

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761306Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: September 11, 2024

To: Renmeet Grewal, PharmD, MS, RAC
Director, Project Management Staff
Division of Dermatology and Dentistry (DDD)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, WOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Jessica Chung, PharmD, MS
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): EBGLYSS (lebrikizumab-lbkz)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761306

Applicant: Eli Lilly and Company

1 INTRODUCTION

On March 14, 2024, Eli Lilly and Company submitted for the Agency's review a Class 2 Resubmission of their original Biologics License Application (BLA) 761306 for EBGLYSS (lebrikizumab-lbkz) injection with the proposed indication for the treatment of adult and pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

This review is written by the Division of Medical Policy Programs (DMPP) in response to edits made to Section 1 Indications and Usage and Section 8.4 Pediatric Use of the Prescribing Information (PI). The Division of Dermatology and Dentistry (DDD) requested on April 14, 2024, for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for EBGLYSS (lebrikizumab-lbkz) injection.

2 MATERIAL REVIEWED

- Draft EBGLYSS (lebrikizumab-lbkz) injection PPI received on March 14, 2024, and received by DMPP on September 10, 2024.
- Draft EBGLYSS (lebrikizumab-lbkz) injection PI received on March 14, 2024, revised by the Review Division throughout the review cycle, and received by DMPP on September 10, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

JESSICA M CHUNG
09/11/2024 10:47:52 AM

BARBARA A FULLER
09/11/2024 10:51:26 AM

LASHAWN M GRIFFITHS
09/11/2024 11:55:29 AM



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memo**

Date: September 09, 2024

Reviewer: Sally Peprah, PhD, MSPH
Division of Epidemiology I

Team Leader: Benjamin J. Booth, PhD, MS
Division of Epidemiology I

Deputy Division Director: Wei Hua, MD, PhD, MS, MHS
Division of Epidemiology I

Subject: ARIA Sufficiency Memo

Drug Name: Ebglyss (lebrikizumab) injection, for subcutaneous use

Application Type/Number: BLA 761306

Applicant/sponsor: Eli Lilly and Company

OSE TTT #: 2022-1962



Expedited ARIA Sufficiency Memo for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. MEDICAL PRODUCT

Lebrikizumab is an IgG4 monoclonal antibody that belongs to the pharmacological class of immunomodulators/interleukin (IL) inhibitors. Lebrikizumab binds to and selectively inhibits IL-13 signaling through the IL-4 receptor alpha/IL-13 receptor alpha-1 pathway, thereby blocking the downstream effects of IL-13. It is a new molecular entity (NME) with the proposed proprietary name “Ebglyss”, for which the Applicant (Eli Lilly and Company) submitted an original BLA 761306 on September 28, 2022. The proposed indication for lebrikizumab is for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Lebrikizumab is proposed to be administered by subcutaneous (SC) injection, with or without topical corticosteroids (TCS), at the recommended initial dose of 500 mg (two 250 mg injections), followed by 250 mg given every other week (b) (4) week 16 or later, when adequate clinical response is achieved, or every 4 weeks for patients who achieve clear or almost clear skin after 16 weeks of treatment.

1.2. DESCRIBE THE SAFETY CONCERN

The Division of Dermatology and Dentistry (DDD) requested that the Division of Epidemiology-I (DEPI-I) assess the sufficiency of ARIA for broad-based safety signal detection studies among women exposed to lebrikizumab during pregnancy.

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.¹ Further, it is estimated up to 10% of adults in the United States are affected by AD although prevalence estimates are limited and vary because AD is a clinical diagnosis.² Approximately half of AD patients are female, and AD affects all age groups including females of reproductive potential.³ It is estimated that 44-57% of adult patients with AD have moderate disease and 12-21% have severe disease based on the Patient Oriented Scoring of Atopic Dermatitis. Systemic immunomodulating therapies may be needed in those with moderate-severe AD.⁴

Eczema is the most common dermatosis of pregnancy, accounting for a third to half of all cases.⁵ Approximately 20-40% of patients with eczema during pregnancy having a pre-existing history of eczema; the rest develop symptoms for the first-time during pregnancy.⁶ Of those with a pre-existing history, approximately 25% improve, more than half of cases deteriorate, and 10% of cases flare postpartum.⁷ Secondary skin infection causing eczema herpeticum, may be associated with preterm

¹ Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR). <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf>. Accessed March 17, 2021.

² Fuxench ZC, Block JK, Boguniewicz M, Boyle J, Fonacier L, Gelfand JM, Grayson MH, Margolis DJ, Mitchell L, Silverberg JI, Schwartz L. Atopic dermatitis in America study: a cross-sectional study examining the prevalence and disease burden of atopic dermatitis in the US adult population. *Journal of Investigative Dermatology*. 2019 Mar 1;139(3):583-90.

³ Heilskov S, Deleuran MS, Vestergaard C. Immunosuppressive and immunomodulating therapy for atopic dermatitis in pregnancy: an appraisal of the literature. *Dermatology and Therapy*. 2020 Dec;10:1215-28.

⁴ Ibid.

⁵ Weatherhead S, Robson SC, Reynolds NJ. Eczema in pregnancy. *Bmj*. 2007 Jul 19;335(7611):152-4.

⁶ Ibid.

⁷ Ibid.



delivery, intrauterine growth restriction, and miscarriage^{8,9} but there is limited evidence that AD increases the risk of adverse pregnancy outcomes.

During the lebrikizumab clinical development program, there were no cases of congenital birth defects reported during the clinical trials and pregnant women were excluded from the clinical trials. During the development, there were 26 pregnancies as of June 6, 2022, among 1,421 subjects. Of the 26 pregnancies, 6 were from paternal exposures and 20 were maternal exposures. Of the maternally exposed pregnancies, the exposure occurred mostly during the first trimester and the outcomes were as follows:

- 6 livebirths (one case of fetal growth restriction, one case of neonatal jaundice)
- 7 spontaneous abortions or terminations due to anembryonic pregnancy
- 4 elective terminations (reasons not included)
- 1 ectopic pregnancy
- 2 lost to follow-up

1.3. FDAAA PURPOSE (PER SECTION 505(O)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. WHY IS PREGNANCY SAFETY A SAFETY CONCERN FOR THIS PRODUCT? CHECK ALL THAT APPLY.

- Specific FDA-approved indication in pregnant women exists and exposure is expected
- No approved indication, but practitioners may use product off-label in pregnant women
- No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- No approved indication, but use in women of childbearing age is a general concern

2.2. REGULATORY GOAL

- Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
- Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of

⁸ See footnote 4.

⁹ Napolitano M, Ruggiero A, Fontanella G, Fabbrocini G, Patrino C. New emergent therapies for atopic dermatitis: a review of safety profile with respect to female fertility, pregnancy, and breastfeeding. *Dermatologic Therapy*. 2021 Jan;34(1):e14475.

statistical precision and certainty (e.g., chart review).

2.3. WHAT TYPE OF ANALYSIS OR STUDY DESIGN IS BEING CONSIDERED OR REQUESTED ALONG WITH ARIA? CHECK ALL THAT APPLY.

- Pregnancy registry with internal comparison group
- Pregnancy registry with external comparison group
- Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- Electronic database study with chart review
- Electronic database study without chart review
- Other, please specify: Other study designs such as a case-control study would be considered if there is a need to collect additional information from the mothers through personal interviews, to obtain additional information on infants, to request permission to review medical records, or to perform long-term follow-up of their offspring, and such a study maybe nested within an electronic database study or conducted independent of it.

2.4. WHICH ARE THE MAJOR AREAS WHERE ARIA NOT SUFFICIENT, AND WHAT WOULD BE NEEDED TO MAKE ARIA SUFFICIENT?

- Study Population
- Exposures
- Outcomes
- Covariates
- Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: The pregnancy registry being considered requires that an expert clinical gynecologist or dysmorphologist independently review and classify medical records of all major congenital malformations.¹⁰ However, ARIA lacks access to medical records. Further, the prospective registry requires clinical information from medical records and risk factors that may not be available in claims data. Also, although in a first stage, the study using claims or electronic medical data may be algorithm-based, if it shows an imbalance in any of the outcomes being investigated, FDA may consider requiring outcome validation in the selected database(s) or a chart-confirmed analysis. However, ARIA precludes access to medical charts.

Covariates: The pregnancy registry being considered would collect detailed narratives with information on potential covariates such as severity of AD, family history of the disease or outcomes, lifestyle factors, as well as the timing and nature of other drug and concomitant exposures. However, ARIA does not have detailed information on potential confounders for the pregnancy registry.

2.5. PLEASE INCLUDE THE PROPOSED PMR LANGUAGE IN THE APPROVAL LETTER.

¹⁰ Ibid.



The Division of Pediatric and Maternal Health recommends the following PMRs related to pregnancy outcomes:

PMR-1: Conduct or participate in a relevant Pregnancy Exposure Registry, a prospective registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to lebrikizumab during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, neonatal deaths, and infections, will be assessed through at least the first year of life.

PMR-2: Conduct a retrospective pregnancy cohort study using claims or electronic health record data with medical chart validation that is adequately powered to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in individuals exposed to lebrikizumab during pregnancy compared to appropriate comparator population(s).

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/

SALLY A PEPRAH
09/09/2024 03:26:46 PM

HUI L WONG on behalf of BENJAMIN J BOOTH
09/09/2024 05:13:39 PM

WEI HUA
09/09/2024 05:15:01 PM

JUDITH W ZANDER
09/09/2024 06:29:10 PM

PATRICIA L BRIGHT
09/10/2024 08:32:28 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	August 26, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761306
Product Name, Dosage Form, and Strength:	Ebglyss (lebrikizumab-ibkz) injection, 250 mg/2 mL (125 mg/mL)
Applicant Name:	Eli Lilly and Company
FDA Received Date:	July 29, 2024
TTT ID #:	2022-1988-2
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Eli Lilly and Company submitted revised container label and carton labeling received on July 29, 2024 for Ebglyss. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container label and carton labeling for Ebglyss (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

Eli Lilly and Company implemented all of our recommendations and we have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^a Patel, M. Label and Labeling Review for Ebglyss (BLA 761306). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUL 12. TTT ID: 2022-1988.

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/

MADHURI R PATEL
08/26/2024 11:38:31 AM

YEVGENIYA M KOGAN
08/27/2024 09:09:20 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	July 12, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761306
Product Name, Dosage Form, and Strength:	Ebglyss (lebrikizumab-lbkz) injection, 250 mg/2 mL (125 mg/mL)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Eli Lilly and Company
FDA Received Date:	March 14, 2024
TTT ID #:	2022-1988-1
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

As part of the approval process for Ebglyss (lebrikizumab-lbkz) injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Ebglyss Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Eli Lilly and Company previously submitted BLA 761306 on September 28, 2022, which received a Complete Response letter on September 28, 2023 due to issues with the facility evaluation.^a

Thus, Eli Lilly and Company submitted a Class 2 Resubmission on March 14, 2024.^b

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761306.

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
Response to Comments from Previous Label and Labeling Review	D

3 CONCLUSION

We evaluated the proposed Ebglyss Patient Package Insert (PPI) and Instructions for Use (IFU) and determined that they are acceptable from a medication error perspective.

However, the proposed Ebglyss Prescribing Information (PI), container labels, 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 Dermatology and Dentistry (DDD) in Section 4 and for Eli Lilly and Company in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

Table 2. Identified Issues and Recommendations for the Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION

^a Song, Q on behalf of Nikolov, N. Complete Response for BLA 761306. Silver Spring (MD): FDA, CDER, OND, Division of Dermatology and Dentistry (DDD) (US); 2023 SEP 28.

^b Resubmission Lebrikizumab. Indianapolis (IN): Eli Lilly and Company; 2024 MAR 14. Available from: <\\CDSESUB1\EVSPROD\bla761306\0060\m1\us\cover.pdf>.

