CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761312Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)
Division of Epidemiology I (DEPI-I)
Epidemiology: ARIA Sufficiency

Date:	July 31, 2024
Reviewer:	Kate Gelperin, MD, MPH Division of Epidemiology I
Team Leader:	CDR Steven Bird, PhD, PharmD, MS, USPHS Division of Epidemiology I
Associate Director for Oncology and RWE:	Kira Leishear White, PhD, MS Division of Epidemiology I
OPE Deputy Director:	David Moeny, RPh, MPH
OSE Sentinel Program:	Sarah Dutcher, PhD
Subject:	ARIA Sufficiency Memo for visual impairment
Drug Name:	Lymphir™ (E7777, denileukin diftitox-cxdl) for injection
Application Type/Number:	BLA 761312
Applicant/sponsor:	Citius Pharmaceuticals, Inc.
Nexus TTT #:	2024-9789

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

BLA 761312, Lymphir™ (E7777; denileukin diftitox-cxdl) is a new BLA with a proposed indication 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. The recommended dosage of E7777 is 9 mcg/kg/day administered as an intravenous infusion over 60 minutes on Days 1 through 5 of a 21-day treatment cycle. Denileukin diftitox, an IL-2-receptor-directed cytotoxin, is a recombinant DNA-derived fusion protein composed of the amino acid sequences for diphtheria toxin fragments A and B. Once denileukin diftitox internalizes into the cell, the diphtheria toxin fragments inhibit protein synthesis, resulting in cell death. Proposed labeling for Lymphir will include a Boxed Warning for capillary leak syndrome, including life-threatening or fatal reactions. Proposed Warnings and Precautions include visual impairment, infusion-related reactions, hepatotoxicity, and embryo-fetal toxicity. There are no proposed Contraindications for use.

1.2. Regulatory Background

Although denileukin diftitox is the active component of both Lymphir™ (E7777) and Ontak™ (BLA 103767, previously approved), E7777 has an improved purity profile and greater potency compared to Ontak. Ontak received accelerated approval from FDA in 1999, and full approval in 2008 based on results of a randomized, placebo-controlled Phase 3 study in subjects with Stage I-III persistent or recurrent CTCL (Study 11). Of note, cases of serious visual loss (impairment of visual acuity and/or color vision) were reported post-marketing, leading to the addition of a boxed warning to Ontak labeling in 2006. (b) (4) Subsequently, in 2010, FDA advised the Applicant that human clinical study data would be required for commercialization of the more potent product, which was assigned a new development code (E7777). FDA agreed that a single-arm trial of E7777 in CTCL would be adequate for full approval (Study 302). In 2014, the manufacturing of Ontak was discontinued due to manufacturing difficulties.[1] Citius Pharmaceuticals submitted BLA 761312 to FDA on September 28, 2022, seeking approval for E7777; however, a Complete Response was issued on July 28, 2023, based on multiple product quality deficiencies that were identified and not adequately addressed during the BLA assessment period. On March 14, 2024, FDA acknowledged receipt of a complete, class 2 response to the July 28, 2023 action letter based on Citius Pharmaceuticals resubmission to BLA 761312 for E7777 (denileukin diftitox-cxdl) on February 13, 2024. The resubmission package is currently under review, with a PDUFA target date of August 13, 2024.

1.3. Describe the Safety Concern

The pivotal study supporting BLA 761312 (E7777, denileukin diftitox-cxdl) was Study 302, an open-label, single-arm, multicenter trial in patients with relapsed or refractory Stage I to IV

[1] NDA/BLA Multi-disciplinary Review and Evaluation; IND 1110489 / BLA 761312; E7777 (denileukin diftitox); DARRTS Ref ID 5216748; dated July 28, 2023; page 26.

cutaneous T-cell lymphoma (CTCL).[2] The original protocol for Study 302 included visual impairment as a dose limiting toxicity and included either loss of visual acuity or color vision changes. The initial protocol included two visual assessments to check for loss of visual acuity and loss of color vision at screening, end of treatment, and extension phase (when a patient presented with a symptom). Any visual loss including visual acuity impairment, color or shape distortion, or blurred vision compared to baseline was to lead to permanent study treatment discontinuation. However, the protocol was amended and the previously required visual acuity tests were removed.[3] Nine patients (13%) in the Stage I to III Safety Analysis Set (N = 69 patients) had an event related to visual impairment, and all of these were described as blurred vision. Of the patients with visual impairment, 67% had resolution of their visual impairment. DHM2 consulted Dr. Wiley Chambers (FDA ophthalmologist) on March 2, 2023, to request his assessment and recommendations regarding visual impairment with E7777. Dr Chambers concluded that: [4]

- Study 302 was amended to remove all ocular testing. No reliable ophthalmic testing was included in the study. The actual frequency and cause of the ocular adverse events is unknown.
- Study 302 did not appropriately monitor or evaluate the test product in spite of known toxicities of a related drug product. The cause of the blurred vision is unknown because it was not evaluated. A future study evaluating the ocular effects should be required.
- Labeling of the product should include the potential for blurred vision of unknown etiology. Labeling of the product should require baseline and regular interval monitoring with ophthalmic examinations including visual acuity, slit lamp examinations, dilated funduscopic examination and optical coherence tomography.

Visual impairment is a notable medical event and an identified risk with denileukin diftitox. Thus, additional data are required to characterize ophthalmologic toxicity and inform patient labeling regarding risk, recommended assessments, and mitigation strategies. The goal of a postmarket study is to assess the risk of and characterize visual impairment in patients receiving E7777 (denileukin diftitox-cxdl) for the treatment of relapsed or refractory CTCL.

A **Warning and Precaution** is planned for LYMPHIR™ (denileukin diftitox-cxdl), as follows:

5.2 Visual Impairment

LYMPHIR can cause serious visual impairment, including changes in visual acuity and color vision. In the pooled population across 3 clinical trials, visual impairment occurred in 9%, with Grade 1 in 8% and Grade 2 in 1%. The most commonly reported symptom was blurred vision. Of the patients with visual impairment, 67% had resolution of their visual impairment.

Perform baseline ophthalmic examination and monitor as clinically indicated. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, or blurred vision, refer for ophthalmologic evaluation.

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[2] *Note*: Subjects with Stage IV disease were excluded from the primary efficacy analysis set to match the population of Ontak Study 11. Substantial evidence of efficacy of E7777 in patients with relapsed or refractory Stage I-III CTCL is based on overall response rate in Study 302. Sixty-nine patients with Stage I-III CTCL were evaluable for efficacy.

[3] Excerpted from data summary in DHM2 Request for OSE Consultation; DHM2; DARRTS Ref ID 5396676; dated June 12, 2024.

[4] Wiley A. Chambers, MD; Ophthalmology Consultation; Medical Officer's Review of BLA 761312; DARRTS Ref ID 5142340; dated March 15, 2023

Withhold or permanently discontinue LYMPHIR based on severity [see Dosage and Administration (2.4)].

1.4. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.5. Statement of Purpose

The purpose of this ARIA memo is to evaluate whether ARIA is sufficient to characterize the safety of E7777 regarding the incidence of and risk factors for visual impairment and to provide clinical details on results of testing for visual acuity, slit lamp examination, dilated funduscopic examination, and optical coherence tomography before and at multiple timepoints after administration of E7777. The goal of the post-market study is signal evaluation, to assess the incidence of and risk factors for visual impairment and to further characterize the clinical characteristics of visual impairment cases, including results of specialized ophthalmologic testing. The results of a post-market study will be used to refine the risk mitigation strategies included in labeling.

