee.bow@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nicholas Richardson, DO, MPH
Deputy Director
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
- Carton and Container Labeling

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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/

NICHOLAS C RICHARDSON
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