Table 2. Identified Issues and Recommendations for the Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	For the prefilled syringe, the product strength is not expressed as a total quantity per total volume followed by the concentration per mL.	The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling. Please note, for autoinjectors, since the entire content of the autoinjector should be administered and there is no possibility of administering a partial dose, including the concentration per mL may lead to dosing errors.	For the prefilled syringe, consider expressing the product strength as total quantity per total volume followed by the concentration per mL in accordance with USP General Chapter <7> (e.g. 250 mg/2 mL (125 mg/mL).

5 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

Table 3. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	For the prefilled syringe container label and carton labeling, the product strength is not expressed as a total quantity per total volume followed by the concentration per mL.	The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling.	For the prefilled syringe, express the product strength as total quantity per total volume followed by the concentration per mL in accordance with USP General Chapter <7> (e.g. 250 mg/2 mL (125 mg/mL). Ensure the total quantity per total volume is prominently displayed.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Ebglyss received on March 14, 2024 from Eli Lilly and Company.

Table 4. Relevant Product Information for Ebglyss			
Initial Approval Date	n/a		
Nonproprietary Name	lebrikizumab-lbkz		
Indication	treatment of adult and pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. can be used with or without topical corticosteroids.		
Dosage Form	injection		
Strength	250 mg/2 mL (125 mg/mL)		
Route of Administration	subcutaneous		
Dose and Frequency	initial dose of 500 mg (two 250 mg injections) at Week 0 and Week 2, followed by 250 mg every two weeks until Week 16 or later, when adequate clinical response is achieved. The maintenance dose is 250 mg every four weeks.		
How Supplied	a sterile, preservative free, clear to opalescent, colorless to slightly yellow to slightly brown solution, available in a single-dose prefilled pen or a single-dose prefilled syringe with needle shield. Each prefilled pen and prefilled syringe with needle shield is designed to deliver 250 mg of EBGLYSS in 2 mL		
		Pack Size	NDC
	Prefilled Pen		
	250 mg/2 mL single-dose	Carton of 1	0002-7772-11
	Prefilled syringe with needle shield		
250 mg/2 mL single-dose	Carton of 1	0002-7797-11	

Table 4. Relevant Product Information for Ebglyss	
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F). If necessary, can be stored at room temperature up to 30°C (86°F) for up to 7 days in the original carton. Dispose of EBGLYSS that has been left at room temperature for longer than 7 days. Store in the original carton to protect from light until use. Do not freeze. Do not use if it has been frozen. Do not shake. Do not microwave, run hot water over it, or leave it in direct sunlight. Not made with natural rubber latex.
Container Closure	2.25 mL clear, (b) (4) glass syringe barrel with small round flange, 27G special thin wall x 1/2" staked needle, and closed with a rigid needle shield and a (b) (4) elastomeric plunger

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,^c along with postmarket medication error data, we reviewed the following Ebglyss labels and labeling submitted by Eli Lilly and Company.

- Prescribing Information received on March 14, 2024, available from <\\CDSESUB1\EVSPROD\bla761306\0060\m1\us\proposed-uspi.docx>
- Patient Package Insert received on March 14, 2024, available from <\\CDSESUB1\EVSPROD\bla761306\0060\m1\us\proposed-ppi.docx>
- Instructions for Use received on March 14, 2024, available from <\\CDSESUB1\EVSPROD\bla761306\0060\m1\us\proposed-ifu-pfs-clean.docx> and <\\CDSESUB1\EVSPROD\bla761306\0060\m1\us\proposed-ifu-pen-clean.docx>
- Container labels received on March 14, 2024
- Carton labeling received on March 14, 2024

B.2 Container Label(s) and Carton Labeling Images



^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX C. PREVIOUS DMEPA REVIEWS

On June 27, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, '761306'. Our search identified four previous review(s)^{d,e,f,g}, and we considered our previous recommendations to see if they are applicable for this current review.

^d Howard, C. Label and Labeling Review for Ebglyss (BLA 761306). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 28. TTT ID No.: 2022-1988.

^e Kumar, N. Human Factors Study Results and Comparative Analyses Review for Ebglyss (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUN 13. TTT ID No.: 2022-1963.

^f Kumar, N. Label and Labeling Review Memo for Ebglyss (BLA 761306). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 16. TTT ID No.: 2022-1963-1.

^g Kumar, N. Label and Labeling Review Memo for Ebglyss (BLA 761306). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 SEP 11. TTT ID No.: 2022-1963-2.

APPENDIX D. RESPONSE TO COMMENTS FROM PREVIOUS LABEL AND LABELING REVIEW

Response to an Information Request with DMEPA and OBP's comments on container labels and carton labeling, received on July 14, 2023, available from

<\\CDSESUB1\EVSPROD\bla761306\0034\m1\us\regulatory-response-25-fda-july-2023.pdf> .

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/

MADHURI R PATEL
07/12/2024 02:15:10 PM

YEVGENIYA M KOGAN
07/12/2024 03:19:07 PM

MEMORANDUM
LABEL AND LABELING REVIEW MEMO
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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: September 11, 2023
Requesting Office or Division: Division of Dermatology and Dentistry (DDD)
Application Type and Number: BLA 761306
Product Name, Dosage Form, and Strength: Ebglyss^a (lebrikizumab) injection, 250 mg/2 mL
Applicant/Sponsor Name: Eli Lilly and Company
TTT ID #: 2022-1963-2
DMEPA 1 Safety Evaluator: Neha Kumar, PharmD
DMEPA 1 Team Leader: Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

The Applicant submitted their revised container label received on August 18, 2023 for Ebglyss. The Division of Dermatology and Dentistry (DDD) requested that we review the container label for Ebglyss (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 human factors study results review and label and labeling review memo.^{b,c}

2 CONCLUSION

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

^a The proposed proprietary name, Ebglyss, was found conditionally acceptable on December 14, 2022.

^b Kumar, N. Human Factors Study Results and Comparative Analyses Review for Ebglyss (BLA 761306). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUN 13. TTT ID No.: 2022-1963.

^c Kumar, N. Label and Labeling Review Memo for Ebglyss (BLA 761306). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 16. TTT ID No.: 2022-1963-1.

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/

NEHA KUMAR
09/11/2023 09:24:54 AM

OLUWAMUREWA OGUNTIMEIN
09/11/2023 11:35:00 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8/31/2023

TO: Division of Dermatology and Dentistry (DDD)
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761306

OSIS received an inspection request consult from the Division of Dermatology and Dentistry (DDD) on August 10, 2023, for the below sites. The requested review goal date is September 5, 2023, and the PDUFA date is September 28, 2023.

Rationale

An inspection of the sites below is not able to be completed. Specifically, the requested review goal date of September 5, 2023, to meet the PDUFA date of September 28, 2023, does not provide sufficient time for an inspection or remote regulatory assessment (RRA) to be completed and for OSIS to submit a review to the review division.

We note OSIS's inspection history for the sites is listed below.

(b) (4): OSIS conducted an inspection of the site in (b) (4). The inspection was conducted under the following submission: BLA NON-RESPONSIVE.

OSIS concluded that data from the reviewed studies was reliable.

(b) (4): OSIS conducted an inspection of the site in (b) (4). The inspection was conducted under the following submission: NDA NON-RESPONSIVE.

The following objectionable condition was observed:

- The site used indirectly estimated concentrations of quality control samples and wider limits for accepting bioanalytical runs than recommended in FDA guidance.

After review of the observation and the site's response, OSIS recommended that the data from the audited study be accepted for review with the exception of one run. ([OSIS Review – Nov 2016](#))

Sites

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Analytical		

(b) (4)

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/

JAMES J LUMALCURI
08/31/2023 02:29:58 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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: August 16, 2023
Requesting Office or Division: Division of Dermatology and Dentistry (DDD)
Application Type and Number: BLA 761306
Product Name, Dosage Form, and Strength: Ebglyss^a (lebrikizumab) injection, 250 mg/2 mL
Applicant/Sponsor Name: Eli Lilly and Company
TTT ID #: 2022-1963-1
DMEPA 1 Safety Evaluator: Neha Kumar, PharmD
DMEPA 1 Team Leader: Murewa Oguntimein, PhD, MHS, CHES, CPH

1 PURPOSE OF MEMORANDUM

On July 24, 2023, the Applicant submitted the following revised labeling for Ebglyss:

- Prefilled syringe (PFS) instructions for use (IFU)
- PFP (prefilled pen) IFU
- PFP carton labeling, including the quick reference for injection (QRI)

The Division of Dermatology and Dentistry (DDD) requested that we review the IFUs and carton labeling for Ebglyss (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 human factors study results and label and labeling review.^b

2 DISCUSSION AND CONCLUSION

The Applicant implemented our recommendation to include the statement, "*Leave the needle cap on the syringe until you are ready to inject.*" in the PFS IFU. The Applicant also implemented our recommendation to enlarge the image depicting the needle shield covering the needle in the PFS IFU.

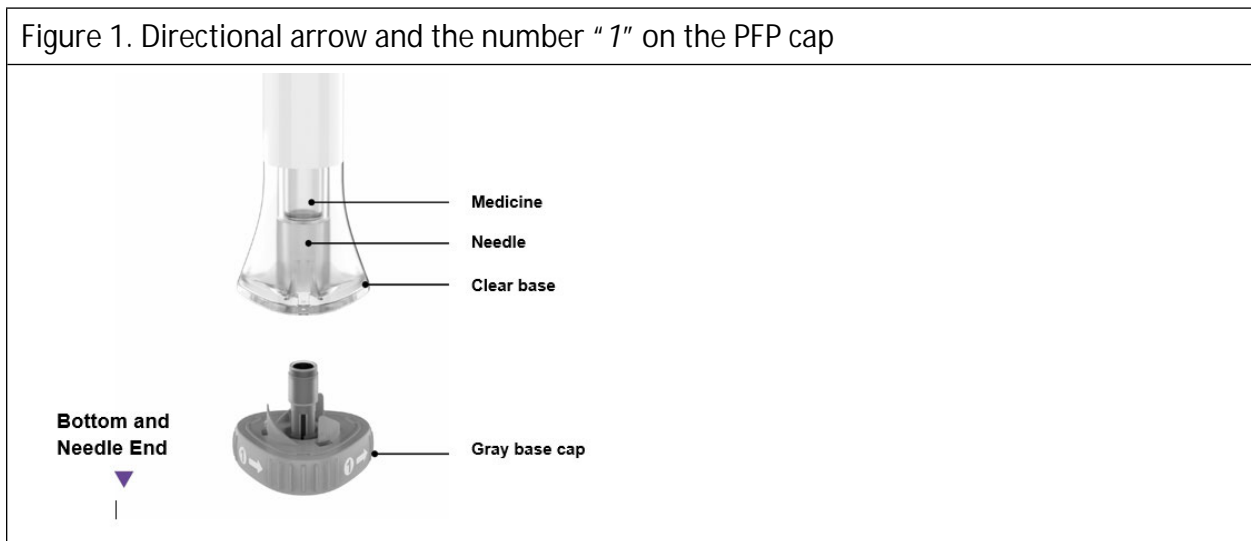
^a The proposed proprietary name, Ebglyss, was found conditionally acceptable on December 14, 2022.

^b Kumar, N. Human Factors Study Results and Comparative Analyses Ebglyss (lebrikizumab) BLA 761306. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUN 13. TTT ID No.: 2022-1963.

However, we note the Applicant did not implement the following recommendations:

- The Applicant did not implement our recommendation to add the statement “*twist to remove cap*” by the “1” on the PFP to improve understanding and clarity of the cap removal task. The Applicant stated that the root cause analysis for the cap removal task indicated that participants did not refer to the product labeling and instead leaned on their own mental models of device use. The Applicant also stated that the PFP cap includes directional arrows by the “1” which shows the direction to remove the base cap. See Figure 1 below. We find this reasoning acceptable, since in lieu of text stating “*twist to remove the cap*”, the directional arrows exist on the cap. Additionally, in actual use, patients may be able to verify that they did not remove the cap, and thus did not receive the dose, when they do not feel the needle.