1.6. Effect Size of Interest or Estimated Sample Size Desired

Because the interest is in assessing risk factors and clinical characteristics of visual impairment cases after administration of E7777 in adults with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL), this study will be a single arm prospective study. The stated goal of the PMR is to characterize the incidence, risk factors, and clinical characteristics of at least 50 patients who develop visual impairment after administration of E7777. Target sample size will be a protocol review issue.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The population of interest is adult patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL). ICD-10 codes can be used to ascertain patients with CTCL.

2.2 Is ARIA sufficient to assess the intended population?

Yes. ARIA is sufficient to assess the intended population based on ICD-10 codes for diagnosis of CTCL in administrative claims data.

3 EXPOSURES

3.1 Treatment Exposure(s)

The treatment exposure of interest is E7777 (denileukin diftitox-cxdl) which is administered by intravenous infusion in a clinical setting.

3.2 Comparator Exposure(s)

There is no comparator exposure of interest.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes, it is expected that billing claims will be available to identify E7777 (denileukin diftitox-cxdl).

4 OUTCOME(S)

4.1 Outcomes of Interest

The primary outcome of interest is visual impairment characterized by results of specialized ophthalmologic testing including, but not limited to, visual acuity, slit lamp examination, dilated funduscopic examination, and optical coherence tomography.

4.2 Is ARIA sufficient to assess the outcome of interest?

No, ARIA is insufficient for the following reasons:

First, diagnostic codes in administrative claims do not provide data on visual acuity and do not have acceptable sensitivity for visual impairment, which is required for assessment of the outcome of interest. A validation study conducted by CDC's Vision and Eye Health Surveillance System [5] (VEHSS) among patients at a university ophthalmology clinic found that diagnosis codes for diagnosed blindness and low vision have very low sensitivity (0.02) and very high specificity (0.83) for detecting best corrected visual acuity loss of 20/40 or worse in the better-seeing eye. Diagnosed legal U.S. blindness had a sensitivity of 0.04 and specificity of 1.0 for detecting best corrected visual acuity loss of 20/200 or worse.[6]

Second, administrative claims do not include information that is necessary to characterize visual impairment and do not provide necessary clinical details to determine the nature and severity of the specific eye disease process. Specifically, results of specialized ophthalmologic testing (visual acuity, slit lamp examination, dilated funduscopic examination, and optical coherence tomography) are not available in ARIA.

5 COVARIATES

5.1 Covariates of Interest

Covariates of interest include concomitant medications and comorbidities, which may be risk factors for visual impairment.

5.2 Is ARIA sufficient to assess the covariates of interest?

Yes. ARIA can capture drug and necessary medical history covariates (e.g., comorbidities).

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

A single arm cohort with incidence rates for study outcomes and analysis of risk factors is needed.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. ARIA's design and analytic tools are expected to be sufficient for a single arm cohort study

[5] Centers for Disease Control and Prevention: Vision and Eye Health Surveillance System (VEHSS). Available at https://www.cdc.gov/vision-health-data/case-definitions/diagnosed-vision-disorders.html.

[6] Wittenborn JS, Lee AY, Lundeen EA, et al. Validity of Administrative Claims and Electronic Health Registry Data From a Single Practice for Eye Health Surveillance. JAMA Ophthalmol. 2023 Jun 1;141(6):534-541. https://pubmed.ncbi.nlm.nih.gov/37140901/

design.

7 NEXT STEPS

Because ARIA is deemed insufficient, DHM2 plans to issue a postmarketing requirement (PMR) to the Applicant for a prospective observational study (registry) to gather detailed clinical safety data on visual impairment associated with administration of E7777 (denileukin diftitox-cxdl).

DHM2 plans to issue the following PMR to the Applicant:

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 treated with denileukin diftitox-cxdl. The visual impairment monitoring procedures in this study should include, but should not be limited to, visual acuity, slit lamp examination, dilated funduscopic 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-cxdl and provide data on at least 50 patients with visual impairment that occurred on denileukin diftitox-cxdl treatment. PMR/PMC Schedule Milestones:

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

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/s/

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DAVID G MOENY
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 3, 2024

To: Ashlee Bow, Regulatory Project Manager
Division of Hematological Malignancies II (DHM2)

From: Louiza Bako, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for LYMPHIR™ (denileukin diftitox-cxdl) for injection, for intravenous use

BLA: 761312

Background:
In response to DHM2's consult request dated June 13, 2024, OPDP has reviewed the proposed Prescribing Information (PI) for the original BLA submission for LYMPHIR™ (denileukin diftitox-cxdl) for injection, for intravenous use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on June 20, 2024, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Louiza Bako at (301) 796-3970 or Louiza.Bako@fda.hhs.gov.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 26, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761312
Product Name, Dosage Form, and Strength:	Lymphir (denileukin diftitox-cxdl)[a] for injection, 300 mcg/vial
Applicant Name:	Citius Pharmaceuticals, Inc. (Citius)
FDA Received Date:	June 25, 2024
TTT ID #:	2022-2055-4
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The nonproprietary name "denileukin diftitox-cxdl" was found conditionally acceptable for this BLA on June 3, 2024.

1 PURPOSE OF MEMORANDUM

Citius Pharmaceuticals, Inc. (Citius) submitted revised carton labeling received on June 25, 2024 for Lymphir. We reviewed the revised carton labeling for Lymphir (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to a recommendation that we made during a previous label and labeling review.[b]

2 CONCLUSION

Citius Pharmaceuticals, Inc. (Citius) implemented our recommendation and we have no additional recommendations at this time.

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[b] Black, S. Label and Labeling Review for Lymphir (BLA 761312). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JUN 13. TTT ID: 2022-2055-3.

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NICOLE F IVERSON
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 13, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761312
Product Name, Dosage Form, and Strength:	Lymphir (denileukin diftitox-cxdl)[a] for injection, 300 mcg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Citius Pharmaceuticals, Inc. (Citius)
FDA Received Date:	July 14, 2023 and February 13, 2024
TTT ID #:	2022-2055-3
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The nonproprietary name "denileukin diftitox-cxdl" was found conditionally acceptable for this BLA on June 3, 2024.

1 INTRODUCTION

As part of the approval process for Lymphir (denileukin diftitox-cxdl) for injection, we reviewed the proposed Lymphir Prescribing Information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

The active ingredient, denileukin diftitox is currently approved under BLA 103767 for Ontak. Ontak was approved on February 5, 1999 for the treatment of adult patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. In 2014, Ontak production was discontinued due to manufacturing issues. The Applicant has indicated that Lymphir will replace Ontak (b) (4).

1.2 REGULATORY HISTORY

Citius Pharmaceuticals, Inc. previously submitted BLA 761312 on September 28, 2022. We completed a label and labeling review on May 3, 2023[b]. Our container label and carton labeling recommendations were provided to Citius on May 3, 2023. In addition, our recommendations for the PI were provided to Citius on May 24, 2023.

Citius submitted revised labels and labeling on May 10, 2023 and May 11, 2023 and we completed a label and labeling memo on May 15, 2023[c]. Subsequently, our container label and carton labeling recommendations were provided to Citius on May 15, 2023.