Figure 1. Directional arrow and the number “1” on the PFP cap



- The Applicant did not implement our recommendation to add a “*needle end*” label to the PFP to further improve understanding and clarification regarding the needle end. The Applicant stated that

(b) (4)

[Redacted text block]

these product labeling changes may not be adequate mitigations to errors related to confusing the needle and button ends. Additionally, per the Agency’s advice letter dated August 10, 2023, under BLA 125521 for Taltz (ixekizumab), which uses the same device platform as Ebglyss, we stated, “*The agency identified 23 use errors cases describing injecting Taltz prefilled autoinjector into the thumb or*

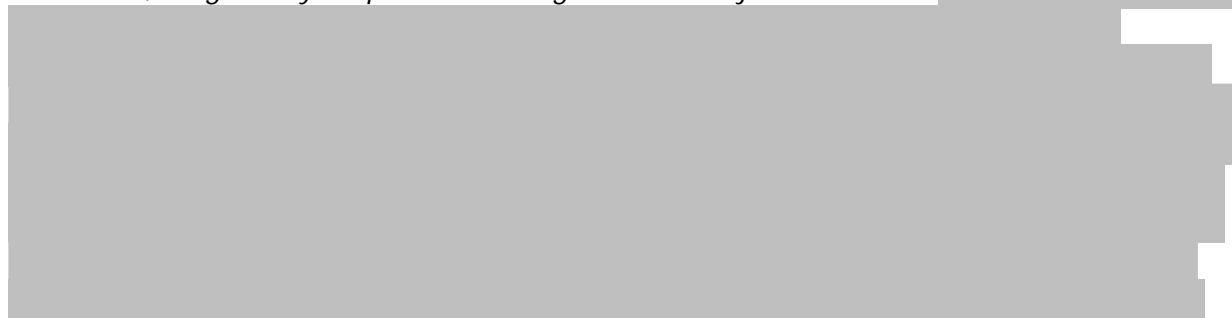
administering the device upside down, resulting in needle sticks and potential underdose or no dose. This medication error could lead to a lack of intended effect of the product. We note that the prefilled autoinjector container label does not indicate the needle end or the button end.”^c We also stated, “To help minimize potential underdose, no dose, or needle stick injuries from the Taltz (ixekizumab) prefilled autoinjector device due to injecting the needle into the thumb or administering the device upside down, we recommend adding a statement to indicate which end of the device is the needle end on the Container Label.” As such, we continue to recommend that the Applicant include a “needle end” label to the PFP.

- The Applicant did not implement our recommendation to increase the expiration date text on the container label and carton labeling. The Applicant stated that participants who could not initially find the expiration could read the expiration date once they located it. We note that in the human factors study results one participant could not initially find the expiration date on the container labeling due to small text and stated that the expiration date did not “stick out”. We also acknowledge that after adding a “needle end” label to the device, including larger expiration text to the container labeling may affect readability. We accept the Applicant’s reasoning to not increase the expiration date text.

3 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

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

We note that you did not implement our recommendation to add a “needle end” label to the PFP to further improve understanding and clarification regarding the needle end. In your document, “Regulatory Response: Labeling Comments” you stated that (b) (4)



may not be adequate mitigations to errors related to confusing the needle and buttons end. Additionally, per the Agency’s advice letter dated August 10, 2023 under BLA 125521 for Taltz (ixekizumab), which uses the same device platform as Ebglyss, we stated, “The agency identified 23 use errors cases describing injecting Taltz prefilled autoinjector into the

^c Aftab, S. General advice letter for Taltz (ixekizumab) postmarket review. Silver Spring (MD): FDA, CDER, OPO, OPRO, DRBPMI, RBPMB2 (US); 2023 August 10. BLA 125521.

thumb or administering the device upside down, resulting in needle sticks and potential underdose or no dose. This medication error could lead to a lack of intended effect of the product. We note that the prefilled autoinjector container label does not indicate the needle end or the button end." We also stated, "To help minimize potential underdose, no dose, or needle stick injuries from the Taltz (ixekizumab) prefilled autoinjector device due to injecting the needle into the thumb or administering the device upside down, we recommend adding a statement to indicate which end of the device is the needle end on the Container Label." As such, we continue to recommend that you include a "needle end" label to the PFP.

APPENDIX A. APPLICANT RESPONSE AND LABEL AND LABELING RECEIVED ON JULY 24, 2023

“Regulatory Response: Labeling Comments” (Applicant’s response to recommendations):

<\\CDSESUB1\EVSPROD\bla761306\0036\m1\us\cover.pdf>

Prefilled syringe instructions for use (Image not shown) available from:

Prefilled syringe <\\CDSESUB1\EVSPROD\bla761306\0036\m1\us\lebrikizumab-pfs-ifu-new-draft.docx>

Prefilled pen instructions for use (Image not shown) available from

<\\CDSESUB1\EVSPROD\bla761306\0036\m1\us\proposed-ifu-pen.docx>

Prefilled pen carton labeling:



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

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/

NEHA KUMAR
08/16/2023 10:03:59 AM

OLUWAMUREWA OGUNTIMEIN
08/16/2023 11:46:11 AM

Clinical Inspection Summary

Date	7/10/2023
From	Stephanie Coquia, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Shera Schreiber, Clinical Reviewer David Kettl, MD, Clinical Team Leader Qianyiren Song, Regulatory Project Manager Division of Dermatology and Dentistry (DDD)
BLA #	761306
Applicant	Eli Lilly and Company
Drug	Lebrikizumab (Ebglyss™)
NME (Yes/No)	Yes
Therapeutic Classification	Interleukin-13 antagonist
Proposed Indication	For the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Ebglyss™ can be used with or without topical corticosteroids.
Consultation Request Date	11/29/2022
Summary Goal Date	07/28/2023
Action Goal Date	09/28/2023
PDUFA Date	09/28/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Eli Lilly and Company, submitted clinical data from Studies KGAB (NCT04146363), KGAC (NCT04178967), and KGAD (NCT04250337) to the Agency in support of a Biologics License Application (BLA 761306) for lebrikizumab. The proposed indication is for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Four clinical investigators were selected for clinical inspections (Drs. Mendez, Carpio, Wallace, and Torkan). All inspections were conducted on-site.

The inspections of Drs. Mendez, Wallace, and Torkan did not find significant concerns regarding the oversight of the clinical trial or Good Clinical Practice (GCP) or regulatory

compliance, and based on the results of these inspections, data generated by these inspected clinical investigators appear acceptable in support of the proposed indication.

The inspection of Dr. Carpio yielded unreported protocol deviations and inconsistent statements that indicated his lack of command of study details and procedures, including those related to eligibility and blinding. Combined with the data anomalies identified by the sponsor (and confirmed by OSI), we recommend a sensitivity analysis excluding data from Dr. Carpio's site for Study KGAC and Study KGAD.

II. BACKGROUND

Eli Lilly and Company seeks approval for a BLA for lebrikizumab for AD. In support of the BLA, the Applicant submitted clinical data from Studies KGAB, KGAC, and KGAD. The following is a summary of the study protocols and key study information relevant to the clinical inspections.

To support the indication, three phase 3 trials were performed: KGAB, KGAC, and KGAD.

- KGAB and KGAC were identically designed, randomized, double-blind, placebo-controlled, parallel-group studies that compared the safety and efficacy of lebrikizumab monotherapy to placebo in patients with moderate-to-severe AD. A 16-week induction period was followed by a maintenance period of 36 weeks (52-week total study duration).
- KGAD was a randomized, double-blind, placebo-controlled, parallel-group study that compared the safety and efficacy of lebrikizumab + topical corticosteroids (TCS) to placebo + TCS in patients with moderate-to-severe AD for 16 weeks. After the 16-week visit, subjects were allowed to either enter a separate long-term extension study (DRM06-AD07) or terminate participation. Those who terminated entered a separate follow-up period lasting 12 weeks under KGAD.

The primary endpoint was the same in all three trials: the proportion of subjects who achieved an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) and at least a 2-point improvement from Baseline at Week 16.

The following major secondary endpoints were also the same in all three trials:

- The proportion of subjects achieving EASI-75: The proportion of subjects who achieved at least a 75% reduction from Baseline in the Eczema Area and Severity Index (EASI) at Week 16
- The proportion of subjects achieving EASI-90 at Week 16

Major eligibility criteria for the three trials were as follows:

- Adult or adolescent (≥ 12 years to < 18 years with weight ≥ 40 kg)

- Diagnosis of chronic AD as defined by the American Academy of Dermatology Consensus Criteria, for at least one year before the screening visit
- Moderate to severe AD, defined as having all the following at the Baseline Visit
 - EASI ≥ 16
 - IGA ≥ 3
 - Affected body surface area (BSA) of $\geq 10\%$
- Inadequate response to topical medications or for KGAB/KGAC – they are medically inadvisable
- No prior enrollment in a lebrikizumab clinical study

Study KGAB was conducted at 89 centers, enrolled 536 subjects, and randomized 424 subjects in Australia, Canada, Estonia, France, Latvia, Lithuania, Poland, South Korea, Spain, and the United States. Study KGAC was conducted at 82 centers, enrolled 606 subjects, and randomized 445 subjects in Bulgaria, Canada, Germany, Mexico, Singapore, Taiwan, Ukraine, and the United States. A total of 444 subjects were treated. Study KGAD was conducted at 54 centers and enrolled 228 subjects, in Canada, Germany, Poland, and the United States.

RESULTS

1. Dr. Jose Mendez (Sites 5016 for Study KGAC and 6011 for Study KGAD)

425 West 51st Place
Hialeah, FL 33012-3618

Inspection Dates: February 15-28, 2023

This investigator was inspected as a routine PDUFA inspection for Study KGAC and KGAD. This was the first FDA inspection for this investigator.

For KGAC, 27 subjects were screened, and 19 subjects were randomized (eight screen failures). Records for 10 out of the 19 randomized subjects were fully reviewed. However, IGA and EASI source documentation were reviewed and compared to data line listings for all 19 randomized subjects.

For KGAD, 21 subjects were screened, and 13 subjects were randomized (eight screen failures). Records for all 13 randomized subjects were reviewed.

Subject records (paper) reviewed included: informed consents (ICFs)/assents, concomitant medications, vital signs, physical examinations, adverse event (AE) reports, investigational product (IP) administration and accountability, laboratory reports and requisition forms, urine pregnancy tests, efficacy assessments, and progress notes. For investigator (e.g., IGA, EASI, and BSA) and subject assessments that were directly entered into a tablet device during the study, electronic case report forms (eCRFs) from the Electronic Data Capture (EDC) were available.

Study records reviewed included: protocols, signed investigator agreements, financial disclosure statements, institutional review board (IRB) submissions and correspondence, AE and serious adverse event (SAE) reporting, protocol deviation logs, IP accountability, and sponsor and monitoring communications.

The submitted line listings, including the efficacy line listings for IGA and EASI at Baseline and at Week 16, were compared to source records without major discrepancies identified. There was no underreporting of AEs or important protocol deviations identified.

2. Dr. Bruce Torkan (Site 5014 for Study KGAC and Study 6055 for KGAD)

820 A South Alvarado St.
Los Angeles, CA 90057-4010

Inspection Dates: June 7-13, 2023

This investigator was inspected as a routine PDUFA inspection for Study KGAC and KGAD. This was the first FDA inspection for this investigator.

Subject records reviewed included: ICFs, IP dispensing/accountability, AE reports, and efficacy source data for primary and secondary endpoints. Source records for all screened subjects for both KGAC and KGAD were reviewed (16 and 11 subjects, respectively). Except for patient-reported outcomes that were entered into devices with data directly transferring to the EDC, all source data, including those for IGA and EASI, were in paper format. eCRFs provided on a USB were also reviewed.

Study-related documents reviewed included: delegation logs, financial disclosure forms, monitoring logs and correspondence, IP accountability records, training logs, investigator agreements, IRB documentation, and sponsor correspondence.

The source records were compared to the submitted line listings, including those for efficacy (IGA and EASI at Baseline and Week 16), without discrepancies identified. There was no evidence of underreporting of AEs or protocol deviations.

3. Dr. Paul Wallace (Site 4013 for Study KGAB)

5120 West Goldleaf Circle, Suite 20
Los Angeles, CA 90056

Inspection Dates: June 12-16, 2023

This investigator was inspected as a routine PDUFA inspection for Study KGAB. This was the second FDA inspection for this investigator. The previous inspection was conducted in June 2018 with observations of not conducting investigation in accordance with the signed investigator statement, failure to prepare or maintain adequate case histories, and failure to retain investigational records for a period of two years.

Subject records reviewed included: case histories, medical records, laboratory reports, ICFs,

protocol-required activities, and the EDC for efficacy assessments. The source records for all 16 subjects enrolled were reviewed for eligibility, AEs, concomitant medications, discontinuations, protocol deviations, and efficacy.

Study related documents reviewed included: site standard operating procedures, monitoring records, IP accountability records, sponsor correspondence, IRB correspondence, and financial disclosure records.

The source records were compared to the submitted line listings, including those for efficacy (IGA and EASI), without discrepancies identified. There was no evidence of underreporting of adverse events.

4. Dr. Jose Carpio (Sites 5042 for Study KGAC and 6006 for Study KGAD)

Quality Research of South Florida
14750 Nw 77th Ct Ste 207
Miami Lakes, FL 33016-1507

Previous name and location: The Community Research of South Florida in Hialeah, FL

Pre-FDA Inspection History: Data Anomalies Identified, Sponsor Audit, and Site Termination

Following primary outcome database lock for Study KGAD, Lilly study statisticians conducted a routine data validation for the primary efficacy endpoint. Their review identified statistically implausible homogeneity of the efficacy results from Site 6006. All subjects, irrespective of arm, were recorded as having an IGA of 1 at Week 16 and were thus all classified as responders. The data submitted in the BLA confirm this pattern:

USUBJID	Treatment Arm	IGA Score at Week 0 (Baseline)	IGA Response at Week 16 (Endpoint)	IGA Score at Week 0 (Baseline)	IGA Score at Week 16 (Endpoint)
(b) (6)	Screen Failure	3 - Moderate	N/A	3	N/A
	Placebo	4 - Severe	1 - Almost clear	4	1
	Lebrikizumab	3 - Moderate	1 - Almost clear	3	1
	Lebrikizumab	3 - Moderate	1 - Almost clear	3	1
	Lebrikizumab	4 - Severe	1 - Almost clear	4	1
	Placebo	4 - Severe	1 - Almost clear	4	1
	Placebo	4 - Severe	1 - Almost clear	4	1
	Lebrikizumab	3 - Moderate	1 - Almost clear	3	1
	Placebo	4 - Severe	1 - Almost clear	4	1
	Lebrikizumab	3 - Moderate	1 - Almost clear	3	1
	Lebrikizumab	3 - Moderate	1 - Almost clear	3	1
	Lebrikizumab	3 - Moderate	1 - Almost clear	3	1
	Placebo	3 - Moderate	1 - Almost clear	3	1
	Placebo	3 - Moderate	1 - Almost clear	3	1
	Lebrikizumab	3 - Moderate	1 - Almost clear	3	1

(b) (6)	Placebo	3 - Moderate	1 - Almost clear	3	1
	Screen Failure	3 - Moderate	N/A	3	N/A
	Placebo	3 - Moderate	1 - Almost clear	3	1
	Placebo	3 - Moderate	1 - Almost clear	3	1

The Sponsor study statisticians also identified other IGA data anomalies at other timepoints for both studies. For example, all subjects in Study KGAC at Site 5042 had identical IGA scores at Weeks 4, 6, and 8.

Based on the data anomalies, the Sponsor conducted an audit of Dr. Carpio's site. Per the audit report, Dr. Carpio lacked familiarity with the AD disease severity assessments of IGA and BSA, which were critical to determining eligibility and assessing efficacy. For example, he confused the use of palm measurements for assessment of IGA, when it was used for BSA. He also lacked understanding of the required baseline disease status of AD. When first questioned on the possibility that the subjects enrolled might not have had moderate-to-severe AD, Dr. Carpio responded that this was "possible". In a meeting later that day, Dr. Carpio provided a definitive answer, saying "yes" to whether subjects enrolled at his site had mild rather than moderate-to-severe AD.

The Sponsor's audit concluded that the explanation for the implausible data was that Dr. Carpio failed to conduct the studies in accordance with protocol entry criteria related to the severity of AD at Baseline. As a result of the audit, the site was terminated from Studies KGAC and KGAD on October 21, 2021. At the time of termination, study activities for Study KGAC were ongoing while study activities for Study KGAD were complete.

FDA Inspection Findings

Inspection Dates: March 8 – 17, 2023

This clinical investigator was inspected as a routine PDUFA inspection for Study KGAC and KGAD. This was his second FDA inspection. The previous inspection was in April 2015 and resulted in regulatory observations of the investigation not being conducted in accordance with protocol, failure to maintain adequate case histories, and failure to obtain informed consent.

For KGAD, 19 subjects were screened, and 17 subjects were randomized (two screen failures). Consent/assent forms for 10 of 19 screened subjects were reviewed, and source records for both screen failures and 8 of 17 randomized subjects were fully reviewed. IGA documentation was reviewed and compared to data line listings for all 17 randomized subjects.

For KGAC, 18 subjects were screened and randomized (no screen failures). Records for 6 of 18 randomized subjects were fully reviewed. IGA documentation was reviewed and compared to data line listings for all 18 randomized subjects.

Subject-related paper source records reviewed included: ICFs/assents, vital sign entries, efficacy data, AEs, prior and concomitant medications, physical examinations, IP dosing and

accountability logs, phone call logs, protocol deviation forms, laboratory reports and requisition forms, and progress notes. The EDC was reviewed for the assessments entered electronically (e.g., IGA, EASI, and various patient-reported outcome measures).

Study-related documents reviewed included: the protocols, training records, signed investigator agreements, screening and enrollment logs, informed consent logs, IP shipping and receipt documentation, IP accountability logs, protocol deviation logs, AE reporting, IRB documentation, financial disclosures, study monitoring documents, and email correspondence between the site and the monitor or sponsor.

There did not appear to be under-reporting of SAEs or AEs of Special Interest. There were no discrepancies between the reviewed IGA and EASI source data, data in the EDC, and the submitted data line listings, however, it is not clear that disease severity documented by Dr. Carpio at eligibility was accurate (*see reviewer comments below*).

Reviewer comments: During ORA's questioning of Dr. Carpio as to why his site was terminated, he initially gave conflicting statements regarding the randomized subjects' disease severity at Baseline (e.g., mild, moderate-to-severe, mild-to-moderate). Ultimately, he provided a written statement on the last day of the inspection stating that all randomized subjects had moderate-to-severe AD as per protocol. This statement contradicted what he told the Sponsor during their audit when he stated "yes" in response to whether subjects enrolled at his site had mild rather than moderate-to-severe AD at Baseline.

Dr. Carpio underwent all required training for the protocol and for the efficacy assessments. All sub-Investigators who performed the efficacy assessments were specifically trained. However, sub-Investigators were added to the delegation of authority log before they completed training.

Reviewer's Comments:

- *Although he completed training, when questioned at various points during the inspection, Dr. Carpio did not appear to be aware of the nature of the protocols. For example, he stated that as a clinical investigator, he was not blinded. Later, he asked the ORA investigator if he was blinded.*
- *While the sub-Investigators were delegated the authority of performing the assessments prior to completing training, there was no clear evidence that the assessments were performed by them prior to actual completion of training.*

The following protocol deviations were observed at the site:

Study KGAD

- Subject (b) (6) met exclusion criterion #10 by having an active acute infection requiring treatment with systemic antibiotics within two weeks of Baseline. The subject completed treatment for a urinary tract infection (UTI) on (b) (6) but was randomized on (b) (6). This was not reported as a protocol deviation.

Reviewer comment: The randomization of the subject less than two weeks after completing treatment likely did not impact the subject's safety. A post-treatment urinalysis was performed on (b) (6), prior to randomization. It was negative for leukocyte esterase and nitrite, confirming clearance of the UTI.

- Four subjects did not complete their subject questionnaires characterizing disease severity before the investigator assessments as required by the protocol. The protocol deviation for Subject (b) (6) was not reported.

Subject Number	Visit	Time Subject Questionnaire Completed	Time Investigator Assessment Completed	Reported as a Protocol Deviation?
(b) (6)	Baseline	DLQI: 2:07PM EQ-5D-5L: 2:09PM Anxiety: 3:14PM Depression: 3:15PM	IGA: 1:52PM BSA: 1:53PM EASI: 1:55PM SCORAD: 2:01PM	No
	Week 4	DLQI: 12:42PM	IGA: 12:36PM BSA: 12:38PM EASI: 12:41PM	
	Baseline	DLQI: 3:46PM EQ-5D-5L: 3:49PM	IGA: 3:17PM BSA: 3:19PM EASI: 3:30PM SCORAD: 3:39PM	Yes
	Baseline	DLQI: 2:46PM EQ-5D-5L: 2:50PM Anxiety: 2:59PM Depression: 3:01PM	IGA: 2:07PM BSA: 2:22PM EASI: 2:28PM SCORAD: 2:33PM	Yes
	Baseline	IGA: 2:09PM BSA: 2:13PM EASI: 2:26PM SCORAD: 2:34PM	DLQI: 2:49PM EQ-5D-5L: 2:51PM	Yes

Reviewer comment: The deviations were isolated, and any inaccuracies of the subject questionnaire results related to improper timing would not have affected study outcome as they only contributed to secondary efficacy endpoints.

Study KGAC

- Subjects (b) (6) did not have their safety follow-up visits 12 weeks after the last dose of medication as required by the protocol. These were not reported as protocol deviations.

Reviewer Comment: These were the subjects who had their participation ended after the site was terminated by the sponsor. These subjects had their safety follow-up visits before the early termination visit. These out of window visits were unlikely to affect the safety of the subjects.

- There was one unreported AE: Subject (b) (6) was randomized on (b) (6), to the placebo arm. The subject had elevated alkaline phosphatase of 260 U/L (reference range: 35-104 U/L) on (b) (6) (Week 10), which was deemed clinically significant by the investigator, but not reported as an AE. There was no documentation that the subject was informed. Per the protocol, “new or worsening abnormal laboratory values...are to be recorded as AEs if they are considered to be of clinical significance by the Investigator.”

Reviewer comments: The subject’s alkaline phosphatase values were elevated over the study, but not deemed clinically significant by the investigator until Week 10, as shown in the following table:

Subject (b) (6)’s Alkaline Phosphatase Laboratory Values During the Study

Date	Laboratory Value**	Range	Deemed Clinically Significant by CI
(b) (6) (Screening)	235 U/L	35-104 U/L	No
(b) (6)* (Unscheduled)	255 U/L	35-104 U/L	No
(b) (6) (Week 8)	226 U/L	35-104 U/L	No
(b) (6) (Week 10)	260 U/L	35-104 U/L	Yes

* (b) (6), the progress note accompanying the visit states that the subject was diagnosed with hepatic steatosis by her primary care physician.

** The subject’s serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) laboratory results were elevated at all four dates, but not to the same degree as alkaline phosphatase and were not deemed clinically significant.

The subject’s alkaline phosphatase, ALT, and AST do not appear to have significantly changed over the course of the study participation, which is reassuring, but the investigator did not report it when it became clinically significant. Since the subject was randomized to the placebo arm, the observed liver function abnormalities were not related to the study drug and likely related to the subject’s diagnosis of hepatic steatosis.

OSI Recommendations

Due to the above data anomalies found by the Sponsor and confirmed by OSI, and inspection findings which included inconsistent statements by the clinical investigator that indicate a lack of command of study details related to eligibility and blinding, we recommend sensitivity analyses excluding data from Dr. Carpio’s site from Study KGAC and KGAD.

{ See appended electronic signature page }

Stephanie Coquia, M.D.

Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division /Division Director/Shari Targum
Review Division /Project Manager/Qianyiren Song
Review Division/Cross Discipline Team Lead/David Kettl
Review Division/Clinical Reviewer/Shera Schreiber
OSI/Office Director/Dave Burrow
OSI/GCP Program Analysts/Yolanda Patague

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/

STEPHANIE F COQUIA
07/10/2023 11:03:42 AM

MICHELE B FEDOWITZ
07/10/2023 12:58:00 PM

JENN W SELLERS
07/10/2023 01:24:13 PM



DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	6/21/2023		
To:	Andrew Shiber, CDER/OPQ/OPRO/DRBPMI/RBPMB1 ANH-THY LY, FDA/OC/CDER/OPQ/OPRO/DRBPMI/RBPMB1		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From	Florencia Wilson OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761306 , Lebrikizumab ICC2200915 ICC2200914 Case 00878369 Case 00878385		
Recommendation	Filing Recommendation Date: Click or tap to enter a date. ☒ CDRH did not provide a Filing Recommendation Device Constituent Parts of the Combination Product are acceptable for Filing. Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies *filing review was done by original reviewer, Porsche Bennett. Please see page 2 and Section 15.1. Mid-Cycle Recommendation Date: 5/22/2023 CDRH did not provide a Mid-Cycle Recommendation CDRH has no approvability issues at this time. CDRH has additional Information Requests, See Appendix A CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 6/21/2023 ☒ Device Constituent Parts of the Combination Product are Approvable. Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (*Optional)
Florencia T. Wilson -S Digitally signed by Florencia T. Wilson -S Date: 2023.06.21 10:04:44 -04'00'	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2023.06.26 10:03:31 -04'00'	

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	11/23/2022		
To:	Anh-Thy Ly		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From	Porsche Bennett OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CAPT Alan Stevens, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA761306 , Lebrikizumab ICC2200914/ICC2200915 ICCR00878385		
Recommendation	Filing Recommendation Date: 11/23/2022 ☐ CDRH did not provide a Filing Recommendation ☒ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies ☒ Pre-approval inspection recommended		

Digital Signature Concurrence Table	
Reviewer	
Porsche P. Bennett -S	Digitally signed by Porsche P. Bennett -  Date: 2022.12.19 08:10:17 -05'00'

Date	6/20/2023		
To:	Florenca Wilson		
Requesting Center/Office	Other	Clinical Review Division	Other
From	Courtney Evans OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C GHDB		
Subject	BLA 761306 , Lebrikizumab N/A N/A		
Recommendation	Filing Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Filing Recommendation ☒ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 for Deficiencies Mid-Cycle Recommendation Date: Click or tap to enter a date. ☒ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 6/21/2023 ☒ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

v09.23.2019

Page 1 of 13

Engineering Consult – PFS+NSD
Lebrikizumab
Eli Lilly and Company

Reviewer	Team Lead (TL)	Division (*Optional)
Courtney Evans -S	Digitally signed by Courtney Evans -S Date: 2023.06.21 02:01:32 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information		
Submission Number	BLA 761306	
Sponsor	Eli Lilly and Company	
Drug/Biologic	Lebrikizumab	
Indications for Use	Moderate to severe Atopic Dermatitis (AD)	
Device Constituent	Pre-Filled Syringe	Auto-Injector
Related Files	IND 119866	

Review Team		
Lead Device Reviewer	<i>Florencia Wilson</i>	
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #

Important Dates	
Discipline-Specific Review Memos Due	N/A
Final Lead Device Review Memo Due	6/23/2023
Interim Due Dates	Meeting/Due Date
Filing	11/16/2023 (per the original reviewer, Porsche Bennett)
74-Day Letter	12/11/2022
Mid-Cycle	2/27/2023 (Internal), 3/6/2023 (Sponsor meeting)
Primary Review	2/28/2023
Internal Meeting(s)	TBD
Sponsor Meeting(s)	3/28/2023

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

Approvable – the device constituent (Autoinjector) of the combination product is approvable for the proposed indication.

Approvable with PMC or PMR, [See Section 2.3](#)

Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation			X	Deferred to CDER
Human Factors Validation			X	Deferred to DMEPA
Facilities & Quality Systems	X			

2.1. **Comments to the Review Team**

CDRH does not have any further comments to convey to the review team.

CDRH has the following comments to convey to the review team:

2.2. **Complete Response Deficiencies**

There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. **Recommended Post-Market Commitments/Requirements**

CDRH has Post-Market Commitments or Requirements	
CDRH does not have Post-Market Commitments or Requirements	

TABLE OF CONTENTS

1. SUBMISSION OVERVIEW.....	5
2. EXECUTIVE SUMMARY AND RECOMMENDATION	6
2.1. Comments to the Review Team	6
2.2. Complete Response Deficiencies	6
2.3. Recommended Post-Market Commitments/Requirements	6
3. PURPOSE/BACKGROUND	9
3.1. Scope	9
3.2. Prior Interactions	9
3.2.1. Related Files.....	9
3.3. Indications for Use	9
3.4. Materials Reviewed.....	9
4. DEVICE DESCRIPTION.....	10
4.1. Device Description.....	10
4.2. Steps for Using the Device.....	10
4.3. Device Description Conclusion.....	11
5. FILING REVIEW.....	11
6. LABELING	12
6.1. General Labeling Review.....	12
6.2. Labeling Review Conclusion	12
7. DESIGN CONTROL SUMMARY	13
7.1. Summary of Design Control Activities.....	13
7.2. Design Inputs and Outputs	14
7.3. Applicable Standards and Guidance Documents	14
7.4. Design Control Review Conclusion.....	15
8. RISK ANALYSIS	15
8.1. Risk Management Plan.....	15
8.2. Risk Analysis Review Conclusion	15
9. DESIGN VERIFICATION REVIEW	16
9.1. Performance/Engineering Verification	16
9.1.1. Essential Performance Requirement Evaluation.....	21
9.1.2. Verification of Design Inputs Evaluation	22
9.2. Design Verification Review Conclusion.....	33
9.3. Discipline Specific Sub-Consulted Review Summary.....	35
10. CLINICAL VALIDATION REVIEW	36
10.1. Review of Clinical Studies Clinical Studies.....	36
10.2. Clinical Validation Review Conclusion	38
11. HUMAN FACTORS VALIDATION REVIEW	38
12. FACILITIES & QUALITY SYSTEMS	39
12.1. Facility Inspection Report Review	39
12.2. Quality Systems Documentation Review	39
12.2.1. Description of the Device Manufacturing Process.....	39
12.2.2. cGMP Review	41
12.2.3. Corrective and Preventive Action Review	42

12.3.	Control Strategy Review	43
12.4.	Facilities & Quality Systems Review Conclusion.....	44
13.	APPENDIX A (INFORMATION REQUESTS).....	45
13.1.	Filing/74-Day Information Requests	45
13.2.	Mid-Cycle Information Requests	45
13.3.	Interactive Information Requests.....	45
13.3.1.	Interactive Information Requests sent on 5/22/2023.....	45
14.	APPENDIX B (CONSULTANT MEMOS)	45
14.1.	Human Factors Review Memo – Insert Consultant Name	45
14.2.	Clinical Review Memo – Insert Consultant Name	45
14.3.	Insert Discipline Review Memo – Insert Consultant Name	45
15.	Appendix C (other reviewers).....	45
15.1	Facilities Review by Porsche Bennett.....	45
15.2	PFS-NSD Review by Courtney Evans.....	45

3. PURPOSE/BACKGROUND

3.1. Scope

Eli Lilly and Company is requesting approval of Lebrikizumab. The device constituent of the combination product is an Auto-Injector.

CDER/OPQ has requested the following [consult](#) for review of the device constituent of the combination product:

We are requesting a CDRH consultative review of the device-related product quality information and data provided in the original BLA for EBGLYSS (lebrikizumab). The drug product is intended to be supplied (b) (4) as a pre-filled syringe with needle safety device (PFS-NSD) or autoinjector (AI)/pre-filled pen (PFP) for subcutaneous injection. Please perform a device review of the relevant information and data provided in the BLA (e.g., device description, manufacturing and controls including drug product specifications, characterization and device verification, sterilization, biocompatibility, draft labeling) and make a determination on the adequacy of the lebrikizumab device components for commercial use.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following [review areas](#):

- Device performance of the autoinjector

This review will not cover the following review areas:

This review will not cover the pre-filled syringe with needle safety feature. This review is performed by Porsche Bennett/Courtney Evans and the full memo is attached in Section 15.2 [Error! Reference source not found.](#)
 APPEARS THIS WAY ON ORIGINAL

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

IND 119866	• Initial IND for atopic dermatitis • Change in Sponsor from Genentech to Dermira to Lilly

3.3. Indications for Use

Combination Product	Indications for Use
Lebrikizumab	Moderate to severe Atopic Dermatitis (AD)
Pre-Filled Syringe Auto-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0001	
0011	Has Stability data in 3.2.P.8.3 – support-stab-data
0019	Post approval stability protocol and stability commitment in 3.2.P.8.2 – post-appr-stab Stability data in 3.2.P.8.3 - support-stab-data-ai-pfs-device-pv

0020	3.2.P.5 – specifications and justifications
0028	Module 1 – response to IR
0032	Module 1 – response to IR

4. DEVICE DESCRIPTION

4.1. Device Description

The following are taken from Seq0001, 3.2.R, medical device autoinject:

3.2.R Medical Device (Autoinjector 2 mL)

3.2.R.1 Introduction

This document describes the device constituent part of lebrikizumab for injection in an autoinjector (AI). The autoinjector is a needle-based injection system (NIS) that, when activated, automatically inserts the needle and delivers the drug product. Providing the injectable product in an autoinjector reduces the steps needed to transfer the injectable product from a vial to a hypodermic syringe and minimizes the risk of contamination present during transfer of the product. Prefilled syringes ensure safe use of the injectable product by permitting immediate injection of the product after following relatively simple handling steps, and autoinjectors automate the needle insertion and drug delivery steps.

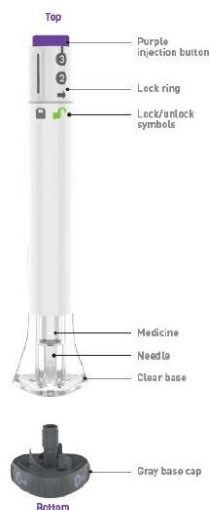


Figure 3.2.R.2-1 Lebrikizumab Autoinjector

The following are taken from Seq0001, 3.2.P.7, container closure system:

4.2. Steps for Using the Device

The following are taken from Seq0001, 3.2.R, medical device autoinject:

Operation Steps

1. Remove the base cap and discard.
2. Position the autoinjector for injection and unlock.
3. Press the injection button to start the injection and hold the device until the injection is complete.

The user activates the device by pressing the injection button. This generates an audible and tactile click and the device automatically performs the following steps:

- 4. Needle insertion: (b) (4)
- 5. Drug injection: (b) (4)
- 6. Delay: (b) (4)
- 7. Needle retraction: (b) (4)

The user must hold the device against the skin during the injection cycle but is not required to maintain pressure on the injection button. The device generates an audible and tactile click at the end of the needle retraction process. The user can confirm that the injection is complete by looking for the gray plunger position as shown in the Instructions for Use (IFU), see Figure 3.2.R.2-2. The device locks the retracted needle in place for disposal of the used autoinjector in a sharps container.

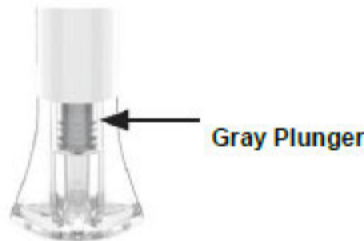


Figure 3.2.R.2-2 IFU Graphic Showing Plunger Position for Confirmation of Complete Injection

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION									
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:			
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A	
Reviewer Comments									
The provided Device description is acceptable.									
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor:							Yes	No	

5. FILING REVIEW

CDRH performed Filing Review Finalize Filing Review Section	
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	

Please note that the filing and facilities review was performed by the original reviewer, please see Section 15.1 [Facilities Review by Porsche Bennett](#)



BLA761306.Lebrikizu
 mab.CDRH-OPEQ Rev

PFS-NSD Review by

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors: *deferred to CDER			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments

The provided labeling is adequate in meeting the general labeling guidelines per CDRH. However, the full review and the adequacy of the human factors validation of the instructions for use is deferred to CDER.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION								
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A
Reviewer Comments								

The provided labeling is adequate in meeting the general labeling guidelines per CDRH. However, the full review and the adequacy of the human factors validation of the instructions for use is deferred to CDER.

CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: Yes No

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

The following are taken from Seq0001, 3.2.R, medical device autoinject:

Design Controls

Lilly design control activities are governed by GQS161 Design Control for Medical Devices. Table 3.2.R.9-1 lists the Lilly PDS detailed procedures that demonstrate compliance with 21 CFR 820.30. Note IDAP is responsible for only design transfer.

Table 3.2.R.9-1 Design Control Information

21 CFR 820.30 Section	Lilly Procedures
Design Controls, General, 820.30(a)	PDS-SOP-PDS0014 Design Control
Design and Development Planning, 820.30(b)	PDS-SOP-PDS4049 Design and Development Planning
Design Input, 820.30(c)	PDS-SOP-PDS4128 Design Input
Design Output, 820.30(d)	PDS-SOP-PDS4130 Design Outputs
Design Review, 820.30(e)	PDS-SOP-PDS4129 Design and Manufacturability Review
Design Verification, 820.30(f), Design Validation 820.30 (g)	PDS-SOP-PDS4131 Design Verification and Design Validation Studies, PDS-SOP-PDS0024 Risk Management.
Design Transfer, 820.30(h)	PDS-SOP-PDS4129 Design and Manufacturability Reviews PDS-SOP-PDS0224 Technology Transfer
Design Changes, 820.30(i)	PDS-SOP-PDS0010 Change Management
Design History File, 820.30 (j)	PDS-SOP-PDS4132 Design History File and Design History File Index

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	Yes	No	N/A

Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)			X
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments

Risk analysis was performed by the applicant per ISO 14971 of the combination product. This is adequate.

7.2. Design Inputs and Outputs

Essential Performance Requirements

The following pertains to the Autoinjector

<u>Design Inputs (Essential Performance Requirement)</u>	<u>Design Outputs (Specification)</u>
Dose Accuracy	(b) (4) mL
Button Activation Force	(b) (4) N
Injection Time	≤ 15 secs
Extended Needle length	(b) (4) mm

Reviewer Comments

The design inputs and outputs is adequate for an autoinjector. It is noted that these EPRs are also validated per human factors (HF) testing, including validation of the instructions for use. The adequacy of the HF testing is deferred to CDER.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

<u>Standard or Guidance</u>	<u>Conformance (Y/N/NA)</u>
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	N/A
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	N/A (for autoinjector)
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION									
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:			
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A	
<u>Reviewer Comments</u>									
The provided design control is adequate.									
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor:							Yes	No	

8. RISK ANALYSIS

8.1. Risk Management Plan

3.2.R.7 Compliance to ISO14971:2012

The overall residual risk of the lebrikizumab autoinjector has been reduced as far as possible given the limits of the autoinjector technology. The medical benefit of lebrikizumab as a (b)(4) treatment for atopic dermatitis outweighs the residual risk of the autoinjector. Lilly performs risk management according to the requirements provided in ISO 14971. The lebrikizumab autoinjector hazards are the same as those identified for the approved autoinjectors and similar to other autoinjectors on the market. Risk management activities are conducted throughout the lifecycle of a device, from concept through post-market. Risk tools, such as the Failure Mode and Effects Analyses (FMEA), document design requirements, risk control measures, and verification of implementation and effectiveness of controls for each identified risk line item. The overall residual risk report is used to confirm the design, application, process, and distribution FMEAs address all preliminary hazard analysis hazards, and that appropriate controls are in place. Table 3.2.R.7-1 summarizes the autoinjector clinical performance requirements, the requirement descriptions, the key risk controls and the identification of the verification and validation reports for these requirements.

Reviewer Comments
The Sponsor conformed to ISO 14971 for their risk analysis of the combination product.

8.2. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION									
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:			
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A	
<u>Reviewer Comments</u>									
This is adequate.									
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor:							Yes	No	

17 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION								
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A
<u>Reviewer Comments</u>								
Interactive deficiencies are sent to the Sponsor (see below). The responses to all th IR are adequate.								
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: Yes No								

	Date Sent: 5/22/2023	Date/Sequence Received: 6/5/2023
Information Request #1	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	
Response Adequate:	Yes No, See IR 1.1 Sent on 6/14/2023

Follow-On Deficiency	Date Sent: 6/14/2023	Date/Sequence Received: 6/15/2023
Information Request #1.1	(b) (4)	

	(b) (4)
Sponsor Response	
Reviewer Comments	The provided response is adequate. The Sponsor added injection time to the post-approval stability protocol. Resolved
Response Adequate:	Yes No, See IR # Sent on Click or tap to enter a date.

	Date Sent: 5/22/2023	Date/Sequence Received: 6/5/2023
Information Request #2	(b) (4)	
Sponsor Response		
Reviewer Comments	The Sponsor provided an adequate response, which demonstrated that the AI will perform as intended up to expiry. Resolved	
Response Adequate:	Yes No, See IR # Sent on Click or tap to enter a date.	

9.3. Discipline Specific Sub-Consulted Review Summary

No Additional Discipline Specific Sub-Consults were requested

The following additional Discipline Specific Sub-Consults were requested:

10. CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

There is no device related clinical studies for review
 There are clinical studies for review

This information was obtained from the following [documents](#):

The following are taken from Seq001, 5.2 Tabular Listing All Clinical studies, p. 6 of 20:

Study Name						
Study Type	Bioavailability and Bioequivalence Studies J2T-MCKGBG; Phase 1; Module 5.3.1.2					
Objectives/Endpoints	To evaluate the PK of lebrikizumab after SC administration of 250-mg dose using a 2-mL PFS-NSD and a 2- mL AI in healthy participants.					
Drug/Device Studied	2-mL (125 mg/mL) SC injections of lebrikizumab using PFS-NSD and AI in the arm, thigh, or abdomen for a total administered dose of 250 mg.					
Number and Type of Subjects	119 for AI 122 to PFS-NSD Healthy subjects, single dose					
Brief description of protocol	Phase 1, multisite, randomized, parallel design, open-label, 2- arm, single-dose study in healthy participants.					
Results					Ratio of geometric LS means (PFS-NSD:AI)	90% CI for the ratio (lower, upper)
	Parameter	Treatment	N	Geometric LS mean		
	AUC(0-t _{last}) (µg.day/mL)	PFS-NSD	117	1262	1.09	(1.03, 1.14)
		Autoinjector	117	1370		
	AUC(0-∞) (µg.day/mL)	PFS-NSD	106	1357	1.07	(1.02, 1.14)
	Autoinjector	100	1458			
C _{max} (µg/mL)	PFS-NSD	120	38.6	1.09	(1.03, 1.16)	
	Autoinjector	118	42.2			
Device Related Comments	Based on a comparison of descriptive statistics, injection-site location did not appear to impact lebrikizumab systemic exposure (AUC(0-t_{last}), AUC(0-∞), and C_{max}) for either device, considering there was substantial overlap in systemic exposure between study intervention groups and across injection sites and the small differences in geometric mean systemic exposure estimates were within the observed between-subject variability.					

	• No notable difference in safety based on TEAEs, SAEs and/or ISRs following PFS-NSD administration compared to autoinjector administration. • A similar number of participants reported TEAEs following PFS-NSD administration (N=39, 32.0%) compared to autoinjector administration (N=26, 21.8 %). All TEAEs were mild or moderate in severity. • Eight participants reported ISRs following both PFS-NSD administration (N=3, 2.5%) and autoinjector administration (N=5, 4.2%). Out of the 10 total reported ISRs, all were recorded as mild in both study intervention groups, except for 1 ISR which was recorded as moderate following autoinjector administration. • No deaths, SAEs, or AEs leading to study discontinuation were reported. • Six (5.0%) participants were TE-ADA positive following PFS-NSD administration, and 5 (4.2 %) participants were TE-ADA positive following autoinjector administration.
	Abbreviation or Term Definition/Explanation AD atopic dermatitis ADA antidrug antibody AE adverse event AI autoinjector AUC(0-∞) area under the concentration versus time curve from time zero to infinity AUC(0-tlast) area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration AUC(tlast-∞) percentage of AUC(0-∞) extrapolated BQL below the limit of quantification CI confidence interval Cmax maximum observed drug concentration COVID-19 coronavirus disease 2019 CRU clinical research unit IL interleukin ISR injection-site reaction LS least squares NAb neutralizing antibody PFS-NSD prefilled syringe with needle safety device PK pharmacokinetic SAE serious adverse event SAP statistical analysis plan

	SC subcutaneous(ly) t_{1/2} half-life associated with the terminal rate constant (λ_z) in noncompartmental analysis TE-ADA treatment-emergent antidrug antibody TEAE treatment-emergent adverse event t_{last} the last time point with a measurable concentration t_{max} time of maximum observed drug concentration V_z/F apparent volume of distribution during the terminal phase after extra-vascular administration
Reviewer Comments	This is a Bioavailability and Bioequivalence Studies between the PFS-NSD and AI. In this studies, it appears that the only device related adverse event is the injection site-reaction which is recorded as mild and 1 AI injection was reported as moderate out of the 10 reported ISRs. There is no mention of device related use error. It is noted that the site of the Clinical Study was at a clinical research unit, therefore, the users are more likely healthcare providers.
Reviewer Conclusion	As for the Clinical validation per HF, DMEPA will make the final determination if the device usability is adequate for the user population.

Tabular Listing of All Clinical Studies

Table 5.1 and Table 5.2 list all the completed and ongoing clinical trials of lebrikizumab in healthy participants and patients with mild, intermittent asthma and moderate-to-severe atopic dermatitis included in this submission. The pivotal studies used to support the registration of lebrikizumab for the treatment of moderate-to-severe atopic dermatitis are J2T-DM-KGAB, J2T-DM-KGAC, and J2T-DMKGAD.

The full list of the Clinical Studies are located in Seq001, Module 1, 5.2 Tabular Listing of all Clinical Studies.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION									
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:			
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A	
<u>Reviewer Comments</u>									
The adequacy of the clinical studies are deferred to CDER.									
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor:							Yes	No	

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	
Human Factors deferred to DMEPA	

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted (please note that the facility inspection review was performed by the original reviewer. The memo is attached in Section 15.1)	
CDRH Facilities Inspection Review was not conducted	

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	
CDRH Quality Systems Documentation Review was not conducted	

12.2.1. Description of the Device Manufacturing Process

(b) (4)

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



Reviewer Comments

The provided description of the device manufacturing process is adequate.

Device Manufacturing Process Conclusion

The Sponsor provided adequate information for the summary of the manufacturing process / production flow.

Yes

No

12.2.2. cGMP Review



(b) (4)

Reviewer Comments

The Sponsor provided an overview of their Quality System Management (see above). This is acceptable.

GMP Compliance Summary Conclusion

The Sponsor provided adequate summary information about the GMP compliance activities	Yes	No

12.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

Corrective and Preventive Actions

(b) (4)

CAPA Conclusion

The Sponsor provided adequate information for corrective and preventive actions.

Yes

No

12.3. Control Strategy Review

(b) (4)

Reviewer Comments

(b) (4) The control strategy is acceptable.

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

Yes

No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION									
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:			
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A	
<u>Reviewer Comments</u>									
The quality system review of the application is adequate. It is noted that the original reviewer recommended pre-approval inspection. This has been conveyed to the Sponsor. See the memo attached in Section 15.1 below.									
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor:							Yes	No	

<<END OF REVIEW>>

13. APPENDIX A (INFORMATION REQUESTS)

13.1. Filing/74-Day Information Requests

13.2. Mid-Cycle Information Requests

13.3. Interactive Information Requests

13.3.1. Interactive Information Requests sent on 5/22/2023

Please see Section [9.2](#) for the interactive deficiencies sent to the Sponsor.