Citius submitted revised labels and labeling on May 30, 2023 and we completed a second label and labeling memo on June 1, 2023[d]. At that time, we did not have additional recommendations for the container label and carton labeling. However, the application received a Complete Response letter (CRL) on July 28, 2023 due to product quality issues.[e]

Thus, Citius Pharmaceuticals, Inc. submitted a Class 2 Resubmission on February 13, 2024 to address the product quality deficiencies noted in the CRL.[f]

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[b] Iverson, N. Label and Labeling Review for Lymphir (BLA 761312). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 03. TTT ID No.: 2022-2055.
[c] Iverson, N. Label and Labeling Memo for Lymphir (BLA 761312). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 15. TTT ID No.: 2022-2055-1.
[d] Iverson, N. Label and Labeling Memo for Lymphir (BLA 761312). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JUN 01. TTT ID No.: 2022-2055-2.
[e] Bow, A on behalf of Nicolas C. Richardson. Complete Response for BLA 761312. Silver Spring (MD): FDA, CDER, OND, Division of Hematologic Malignancies 2 (DHM 2) (US); 2023 JUL 28. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806e430a.
[f] Cover Letter – Resubmission – Complete Response to Action Letter Issue 28 July 2023. Cranford (NJ): Citius Pharmaceuticals, Inc.; 2024 FEB 13. Available from: \\CDSESUB1\EVSPROD\bla761312\0042\m1\us\11-forms\356h.pdf.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761312.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Citius Pharmaceuticals, Inc. submitted a 351(a) application to obtain marketing approval of denileukin diftitox-cxdl for Injection. Lymphir is proposed 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. We note the active ingredient, denileukin diftitox is currently approved under BLA 103767 for Ontak. Ontak was approved on February 5, 1999 for a similar indication (treatment of adult patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor) as the proposed product. Production of Ontak was discontinued in 2014 due to manufacturing issues. The initial denileukin diftitox dosage form was developed as frozen liquid DP (FDP) formulation which required storage at (b) (4) -10°C and thawing before use. (b) (4) the shelf life storage condition was limited to 12 months for distribution. Because of the limitation of FDP, a lyophilized DP (LDP) formulation was developed to improve the stability of denileukin diftitox DP and to have a more convenient storage temperature (2°C to 8°C). Thus, denileukin diftitox - xxxx will replace Ontak for commercial distribution and use.

We performed a risk assessment of the proposed container label, carton labeling, and PI for Lymphir for Injection to determine whether there are significant concerns in terms of safety related to preventable medication errors. We note that most of recommendations for the PI and all our recommendations for the container label and carton labeling were implemented.

We identified areas of the proposed PI that could be revised to improve clarity and readability of important information. We provide recommendations for the Division in Section 5 and for Citius Pharmaceuticals, Inc. in Section 6 to address these deficiencies.

4 CONCLUSION

We evaluated the proposed Lymphir container label and determined that it is acceptable from a medication error perspective. However, the proposed Lymphir PI and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Hematologic Malignancies 2 (DHM 2) in Section 5 and for Citius Pharmaceuticals, Inc. in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Prescribing Information

1. Section 2 Dosage and Administration
    a. The unit of measure (e.g., mL) does not follow each numeric value in Table 1. To minimize confusion and potential risk of wrong dose errors, we recommend including the unit of measure after each numeric value. Revise "250 to 500 mL" to "250 mL to 500 mL".
    b. In Section 2.5, under subsection "Reconstitution" (bullet 2), we recommend including the temperature range. For example, revise to "Remove the vial(s) of LYMPHIR from the refrigerator and allow to stand for approximately 30 minutes to reach to room temperature [20°C to 25°C (68°F to 77°F)]."
    c. In Section 2.5, under subsection "Dilution" (bullet 5), for consistency within this section, we recommend revising the statement to "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the prepared solution is cloudy or particulates are present."

6 RECOMMENDATIONS FOR CITIUS PHARMACEUTICALS, INC.

A. Carton Labeling

1. The information regarding additional dilution is missing from the side panel. Including this information will inform healthcare providers during product preparation. We recommend revising the reconstitution instructions to "Following reconstitution with 2.1 mL Sterile Water for Injection USP, the resulting concentration of denileukin diftitox-cxdl is 150 mcg/mL. After reconstitution, further dilution is required."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Lymphir received on February 13, 2024 from Citius Pharmaceuticals, Inc.

Table 2. Relevant Product Information for Lymphir	
Initial Approval Date	NA
Nonproprietary Name	denileukin diftitox-cxdl
Indication	Treatment of adult patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy
Dosage Form	for injection
Strength	300 mcg/vial
Route of Administration	intravenous infusion
Dose and Frequency	The recommended dosage of LYMPHIR is 9 mcg/kg/day actual body weight administered as an intravenous infusion on Days 1 through 5 of a 21-day cycle
How Supplied	LYMPHIR (denileukin diftitox-cxdl) for injection is supplied as a sterile, white, lyophilized powder for reconstitution in a single-dose vial containing 300 mcg denileukin diftitox-cxdl. Each carton contains one vial: NDC 52658-7777-01
Storage	Store LYMPHIR in a refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Lymphir labels and labeling submitted by Citius Pharmaceuticals, Inc.

- Prescribing Information received on February 13, 2024, available from \\CDSESUB1\EVSPROD\bla761312\0042\m1\us\114-labeling\114a-draft-label\spl\f190bcab-2a16-40d9-b35a-9a21ef16085d.xml
- Container label received on February 13, 2024
- Carton labeling received on February 13, 2024

B.2 Container Label and Carton Labeling Images

Container label

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[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On May 9, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, "denileukin diftitox-cxdl" and "761312". Our search identified 3 previous reviews[h,i,j], and we considered our previous recommendations to see if they are applicable for this current review.

[h] Iverson, N. Label and Labeling Review for Lymphir (BLA 761312). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 03. TTT ID No.: 2022-2055.

[i] Iverson, N. Label and Labeling Memo for Lymphir (BLA 761312). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 15. TTT ID No.: 2022-2055-1.

[j] Iverson, N. Label and Labeling Memo for Lymphir (BLA 761312). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JUN 01. TTT ID No.: 2022-2055-2.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 1, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761312
Product Name, Dosage Form, and Strength:	Lymphir (denileukin diftitox-cxdl) for Injection, 300 mcg/vial
Applicant/Sponsor Name:	Citius Pharmaceuticals, Inc.
TTT ID #:	2022-2055-2
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on May 30, 2023 for Lymphir. We reviewed the revised container label and carton labeling for Lymphir (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Iverson, N. Label and Labeling Review for Lymphir (BLA 761312). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 15. TTT ID No.: 2022-2055-1.

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Clinical Inspection Summary

Date	5/19/2023
From	Leigh Marcus, M.D., Senior Physician Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Ashlee Bow, Regulatory Project Manager Shyamli Singla, M.D., Medical Officer Nicholas Richardson, D.O., M.P.H., Team Leader Nicole Gormley, M.D., Division Director Division of Hematologic Malignancies 2 (DHM2) Office of Oncologic Diseases (OOD)
BLA #	761312
Applicant	Citius Pharmaceuticals, Inc.
Drug	Denileukin diftitox (E7777)
NME	Yes
Review Priority	Priority
Proposed Indication	For the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma after at least one prior systemic therapy, (b) (4)
Consultation Request Date	11/17/2022
Summary Goal Date	6/3/2023
Action Goal Date	7/19/2023
PDUFA Date	7/28/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study E7777-G000-302 were submitted to the Agency in support of this Biologic License Application (BLA) for denileukin diftitox (E7777) for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy, (b) (4).

Two clinical investigators (CIs) Drs. Madeleine Duvic (Site #1005), and Francine Foss (Site #1007), as well as the study sponsor, Eisai, Inc., were inspected for Study E7777-G000-302.

Based on the inspection results of the above two CIs as well as the sponsor, the clinical data generated by these sites are verifiable. The sponsor's oversight and monitoring of Study E7777-G000-302 were adequate. This study appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Denileukin diftitox injection for intravenous use was being developed under INDs 004682 and 110489 for the treatment of subjects with persistent or recurrent CTCL after at least one prior systemic therapy, (b) (4)
The sponsor has submitted the results of Study E7777-G000-302, an open-label, single-arm, dose-escalation and expansion trial, to support efficacy and safety of denileukin diftitox for the proposed indication.

Study E7777-G000-302

Study E7777-G000-302 was an open-label, single-arm, dose-escalation and expansion trial in subjects with persistent or recurrent Stage I to III CD25(+) CTCL. Eligible subjects were required to have expression of CD25 on ≥ 20% of biopsied malignant cells by immunohistochemistry. The study had 2 parts:

-Lead-In: A continual reassessment method (CRM) was used to establish the maximum tolerated dose (MTD) of denileukin diftitox and to select the dose of denileukin diftitox to be used in the Main Study. An approximate 20% rate of dose-limiting toxicity (DLT) was targeted.

-Main Study: The objectives of the Main Study were to assess the efficacy and safety of denileukin diftitox in Stages I to III subjects with recurrent and persistent CTCL.

The study was comprised of 3 periods: a screening and enrollment period, a study intervention period, and a post study follow up period. The proposed dosing regimen of denileukin diftitox administered by intravenous infusion was 9 mcg/kg/day for 5 consecutive days of each 21-day treatment cycle until unacceptable toxicity or up to 24 weeks (8 cycles). Subjects who attained skin tumor response and were deriving clinical benefit from denileukin diftitox treatment could have continued receiving treatment beyond 8 cycles, at the discretion of the treating physician.

The efficacy of denileukin diftitox in subjects with persistent or recurrent CTCL was assessed by objective response rate (ORR), according to International Society for Cutaneous Lymphomas (ISCL)/European Organization for Research and Treatment of Cancer (EORTC) Global Response Score (GRS) per Independent Review Committee (IRC, Olsen 2011). Tumor assessment and response criteria was a composite measure of tumor burden in skin, lymph node, viscera, and blood (tumor-node-metastasis-blood [TNMB] classification). Tumor

responses were also assessed by the site investigator, and these investigator assessments were used to make subject treatment decisions.

- Skin disease was assessed by quantifying total body surface area involvement using a modified Severity Weighted Assessment Tool (mSWAT) score. mSWAT scoring was performed by the investigator. Skin photographs were submitted for review by the IRC to determine if they appeared consistent with the mSWAT score provided by the investigator.
- Lymph node disease was monitored by palpation and assessed by computed tomography (CT) scan and/or biopsy, as necessary for determination of GRS.
- Blood tumor burden was assessed by quantifying CD4+CD26- cells by flow cytometry by the central laboratory; CD4+CD7-cells were used in CD26+ subjects.
- Visceral disease was assessed by CT scan, as appropriate.

The primary efficacy endpoint analysis included 69 subjects with persistent or recurrent CTCL: 64 subjects from the Stages I to III Main Study and 5 subjects from the Lead-In who had Stage I to III CTCL and received denileukin diftitox at a dose of 9 mcg/kg.

The trial was conducted in 21 sites in 2 countries. Study subjects first enrolled on May 30, 2013. Data cut-off date for the primary analysis was December 6, 2021. The study was closed at the time of the inspection.

Rationale for Site Selection

Two CIs: Drs. Madeleine Duvic (Site #1005), and Francine Foss (Site #1007), as well as the study sponsor, Eisai, Inc. were requested for clinical inspections in support of the application. The clinical sites were chosen primarily based on risk ranking in the BIMO clinical investigator Site selection tool (CISST), numbers of enrolled subjects, and prior inspectional history, each of which may have an impact in the review division's clinical decision-making process.

III. RESULTS

1. Madeleine Duvic, M.D./Site: #1005
   1515 Holcombe Boulevard
   Unit 1452
   Houston, TX 77030

   Inspection Dates: 1/9/2023 – 1/13/2023

   This was a comprehensive, PDUFA routine inspection of Dr. Duvic. The previous inspection of Dr. Duvic was conducted 9/14 - 26/2017, a for cause inspection related to an OSI complaint, in which Study C25001 Amendment 5, and Study RP6530-1401 were inspected. No Form FDA 483 was issued at the conclusion of that inspection.

Dr. Duvic had been removed as the CI of record for Study E7777-G000-302 on 5/2/2016, subsequent to failing a MD Anderson Cancer Center internal audit. On 5/23/2016, MD Anderson Cancer Center advised FDA that Dr. Duvic had been removed due to "serious and continuing noncompliance with human subjects protections" as determined by the investigational review board (IRB). The audit identified consistent nonadherence to IRB-approved studies, lack of adequate supervision of delegated study tasks, and consistent non-adherence to MD Anderson IRB policies on informed consent and authorization, unanticipated adverse event or problem reporting, and the "Principle Investigator (PI) override process". The audit also revealed non-compliance with MD Anderson's institutional conflict of interest (COI) policy and related IRB and Conflict of Interest Committee (COIC) requirements. Dr. Duvic's continued non-compliance with the IRB and institutional policies impacted the safety of subjects that participate in human subjects' research such that Dr. Duvic's research privileges were suspended, and therefore she was no longer CI for Study E7777-G000-302 starting 5/19/2016. Dr. Auris Huen took over as CI on the record for the study. Upon completion of refresher training, developing and implementing a corrective and preventive action plan, Dr. Duvic was reinstated as MD Anderson physician on 8/14/2018 and as CI for Study E7777-G000-302 from 9/24/2018 through the study's database lock on 3/15/2022.

At this site for Study E7777-G000-302, 16 subjects were screened and enrolled in the study, and 5 subjects were screen failures. At the time of the inspection, 10 subjects completed the study, 1 subject was lost to follow up, 3 subjects withdrew consent, and 2 subjects died during the drug treatment phase of the study.

During the inspection, subject records reviewed included informed consent, eligibility, subject medical records, concomitant medication, adverse events/serious adverse events, protocol deviations, and the primary efficacy endpoint. The regulatory records reviewed included IRB approval letters and correspondence; protocol amendments; Form 1572s, financial disclosures, investigational product accountability, site signature and responsibility logs, and site training documentation, and monitoring reports.

Sixteen subject records were reviewed (100%) and primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events. The subjects in the Lead-In phase of the study received the IP doses assigned.

At the end of the inspection, an FDA Form 483 was issued with three observations listed below:

OBSERVATION 1
"An investigation was not conducted in accordance with the investigational plan."