14. APPENDIX B (CONSULTANT MEMOS)

14.1. Human Factors Review Memo – Insert Consultant Name

14.2. Clinical Review Memo – Insert Consultant Name

14.3. Insert Discipline Review Memo – Insert Consultant Name

N/A

15. Appendix C (other reviewers)

15.1 Facilities Review by Porsche Bennett



BLA761306.Lebrikizu
mab.CDRH-OPEQ Rev

15.2 PFS-NSD Review by Courtney Evans



BLA761306.Engineeri
ng Review-PFS-NSD.ç

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/

ANH-THY LY
06/26/2023 12:42:34 PM

HUMAN FACTORS STUDY RESULTS AND COMPARATIVE ANALYSES REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761275
Product Type:	Combination Product
Product Name, Dosage Form, and Strength:	Ebglyss ¹ (lebrikizumab) Injection 250 mg/2 mL
Device Constituent:	Prefilled pen; prefilled syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Eli Lilly and Company
Submission Date:	September 28, 2022; February 21, 2023; February 24, 2023; May 15, 2023
TTT ID #:	2022-1963
DMEPA 1 Safety Evaluator:	Neha Kumar, PharmD
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

¹ The proposed proprietary name, Ebglyss, was found conditionally acceptable on December 14, 2022.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study results report and comparative analyses submitted under BLA 761306 for Ebglyss (lebrikizumab) injection.

1.1 PRODUCT DESCRIPTION

Table 1 presents relevant product information for Ebglyss (lebrikizumab) received on April 12, 2023, from Eli Lilly and Company and US-licensed Taltz (ixekizumab).

Name	Ebglyss (lebrikizumab)	Taltz ²
Initial Approval Date	N/A	March 22, 2016
Therapeutic Drug Class or New Drug Class	Interleukin-13 antagonist	Interleukin-17A antagonist
Indication	Treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Ebglyss can be used with or without topical corticosteroids.	Treatment of: • patients aged 6 years or older with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy • adults with active psoriatic arthritis • adults with active ankylosing spondylitis • adults with active non-radiographic axial spondylarthritis with objective signs of inflammation
Route of Administration	Subcutaneous	
Dosage Form	Injection	
Strength	• 250 mg/2 mL solution in a single-dose prefilled pen • 250 mg/2 mL solution in a single-dose prefilled syringe with needle safety device	• 80 mg/mL solution in a single-dose prefilled autoinjector • 80 mg/mL solution in a single-dose PFS
Dose and Frequency	500 mg (two 250 mg injections) at Week 0 and Week 2, followed by	• Adult Plaque Psoriasis: is 160 mg (two 80 mg injections) at week

² Taltz [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2022 JUL 27. [cited 2023 MAY 5]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125521s024lbl.pdf.

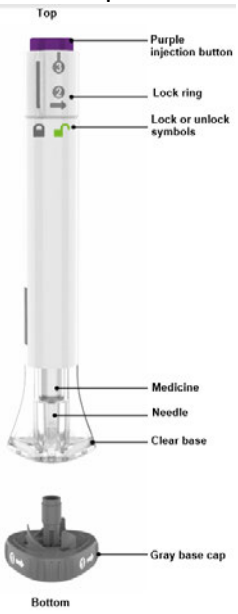
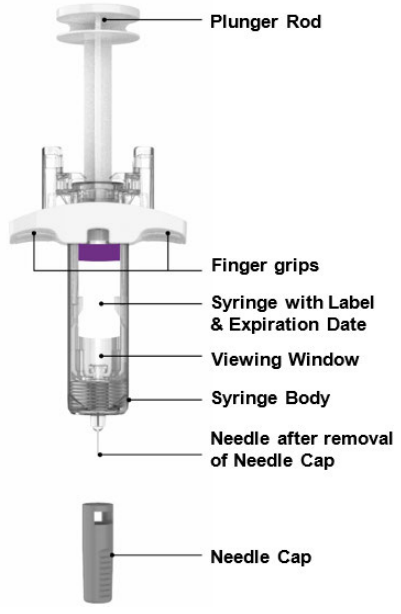
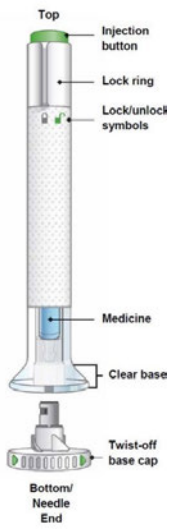
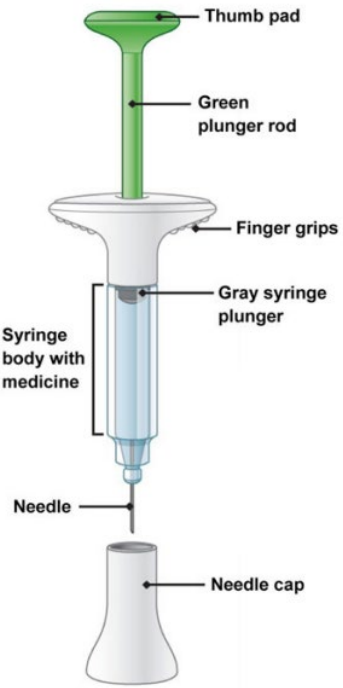
250 mg (one injection) every 2 weeks
(b) (4) Week 16 or later, when
adequate clinical response is achieved.
The maintenance dose is Ebglyss 250
mg every 4 weeks; (b) (4)

0, followed by 80 mg at Weeks
2, 4, 6, 8, 10, and 12, then 80 mg
every 4 weeks.

- Pediatric Plaque Psoriasis:
 - For patients weighing greater than 50 kg, recommended dosage is 160 mg (two 80 mg injections) at Week 0, followed by 80 mg every 4 weeks.
 - For patients weighing 25-50 kg, recommended dosage is 80 mg at week 0, followed by 40 mg every 4 weeks.
 - For patients weighing less than 25 kg, recommended dosage is 40 mg at week 0, followed by 20 mg every 4 weeks.
- Psoriatic Arthritis:
 - 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg every 4 weeks.
 - For psoriatic arthritis patients with coexistent moderate-to-severe plaque psoriasis, use the dosing regimen for adult plaque psoriasis.
 - Taltz may be administered alone or in combination with a conventional DMARD (e.g., methotrexate).
- Ankylosing Spondylitis: 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg every 4 weeks.

		• Non-radiographic Axial Spondylarthritis: 80 mg by subcutaneous injection every 4 weeks
How Supplied	Ebglyss injection is a sterile, preservative free, clear, colorless to slightly yellow solution, (b) (4) available in a single-dose prefilled pen or a single-dose prefilled syringe with needle shield. Each prefilled pen and prefilled syringe with needle shield is designed to deliver 250 mg of Ebglyss in 2 mL. Ebglyss is available as a carton of one (b) (4) 250 mg/2 mL PFP and a carton of one 250 mg PFS with needle safety device.	Taltz injection is a sterile, preservative free, clear and colorless to slightly yellow solution available in a single dose prefilled autoinjector or a single-dose prefilled syringe to deliver 80 mg ixekizumab. Taltz is available as a carton of one, two and three 80 mg/mL autoinjector and a carton of one 80 mg/mL PFS.
Storage	• Store refrigerated at 2°C to 8°C (36°F to 46°F). • If necessary, Ebglyss may be kept at room temperature up to 30°C (86°F) for up to 7 days in the original carton. Throw away Ebglyss if not used within 7 days at room temperature. • Store in the original carton to protect from light until use. • Do not freeze. Do not use Ebglyss if it has been frozen. • Do not shake. • Discard the Ebglyss single-dose prefilled pen or prefilled syringe after use in a puncture-resistant container.	• Taltz must be protected from light until use. • Store refrigerated at 2°C to 8°C (36°F to 46°F). • If needed, patients/caregivers may store Taltz at room temperature up to 30°C (86°F) for up to 5 days in the original carton to protect from light. Once Taltz has been stored at room temperature, do not return to the refrigerator and discard, if unused, within 5 days. • Record the date when Taltz is first removed from the refrigerator in the spaces provided on the carton. • For the 2 or 3 autoinjector pack, remove a single autoinjector at a time leaving the remaining autoinjector(s) in the original carton in the refrigerator. Ensure the unrefrigerated Taltz is protected from light.

		• Do not freeze. Do not use Taltz if it has been frozen. • Do not shake. • Discard the Taltz single-dose prefilled autoinjector or syringe after use in a puncture-resistant container.

Container Closure/Device Constituent	Prefilled pen:  Prefilled syringe with needle shield: 	Autoinjector:  Prefilled syringe: 
Intended Users	Adult patients, caregivers, healthcare professionals (HCPs)	

Intended Use Environment	Home, clinical setting

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT’S HUMAN FACTORS DEVELOPMENT PROGRAM

- On April 15, 2020, the Applicant submitted their comparative analyses (comparator product: US-licensed (b) (4) and use-related risk analysis (URRA) under IND 119866 to determine whether we agree with the Applicant’s justification to not submit HF validation study results with the marketing application for lebrizumab prefilled syringe PFS. We reviewed the comparative analyses and URRA and determined that HF validation study results do not need to be submitted for lebrizumab PFS.³
- On November 9, 2021, the Applicant submitted their revised comparative analyses (comparator product: US-licensed (b) (4) and URRA under IND 119866, since the Applicant was proposing to use a PFS device platform different from the proposed PFS device platform submitted in their April 15, 2020 submission. However, it was not clear whether the Applicant had a right of reference to the data for US-licensed (b) (4). Therefore, on April 6, 2022 we sent an information request (IR) stating the following: *“If you do not have a right of reference to US-licensed (b) (4) validation data, you may leverage HF data from an appropriate approved comparator that you own or you may submit a right of reference to HF validation data. Such data may be used to support your justification to not submit HF validation study data using your proposed product in your proposed 351(a) BLA. In addition, you should submit a revised HF Threshold Analysis Report with any new comparator. Your response should clarify whether you have a right of reference to US-licensed (b) (4) validation data (and, if so, include appropriate documentation), describe your plan to submit a revised Threshold Analysis with an appropriate comparator, or describe your plan to conduct and submit HF validation study data using your proposed product.”*⁴ On April 14, 2022, the Applicant responded to our April 6, 2022 information request stating that they do not have a right of reference to HF validation study data for US-licensed (b) (4). Based on the Applicant’s aforementioned IR response, we determined that the Applicant would need to submit HF validation study results data as part of their marketing application or, with scientifically acceptable bridging data, leverage HF data from an appropriate comparator that they own or to which they have a right of reference to support their justification not to submit HF validation study data for their proposed lebrizumab PFS.⁵

³ Oguntimein, O. Use-related risk analysis and comparative analysis review for lebrizumab (IND 119866). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 22. RCM No.: 2020-1918.

⁴ Anderson, A. FDA Communication: IND 119866 Human Factors Information Request. Silver Spring (MD): FDA, CDER, OSE, PMS (US); 2022 APR 6. IND 119866.

⁵ Oguntimein, O. Memorandum – Human Factors Letter (IND 119866). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 JUL 22. RCM No.: 2021-2179.

- On October 22, 2021, the Applicant submitted their HF validation study protocol for the lebrikizumab prefilled pen (PFP). We reviewed the protocol and provided recommendations.⁶ Aside from those listed in Section 3.2, the Applicant accepted our recommendations.
- On September 28, 2022, the Applicant submitted a Biologics License Application (BLA) for Ebglyss (lebrikizumab) injection under BLA 761306. This submission included the Ebglyss PFP HF validation study results report and *Lebrikizumab Autoinjector and PFS-NSD Human Factors Engineering (HFE) Report* in which the Applicant included *Table 10. Comparison of the proposed lebrikizumab [prefilled syringe with needle safety device] PFS-NSD IFU to the Taltz PFS injection steps and BD's suggested instructions*. For a complete comparative analysis between lebrikizumab PFS-NSD and Taltz (ixekizumab) PFS, on February 14, 2023, we sent the Applicant an information request. The Applicant provided the complete comparative analyses on February 21, 2023. The Ebglyss PFP HF validation study results report and Ebglyss PFS-NSD comparative analyses are the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	Section 1.1
Background Information Previous DMEPA HF Reviews	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Comparative Analyses	E
Information Requests Issued During the Review	F
Labels and Labeling	G

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The Applicant submitted the HF validation study results for the Ebglyss PFP and comparative analyses for the Ebglyss PFS-NSD. The sections below provide a summary of the HF validation study design, errors/close calls/use difficulties observed, and our analysis of the HF validation study results and comparative analyses to determine if the HF validation study results and

⁶ Bhalodia, M. Human factors validation study protocol review for lebrikizumab (IND 119866). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 DEC 21. RCM No.: 2021-2092.

comparative analyses indicate that the user interface supports the safe and effective use of the proposed product.