Specifically,
Subject # (b) (6) died on (b) (6), however a completed SAE form via email was submitted on (b) (6).

Dr. Duvic responded that the completed SAE form was submitted on Monday, (b) (6), the first business day after became Dr. Duvic aware of the subject's death, on Saturday, (b) (6).

Reviewer's comment: According to the protocol, all SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event. This SAE was indeed reported 1 business day after Dr. Duvic was aware of the event due to the weekend. The CI's response is acceptable.

OBSERVATION 2
"The general requirements for informed consent were not met in that the information given was not in a language understandable to the subject or the subject's representative."

Subject # (b) (6) was a non-English speaking subject. On (b) (6), the CI obtained informed consent from this subject using an English language informed consent document.

There were no foreign language informed consent documents (ICD) observed including no short forms. Dr. Duvic communicated with Subject # (b) (6) via a Russian translator; however the subject signed an English language ICD.

Dr. Duvic responded that a Russian interpreter was contemporaneously documented on (b) (6) and an English ICD was signed.

Reviewer's comment: This was an isolated event and unlikely to have a significant impact on the safety or results of the study.

OBSERVATION 3
"Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation."

Dosing documents were missing, neither the site nor the pharmacy maintained the dosing documents for the following 8 subjects: (b) (6).

Reviewer's comment: While it is important to maintain documents relevant to the study to ensure all study procedures were completed in accordance with the study and to potentially minimize harm to the subjects, Citius, the sponsor, did ultimately provide the site with USB drives containing electronic subject data for the study.

Following the inspection, Dr. Duvic responded to the 483 on January 30, 2023 stating that the study team conducted a comprehensive review of the identified cases' source documentation and data discrepancies. Dr. Duvic and the study team plan to complete training on

investigational plan compliance including compliance with SAE reporting provided by MD Anderson's Clinical Research and Training group, and develop and implement additional processes to monitor SAE reporting compliance with investigational plan and sponsor requirements. A complete training specific to the informed consent process for non-English-speaking subjects will be provided by MD Anderson's Clinical Research & Training Education group, and a process flowsheet to ensure consent for non-English speaking subjects in accordance with MD Anderson IRB policy was developed. Dr. Duvic and her team plan also to complete an online training module titled, "Research Education: Source Documentation."

Reviewer's comments: The CI's response and the corrective plan and actions are acceptable. The clinical impact of the above issues was discussed with DHM2 clinical review team. DHM2 concurred that the issues stated in the FDA Form 483 had no significant impact on efficacy or safety results.

2. Francine Foss, M.D./Site: #1007
   333 Cedar Street
   PO Box 208028
   New Haven, CT 06520

   Inspection Dates: 1/30/2023 – 2/3/2023

   This was a comprehensive, PDUFA routine inspection of Dr. Foss. The previous FDA inspection of Dr. Foss was conducted 6/25 – 7/12/2013 and received a final classification of VAI. A FDA Form 483 was issued at the close of that inspection with the following observations: 1) An investigation was not conducted in accordance with the signed statement of investigator and investigational plan; 2) The general requirements for informed consent were not met in that the information given was not in language understandable to the subject or the subject's representative; and 3) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

   At this site for Study E7777-G000-302, 13 subjects were screened, and 8 subjects were enrolled. One subject completed the treatment cycles, 5 subjects did not complete treatment due to disease progression (PD), 1 subject had withdrawal of consent, and Subject (b) (6) discontinued treatment due to adverse event (AE) which was a preexisting medical condition of skin pain with ineffective treatment. The study site was closed to all study activities at the time of the inspection.

   During the inspection, subject records reviewed included informed consent, source documents, subject eligibility, concomitant medications, adverse events/serious adverse events, laboratory results, protocol deviations, and primary efficacy data. The regulatory records reviewed included IRB submissions for initial approval and continuing reviews, protocol amendments, monitoring documents, Form 1572s, financial disclosures, and test article accountability.

There was no under reporting of AEs. The primary efficacy endpoint data were verifiable except one assessment at one timepoint at Cycle 9 for Subject # (b) (6) as described below. At the end of the inspection, an FDA Form 483 was issued for failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation, including inconsistencies with efficacy endpoint assessments.

Subject # (b) (6) was reported as Stable Disease (SD) in Cycle 9 ((b) (6)), however, source documentation demonstrates the subject met the definition of PD for skin response based on mSWAT score at this timepoint. In the data listings, Subject # (b) (6) had partial response (PR) on best overall response (BOR) based on skin response from IRC, and PR on overall BOR from IRC.

Reviewer's comment: The efficacy of denileukin diftitox in subjects with persistent or recurrent CTCL was assessed by ORR according to ISCL/EORTC GRS per IRC. It was discussed with DHM2 clinical team and they concurred that the error of the primary efficacy documented as SD when the subject had PD at one timepoint at Cycle 9 would not change the overall efficacy result for this subject or the entire study.

Subjects (b) (6) were incorrectly and inconsistently staged and enrolled in the Main study, in which subjects with any stage of CTCL were eligible to enroll. TNMB classifications entered in the EDC for all three subjects were not supported by source documentation, resulting in incorrect calculation of CTCL Disease Staging for these subjects. Additionally, the data entry into the EDC were delayed. For example, Subject # (b) (6) was screened in (b) (6) but the TNMB classification was not entered until (b) (6).

Reviewer's comment: Three subjects had incorrect CTCL Disease Staging and thus were "up" staged. DHM2 has analyses of efficacy (ORR) based on Stage, and changing the original Staging by upstaging do not appear to change the overall results. Additionally, all stages were eligible and enrolled on the trial, therefore this is less likely to be clinically significant.

Following the inspection, Dr. Foss responded to the 483 on February 15, 2023 stating that the study team conducted a comprehensive review of the identified subjects source documentation and data discrepancies. A Corrective and Preventive Action (CAPA) Plan was submitted. Training to reinforce understanding of the principles of Good Documentation Practices will be explored, including information to heighten awareness of the ramifications of inadequate documentation, underscoring the investigator's responsibilities to ensure proper and adequate documentation.

Reviewer's comment: The CI's response and the corrective plan and actions are acceptable, and DHM2 concurred that the issues stated in the FDA Form 483 had no clinical effect on efficacy or safety.

In general, the inspection verified adequate source data for the study subjects at the site.

2. Eisai Inc.
200 Metro Blvd
Nutley, NJ 07110

Inspection Dates: 1/30/2023 – 2/9/2023

On 8/31/2021, Eisai, Inc. (Eisai) transferred its rights to the drug product, denileukin diftitox, to Citius Pharmaceuticals, Inc. (Citius). However, all study related activities were conducted by Eisai. According to their agreement, all study related documents will be transferred to Citius after the application is approved.

Previous inspection of Eisai was conducted from 1/18/2018 - 2/16/2018. A FDA Form 483 Inspectional Observations was issued during the inspection and contained the observation for failure to ensure that an investigation was conducted in accordance with the general investigational plan and studies as specified in the Investigational New Drug (IND). The inspection was classified as VAI.

The current inspection covered sponsor practices related to Study E7777-G000-302 and focused on the two clinical investigator sites chosen for inspection, Sites #1005 and #1007. There were no study clinical holds or holds for non-compliance on Study E7777-G000-302. No sites were terminated or discontinued.

Records reviewed during the inspection included, but were not limited to:

- Organizational charts
- Independent Review Committees' activities and responsibilities ((b) (4) , provided the IRC assessment studies and relevant clinical data)
- Vendor list
- Contracts
- Monitoring plans, and reports ((b) (4) contracted monitors but were managed by Eisai, (D) (4))
- Qualifications of monitors
- Case report forms (eCRFs)
- Test article accountability and procedures
- Joint safety review committee
- Handling of adverse events (AE)

The following item were discussed at the end of inspection:

1. Correspondences, surveys, and startup packages to ensure Site #1007 was ready to transmit data to the IRC were no longer available.
2. Some of the monitoring visit reports were cut-off and are no longer accessible.

Templates were used and when printed, not all data were included. Since then, Eisai has new ways of reporting their monitoring visit reports.

3. Inadequate documentation which showed Eisai responded to Site #1005's request for additional resources. Eisai initially noted they had no documentation about them assisting the site, but later found some meetings that they did. They needed to search through the Trial Master File (TMF) to get to the meeting minutes and only found a few sentences regarding their actions. The clinical team also visited the site multiple times but there is no record of what was discussed.
4. Data management was unable to unfreeze data for Site #1007 (one data point), even though the site requested to unfreeze data to correct their primary efficacy data point.

Eisai has implemented a number of corrective steps to ensure documents filed to the electronic Trial Master File (eTMF) are complete. They understood the findings above and will ensure all study documents are stored within the TMF.

Reviewer's comment: The sponsor's corrective actions are acceptable.

At the conclusion of the inspection no FDA Form 483 (Inspectional Observations) was issued. Overall, the sponsor's oversight and monitoring for Study E7777-G000-302 appear adequate except the discussion items noted above.

{See appended electronic signature page}

Leigh Marcus, M.D. Senior Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D. Team Leader
Good Clinical Practice Assessment Branch
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Jenn Sellers, M.D., Ph.D. Branch Chief
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

cc:

Central Document Room/BLA #761312
Division of Division of Hematologic Malignancies 2 (DHM2)
Division Director/Nicole Gormley
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OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Min Lu
OSI/DCCE/GCPAB/Senior Physician/Leigh Marcus
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 15, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761312
Product Name, Dosage Form, and Strength:	Lymphir (denileukin diftitox-cxdl) for Injection, 300 mcg/vial
Applicant/Sponsor Name:	Citius Pharmaceuticals, Inc.
TTT ID #:	2022-2055-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on May 10, 2023 for Lymphir. We reviewed the revised container label and carton labeling for Lymphir (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. The established name lacks prominence and the graphic is prominent on the carton labeling

3 RECOMMENDATIONS FOR CITIUS PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container label and Carton labeling)
    1. The established name is not at least half the size of the proprietary name. We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be

[a] Iverson, N. Label and Labeling Review for Lymphir (BLA 761312). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 03. TTT ID No.: 2022-2055.

printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

2. As currently presented, the established name/proper name does not have adequate legibility. The proprietary name and established or proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). Inadequate legibility of important information like the proprietary and established or proper names may lead to confusion during identification of the medical product, which can lead to medication errors. We recommend improving the legibility of the established name. You could consider utilizing a larger font size or heavier type or other means to achieve this.

B. Carton Labeling

1. As currently presented, the graphic competes with the prominence of the proprietary name on the principal display panel. The proprietary name and established or proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). Furthermore, see 21 CFR 201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter. Consider decreasing the prominence of the graphic relative to the prominence of the proprietary name on the principal display panel needed for proper identification and use of your proposed product in accordance with 21 CFR 201.15(a)(6).
2. As currently presented, the manufacturer name, "Citius" is prominent at the bottom of the principal display panel of the carton labeling, which makes the critical information appear crowded. The proprietary name and established or proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). We recommend decreasing the prominence of the manufacturer name taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 3, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761312
Product Name, Dosage Form, and Strength:	Lymphir (denileukin diftitox-cxdl) for Injection, 300 mcg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Citius Pharmaceuticals, Inc.
FDA Received Date:	September 28, 2022 and April 12, 2023
TTT ID #:	2022-2055
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Lymphir (denileukin diftitox-cxdl) for Injection, we review the proposed Lymphir Prescribing Information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

The active ingredient, denileukin diftitox is currently approved under BLA 103767 for Ontak. Ontak was approved on February 5, 1999 for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. In 2014, Ontak production was discontinued due to manufacturing issues. The Applicant has indicated that Lymphir will replace Ontak [redacted] (b) (4)

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Citius Pharmaceuticals, Inc. submitted a 351(a) application to obtain marketing approval of Lymphir (denileukin diftitox-cxdl) for Injection. Lymphir is proposed for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy, [redacted] (b) (4). We

note the active ingredient, denileukin diftitox is currently approved under BLA 103767 for Ontak. Ontak was approved on February 5, 1999 (b) (4) (b) (4) Production of Ontak was discontinued in 2014 due to manufacturing issues. The initial denileukin diftitox dosage form was developed as frozen liquid DP (FDP) formulation which required storage at a (b) (4) -10°C and thawing before use. (b) (4) the shelf life storage condition was limited to 12 months for distribution. Because of the limitation of FDP, a lyophilized DP (LDP) formulation was developed to improve the stability of denileukin diftitox DP and to have a more convenient storage temperature (2°C to 8°C). Thus, denileukin diftitox - xxxx will replace Ontak for commercial distribution and use.

We performed a risk assessment of the proposed container label, carton labeling, and PI for Lymphir for Injection to determine whether there are significant concerns in terms of safety related to preventable medication errors. We note that the dilution instructions with 0.9% Sodium Chloride Injection, USP lacked clarity in the Dosage and Administration. We sent an Information Request to the Applicant requesting the instructions of how dilution with 0.9% Sodium Chloride Injection, USP was performed in the clinical study and if there is a final concentration that should be maintained for this step. The Applicant responded on April 12, 2023 with preparation instructions used in the clinical study. We will further clarify our recommendations below to the Applicant. See Appendix F for full information request.

We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. For the Division, we note lack of clarity in the recommended dosage, dosage forms and strength, preparation instructions, and storage information. We also note the inclusion of trailing zeroes for lab values and inactive ingredients. For the Applicant, we note the net quantity statement is missing, prominence of the Rx only statement on the carton labeling and missing Rx only statement on the container label. Additionally, we note the format of the expiration date is not defined, the location of the lot number is missing, prominence of the NDC number, trailing zeroes in the inactive ingredients, and storage information inconsistent with the PI. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container label, carton labeling, and PI, that can be improved to increase readability and prominence of important information and promote the

safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Citius Pharmaceuticals, Inc. to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Highlights and Full Prescribing Information

1. As currently presented, the proprietary name is denoted by the placeholder "BRAND NAME". Replace all presentations of the placeholder "BRAND NAME" with the conditionally acceptable proprietary name, LYMPHIR.
2. As currently presented, the nonproprietary name suffix is denoted by the placeholder "denileukin diftitox-xxxx". Replace all presentations of the placeholder "denileukin diftitox-xxxx" with the conditionally acceptable nonproprietary name suffix, denileukin diftitox-cxdl.
3. The dosage instructions do not specify if ideal body or actual body weight should be used for weight-based dosing. To ensure that the intended dose is calculated correctly to prevent wrong dose errors. We recommend specifying whether ideal body or actual body weight should be used to calculate the recommended dosage.
4. The serum albumin values have trailing zeroes (e.g., 3.0 g/dL). Trailing zeros can lead to tenfold errors when the decimal point goes unnoticed (e.g., 3.0 g/dL is seen as 30 g/dL). Consider revising the serum albumin values to remove the trailing zeroes so that the statement states "3 g/dL ".

B. Highlights of Prescribing Information

1. Dosage and Administration Section

   a. The product has complex preparation instructions. It is important to alert healthcare providers that additional important information is in the Full Prescribing Information. Consider adding the statement, "See Full Prescribing Information for preparation and administration instructions. (b) (4) ."

2. Dosage Forms and Strengths Section

   a. We recommend revising the statement, " (b) (4) " to "For injection: 300 mcg as a lyophilized (b) (4) in a single-dose vial." for added clarity.

C. Full Prescribing Information

1. Dosage and Administration Section

a. Section (b) (4) Preparation and Administration

i. We recommend including the following statement at the beginning of the section, "Use aseptic technique to prepare LYMPHIR." after the statement, "Reconstitute and further dilute LYMPHIR prior to (b) (4)„

ii. (b) (4) We recommend removing the statement (b) (4) " as the route of administration (intravenous infusion) is expressed using positive language.

iii. The preparation instructions lack clarity, which may lead to product preparation errors. Therefore, we recommend the following revisions:

<u>Reconstitution</u>

a. We recommend revising the first bullet, "(b) (4) ." to "Calculate the dose (mcg), total volume (mL) of solution required, and number of vials of LYMPHIR needed based on the patient's [actual or ideal body weight]. More than one vial may be needed for a full dose.

b. Remove the vial(s) of LYMPHIR from the refrigerator and allow to stand for approximately XX minutes to reach room temperature (68°F to 77°F [20°C to 25°C]).

c. Reconstitute each LYMPHIR vial with 2.1 mL of Sterile Water for Injection, (b) (4) to obtain a final concentration of 150 mcg/mL. If more than one vial is needed to make a complete dose, use a separate syringe and needle for each vial.

d. Gently swirl the vial. Do not shake.

e. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be clear and colorless.

Discard if the solution is not clear, colorless, and contains particulate matter.

f. Use the reconstituted LYMPHIR solution immediately to prepare the drug product.

Dilution

g. Use only plastic syringes or soft plastic intravenous bags. Do not use glass containers.
h. Maintain concentration of LYMPHIR at 15 mcg/mL or higher during all steps in the preparation of the solution for intravenous infusion. Withdraw the calculated dose from the vial(s) with a sterile syringe and inject it into an empty intravenous bag.
i. Dilute with 0.9% Sodium Chloride Injection, (b) (4) to final concentration of 15 mcg/mL or higher.
j. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the prepared solution is cloudy or particulates are present.
k. If not used immediately, store the diluted LYMPHIR solution at room temperature [20°C to 25°C (68°F to 77°F)] for up to 4 hours. Protect diluted solution from light.

2. Description Section

a. The strength of methionine is presented with a trailing zero (e.g., 3.0 mg). Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 3.0 mg is seen as 30 mg). We recommend revising the strength of methionine to remove the trailing zero.

3. How Supplied/Storage and Handling Section

a. We recommend removing the statements, "(b) (4)

(b) (4)

4.2 RECOMMENDATIONS FOR CITIUS PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container label & Carton Labeling)

1. The route of administration appears less prominent on the principal display panel of the container label and carton label. Lack of prominence of the route of administration statement may lead to administration errors. Revise and relocate the route of administration statement as follows, "For Intravenous Infusion After Reconstitution and Dilution." to appear directly beneath the strength statement, 300 mcg for increased prominence and clarity.
2. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date.
3. As currently presented, the proprietary name is denoted by the placeholder "BRAND NAME". Replace all presentations of the placeholder "BRAND NAME" with the conditionally acceptable proprietary name, LYMPHIR.
4. As currently presented, the nonproprietary name suffix is denoted by the placeholder "denileukin diftitox-xxxx". Replace all presentations of the placeholder "denileukin diftitox-xxxx" with the conditionally acceptable nonproprietary name suffix, denileukin diftitox-cxdl.
5. We recommend revising the storage statement from, "(b) (4) " to "Store Refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze." to be consistent with the Prescribing Information.

B. Container Label

1. As currently presented, the National Drug Code (NDC) number competes in prominence with proprietary name. The proprietary name and proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). We recommend increasing the prominence of the proprietary name by decreasing the prominence of the NDC number.
2. Revise from "(b) (4)" to read as follows: "Dosage: See Prescribing Information".
3. We recommend adding the Rx Only statement to the container label.
4. As currently presented, the location of lot number and expiration date is not clearly defined on the container label. Please confirm the inclusion and location of the lot number and expiration date [refer to 21 CFR 610.60(a)].

C. Carton Labeling

1. The strength of methionine is presented with a trailing zero (e.g., 3.0 mg) on the side panel of the carton labeling. Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 3.0 mg is seen as 30 mg). We recommend revising the strength of methionine to remove the trailing zero on the side panel of the carton labeling.
2. The Rx Only statement is prominent. The Rx Only statement appears prominent on the principal display panel. We recommend decreasing the prominence by debolding the Rx Only statement.
3. The net quantity statement does not appear on the principal display panel of the carton labeling. Failure to include the net quantity statement on the principal display panel may result in confusion regarding the contents of the carton. We recommend including a net quantity statement (e.g., 1 Vial or One Vial) on the principal display panel and ensure it is located away from and less prominent than the product strength.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lymphir received on September 28, 2022 from Citius Pharmaceuticals, Inc..

Table 2. Relevant Product Information for denileukin diftitox-cxdl	
Initial Approval Date	N/A
Nonproprietary Name	denileukin diftitox-cxdl
Indication	For the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy, (b) (4) .
Route of Administration	Intravenous infusion
Dosage Form	for Injection
Strength	300 mcg/vial
Dose and Frequency	9 mcg/kg/day administered as an intravenous infusion over 60 minutes on 5 consecutive days, followed by a rest period of 16 days.
How Supplied	BRAND NAME (denileukin diftitox-xxxx) for injection is supplied as a sterile, white, lyophilized powder for reconstitution in a single-dose vial containing 300 mcg denileukin diftitox-xxxx. Each carton contains one vial: NDC XXXXX-XXX-XX
Storage	Store BRAND NAME in a refrigerator between 2°C to 8°C (36°F to 46°F). Do not freeze.

APPENDIX E. INFORMATION REQUEST

FDA Information Request: We note the preparation instructions described in the Prescribing Information indicate to, (b) (4) withdraw the calculated dose from the vial(s) with a sterile syringe and inject it into an empty intravenous bag. (b) (4) (b) (4) ."
We request that you provide the instructions of how this step was performed in your clinical study and if there is a final concentration that should be maintained for this step?

Applicant Response received on April 12, 2023:
\\CDSESUB1\EVSPROD\bla761312\0019\m1\us\1113-clinical-info-amend.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Lymphir labels and labeling submitted by Citius Pharmaceuticals, Inc..

- Container label received on September 28, 2022
- Carton labeling received on September 28, 2022
- Prescribing Information (Image not shown) received on September 28, 2022, available from \\CDSESUB1\EVSPROD\bla761312\0001\m1\us\11413-draft-labeling-text.docx

F.2 Label and Labeling Images

Container label

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

NICOLE F IVERSON
05/03/2023 02:22:55 PM

HINA S MEHTA
05/03/2023 03:01:46 PM

Medical Officer's Review of BLA 761312
Ophthalmology Consultation

BLA 761312

Submission date: 9/28/2022
Consult Request: 3/ 2/2023
Review date: 3/15/2023

Sponsor: Citrus Pharmaceuticals Inc.

Drug Name: E7777 (denileukin diftitox)

Indications: Treatment of persistent or recurrent Cutaneous T-Cell Lymphoma (CTCL)

Consult Request: We would like to request a formal consult with the Division of Ophthalmology for BLA 761312. The study medication E7777 has the same active component as ONTAK (denileukin diftitox) which was granted accelerated approval in 1999 for the treatment of patients with persistent or recurrent CTCL (b) (4), who malignant cells express the CD25 component of the IL-2 receptor. E7777 was born out of a PMC and is a purified and more potent agent that was considered a new product and required a single arm clinical study to support its registration. Impairment of visual acuity and/or color vision was reported in the post-marketing period after accelerated approval of Ontak, leading to changes in the label in 2006. In the current BLA 761312, patients were also monitored for visual impairment after receiving E7777 (in Study 302 and supportive studies 101 and 205). Nine percent of patients were reported to have Grade 1 or 2 visual impairment. Our consult questions regarding this application are as follows:

1. Please provide your assessment of the visual tests that were employed in study 302.

2. Please provide your assessment of the visual toxicities that were exhibited by patients including grading and characterization of visual impairments.

3. We would also appreciate your input on information to be included in the label.

Clinical Studies:

Study Protocol: E7777-G000-302
Study Protocol Title: A Clinical Study to Demonstrate Safety and Efficacy of E7777 in Persistent or Recurrent Cutaneous T-Cell Lymphoma

Ophthalmologic Monitoring: The original protocol included visual impairment as a dose limiting toxicity and included either visual acuity or color vision. The safety analysis was to include visual assessments. Any visual loss including visual acuity impairment, color or shape distortion, or blurred vision compared to baseline was to lead to permanent study treatment discontinuation. However, the protocol was amended and the previously required visual acuity tests were removed.

The initial protocol included Section 9.5.4.7, however, the amendment removed Section 9.5.4.7.

"9.5.4.7 Visual Tests
Two visual tests, to check for loss of visual acuity and loss of color vision, will be administered at screening, the end of treatment, and during the Extension Phase when a subject presents with symptoms as designated on the Schedule of Assessments (Table 4). The visual tests are a visual acuity (VA) test using the validated web-based system of Michael Bach from Freiburg, Germany (http://www.uniklinik-freiburg.de/augenklinik/live/homede/mit/bach_en.html) and the Color Distortion (CS) test (http://www.univie.ac.at/Vergl-Physiologie/colortest/colortestF-en.html)."

Reviewer's Comments:

1. *Visual acuity testing as described in Section 9.5.4.7 was not performed because a protocol amendment removed it from the protocol.*
2. *Color Distortion (CS) testing is not a generally recognized test. The website listed in the instructions does not appear to include any color vision tests.*
3. *Nine subjects (13%) in the trial were reported to have blurred vision. Based on the protocol, these patients should have been discontinued from treatment. All, but one were not removed from the clinical trial.*

Reported Ocular Adverse Events:
Nine subjects of the 69 (13.0%) in the Stage I to III Safety Analysis Set had any event related to Visual impairment; all were AEs of blurred vision, which were Grade 1 in 8 subjects (11.6%) and Grade 2 in 1 subject (1.4%). One subject (1.4%) had an event of study drug interruption; no events led to study drug dose reduction.

Table 49 Treatment-Emergent Adverse Events of Special Interest for E7777 (Visual Impairment) – Safety Analysis Set

Subject ID	Age/Race/ Sex	Study Cycle	AE Start Date/ End Date/ Duration (days)	Preferred Term	Serious (Y/N)	Grade	Relationship to Study Drug	Study Drug Action Taken	Outcome
(b) (6)	68/W/M	1	(b) (6)	Vision blurred	N	1	Possibly related	Dose not changed	Recovered/resolved
	69/B/M	1		Vision blurred	N	1	Not related	Dose not changed	Recovered/resolved
	78/W/F	1		Vision blurred	N	3	Probably related	Dose not changed	Recovered/resolved
	76/B/M	2		Vision blurred	N	1	Possibly related	Dose not changed	Not recovered/not resolved
	55/W/M	3		Vision blurred	N	1	Possibly related	Dose not changed	Recovered/resolved
	54/W/F	3		Vision blurred	N	1	Possibly related	Dose not changed	Not recovered/not resolved
	51/M/W	11		Vision blurred	N	1	Not related	NA	Not recovered/not resolved
	47/B/M	1		Vision blurred	Y	2	Possibly related	NA	Recovered/resolved
	67/W/M	2		Vision blurred	N	1	Not related	Drug interrupted	Recovered/resolved

Adverse event terms were coded using MedDRA version 24.1.
AE = adverse event, B = Black or African American, CTCL = cutaneous T-cell lymphoma, F = female, ID = identification, M = male, MedDRA = Medical Dictionary for Regulatory Activities, N = no, NA = not applicable; W = White, Y = yes.
[a]The subject was withdrawn from the study. Source: Listing 16.2.7.1.

Rare visual problems involving loss of visual acuity, usually with loss of color vision, with or without retinal pigment mottling, had been identified with ONTAK and hence were an AESI for E7777. The Lead-in Part of the current study (Study 302) included formal assessment of visual acuity and color vision and, although there were limitations to the methodology, did not identify major problems with

vision. AEs relating to visual impairment were defined as a CMQ that included high-level group term vision disorders and preferred terms of retinopathy and maculopathy; a search of these terms identified only the preferred term vision blurred, which was reported in 9 subjects in both safety sets. As a symptom, blurred vision has multiple potential etiologies and is difficult to interpret in the absence of ophthalmological examination and visual acuity testing. In addition, the ability of the study to detect a rare event of vision loss is limited by the number of subjects. The TEAEs of blurred vision were typically reversible; 8 were Grade 1, and 1 was Grade 2; the latter event was considered medically significant and reported as an SAE, and occurred during an SAE of capillary leak syndrome.

Consult Questions:

1. Please provide your assessment of the visual tests that were employed in study 302.

Consult Response: Study 302 was amended to remove all ocular testing. No reliable ophthalmic testing was included in the study. The actual frequency and cause of the ocular adverse events is unknown.

2. Please provide your assessment of the visual toxicities that were exhibited by patients including grading and characterization of visual impairments.

Consult Response: Study 302 did not appropriately monitor or evaluate the test product in spite of known toxicities of a related drug product. The cause of the blurred vision is unknown because it was not evaluated. A future study evaluating the ocular effects should be required.

3. We would also appreciate your input on information to be included in the label.

Consult Response: Labeling of the product should include the potential for blurred vision of unknown etiology. Labeling of the product should require baseline and regular interval monitoring with ophthalmic examinations including visual acuity, slit lamp examinations, dilated funduscopic examination and optical coherence tomography.

Wiley A. Chambers, MD
Supervisory Physician, Ophthalmology

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/

WILEY A CHAMBERS
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