3 HF VALIDATION STUDY RESULTS REPORT FOR EBGLYSS PFP

3.1 SUMMARY OF HF VALIDATION STUDY DESIGN

Table 3 presents a summary of the HF validation study design to evaluate the Ebglyss PFP. See Appendix C and D for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details provided by the Applicant
Participants	• 15 injection experienced adult patients diagnosed with atopic dermatitis • 15 injection naïve adult patients diagnosed with atopic dermatitis • 15 injection experienced caregivers of patients diagnosed with atopic dermatitis • 15 injection naïve caregivers of patients diagnosed with atopic dermatitis • 15 healthcare professionals (HCPs)
Training	Study participants did not receive training.
Test Environment and Materials	The study rooms were arranged to represent the expected use environment (e.g., at home or in a workplace), with respect to seating, lighting, sound levels, and temperature/humidity to allow participants to use the product naturally. No specific effort was made to control or minimize interruptions or distractions that occurred during testing (e.g., phones ringing, doors shutting, etc.). The rooms were each equipped with a table, chairs, alcohol wipes, cotton balls, bandages, hand sanitizer, sink, hand soap, microwave, refrigerator, and sharps container. (b) (4)

Sequence of Study	1. Simulated use scenario 2. Moderator interviewed participants for root cause analysis (RCA) 3. Break 4. Knowledge assessment 5. Moderator interviewed participants for RCA

3.2 DISCUSSION

During the course of our review of the HF validation study for Ebglyss PFP, we noted that the Applicant did not implement all our HF validation study protocol recommendations.

- We recommended the Applicant include adolescent patient participants. However, the Applicant did not include adolescent patient participants because the Applicant determined that adolescent patients should not self-inject. The Applicant states in the Prescribing Information (PI), *“For adolescent patients, caregivers may give injections after training in subcutaneous injection technique.”* Based on the aforementioned information, in this particular instance, we find the Applicant’s rationale to not include adolescent patients in their HF validation study acceptable. However, the aforementioned PI statement, as written, is ambiguous and may imply that it is optional for caregivers to administer the injection to adolescents. We provide our recommendations in Table 5 for the Division of Dermatology and Dentistry to consider.
- We recommended revising the Instructions for Use (IFU) to include which cue(s) the user should use to verify the injection is complete. However, the Applicant clarified that there are multiple ways for the user to know that they have completed the injection by providing the following information:
 - *“1st – Auditory, the second click is the primary indicator*
 - *2nd – If they cannot hear the click (environmental, hearing abilities), an approximate time for when the second click may be heard is provided. This was determined through risk analysis, previous HF studies and FDA feedback.*
 - *3rd – final confirmation is achieved by observing the gray plunger position at the needle end of the syringe.”*

Based on the aforementioned information, in this particular instance, we find the Applicant’s rationale reasonable, since the Applicant has included the definition of each cue in the IFU and quick reference for injection (QRI) and we acknowledge that there is more than one way to confirm a complete injection. Additionally, the IFU and QRI were evaluated in the HF validation study. See Section 4 for our analyses.

- We recommended that the Applicant include injection site rotation information in the QRI. However, the Applicant stated, *“The QRI does not include information to rotate the injection site because including this could incorrectly imply that* (b) (4)

Note that the harm associated with not rotating injection sites (Risk ID 5.2) is minor temporary pain or discomfort (severity 2). Additionally, due to space constraints on the QRI, it would not be possible to include the statement as presented in the IFU; instead, the QRI includes a general statement directing the user to the IFU for full

instructions.” Additionally, we recommended the Applicant to revise the QRI step 2 to match the IFU step 2 image. However, the Applicant stated, *“This image was not updated, as adding the inset presented in this image in the IFU could introduce visual clutter into the QRI, and it was assessed that this visual clutter could negatively impact usability.”* Based on the aforementioned information, in this particular instance, we find the Applicant’s rationale reasonable. Additionally, the QRI was evaluated in the HF validation study. See Section 4 for our analyses.

4 HF VALIDATION STUDY RESULTS AND ANALYSES

We have carefully reviewed each observed event, the Applicant’s URRAs, the participants’ subjective feedback, the Applicant’s RCA, the Applicant’s comments and proposed mitigations below.

Table 4. Focused Analysis of Use Errors, Use Difficulties and Close Calls and DMEPA’s Recommendations

Information Supplied by Applicant		DMEPA’s Findings and Recommendations				
Legend: UE = use error; CC = close call; UD = use difficulty; URRRA = use-related risk analysis; RCA = root cause analysis; IFU = instructions for use; QRI = quick reference for injection Participants ID: AE= injection experienced adult patient; AN = injection naïve adult patient; CE = injection experienced adult lay-caregiver, CN = injection naïve adult lay-caregiver, HC = healthcare professional						
Task: Uncap the pen <table border="1"> <thead> <tr> <th>Errors:</th> <th>Participant Type:</th> </tr> </thead> <tbody> <tr> <td>UE (n=4)</td> <td>AN= 1; HC: 1; CN = 1; CE = 1</td> </tr> </tbody> </table>		Errors:	Participant Type:	UE (n=4)	AN= 1; HC: 1; CN = 1; CE = 1	
Errors:	Participant Type:					
UE (n=4)	AN= 1; HC: 1; CN = 1; CE = 1					
Observed error(s): Participants injected into the base cap.						
Risk associated with Task Errors (Per Applicant URRRA): if this task is omitted or performed incorrectly, it may lead to no dose delivered and less than full therapeutic effect or delay in therapy if dose replaced within a reasonable time.						
Relevant RCA/Subjective Feedback/Observation: • Misunderstanding the device: two participants tried removing the button end of the device instead of the base cap and in the process actuated the injection into the base cap. • Unaware of device use order: one participant unlocked the pen first because they noticed the lock and unlock icons before the “1”, “2” and “3” on the device indicating the order of actions and then inadvertently pressed on the button leading to medication coming out. • Assumption that pen would not start injecting until the pen was pressed against skin: one participant was						

“exploring” the pen and pressed the button without taking base cap off, since they assumed the pen would not start injecting until the pen was pressed against the skin. The participant had referred to the QRI but wanted to “do [their] own thing.” • Three of the participants did not refer to the IFU or QRI and one participant did refer to the QRI but wanted to “do [their] own thing”.									
Applicant Comment and Proposed Mitigations: The Applicant concluded that the mitigations implemented to reduce the errors are appropriate. The QRI and IFU appropriately describe through graphics and text the proper operational sequence and technique. The QRI and IFU instruct to remove the gray base cap by twisting, and both show a directional arrow to indicate the direction to twist. The pen includes sequential numbering on various parts of the pen, starting with ‘1’ on the gray base cap. The gray base cap also includes a directional arrow to indicate the direction to twist, consistent with the illustrated instructions. In the QRI and IFU, the illustrations for steps after removing the base cap depict devices without base caps. The Applicant did not propose any risk mitigation strategies for these use errors.	Based on the errors (i.e., participants did not realize that they must remove the base cap and participants tried removing the button end of the device instead of the base cap and in the process actuated the injection into the base cap) observed with this task and our overall assessment, we find that the user interface can be improved to provide understanding and clarity of the base cap removal task. We provide our recommendations in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.								
KBA question: What should you inspect or check for on this pen before you use it? KBA answer: Check expiration date. <table border="1" data-bbox="212 1198 884 1344"> <thead> <tr> <th>Errors:</th> <th>Participant Type:</th> </tr> </thead> <tbody> <tr> <td>UE (n = 2)</td> <td>CE =1; AN = 1</td> </tr> <tr> <td>CC (n=1)</td> <td>CN = 1</td> </tr> <tr> <td>UD (n=1)</td> <td>AE = 1</td> </tr> </tbody> </table> Observed error(s):	Errors:	Participant Type:	UE (n = 2)	CE =1; AN = 1	CC (n=1)	CN = 1	UD (n=1)	AE = 1	
Errors:	Participant Type:								
UE (n = 2)	CE =1; AN = 1								
CC (n=1)	CN = 1								
UD (n=1)	AE = 1								

• One participant initially stated that the pen would expire in 7 days if storing at room temperature, but then called the helpline and found the expiration date. • Two participants found the expiration on the pharmacy label, but not the container label or carton labeling. • One participant stated that they do not need to check the expiration date since the pharmacy would do that.	
Risk associated with Task Errors (Per Applicant URR): if this task is omitted or performed incorrectly it may lead to: • Injection site reaction associated with discomfort • Delivery of drug with less than full potency associated with decreased therapeutic benefit • hypersensitivity reaction (e.g., anaphylaxis) requiring major medical intervention	
Relevant RCA/Subjctive Feedback/Observation: • Confusion between checking expiration date and leaving PFP at room temperature for up to 7 days: one participant focused on storing the PFP at room temperature and missed the checking expiration date task in the IFU. • Negative transfer: two participants expected this information to be on the pharmacy label, which it was. One participant also looked for the expiration date on the carton but did not see it and one participant stated that the expiration date on the container did not stick out due to the black background and small text. • Mental model: one participant does not typically check the expiration date, since they expect the pharmacy to do so.	

Applicant Comment and Proposed Mitigations: The Applicant noted that two participants found the expiration date on the pharmacy label only, which would lead to no harm. For the participant who would not check the expiration date and rely on the pharmacy to provide unexpired product, the Applicant stated that they cannot control a user not wanting to check for the expiration date. The Applicant mentioned that there are two places, the carton labeling and container label, for users to check the expiration date. The Applicant did not propose any risk mitigation strategies for these use errors, close call, and use difficulty.	Based on subjective feedback (one participant who could not find the expiration date on the container label because of the small text), and our overall assessment, we find that the expiration date text can be improved to be more prominent in order to increase readability. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.

4.1 ANALYSIS OF OTHER CRITICAL AND NON-CRITICAL TASK ERRORS

The HF validation study showed use errors, use difficulties, and close calls with the tasks listed below in this section; however, based on our review of the available assessment of these use errors/use difficulties/close calls, the available participants' subjective feedback, the Applicant's root cause analysis and the Applicant's mitigation strategies, we determined the residual risk is acceptable. Specifically, users did not provide subjective feedback that indicated any potential issues with the user interface for the tasks identified. Based on our assessment, we find that the labeling mitigations in place include information that is prominently placed within the labels and labeling to address the tasks below. Subsequently, we did not identify further need for risk mitigation strategies at this time to address the use errors related to the following tasks and find the residual risks are acceptable:

- Wash hands
- Choose injection site
- Clean injection site
- Dispose of the base cap
- Hold the PFP at injection site until injection is complete: there were six use errors and one difficulty observed with this task. The RCA indicated negative transfer (four participants had experience with other injectables that they did not have to hold at the injection site as long as they had to with Ebglyss), misunderstanding the meaning of the clicks (one participant assumed the first click signaled the end of the injection; however the participant did not read the IFU or the QRI in which the meanings of clicks are included); mishearing the clicks (one participant thought they heard two clicks before the second click actually occurred and one participant was unsure if both clicks occurred but did administer the full injection). We note that the Applicant stated that the mean injection time (i.e., time (in seconds) required for the PFP to complete the delivery of the drug) is 4.58 seconds. Additionally, we note that three of the six participants who experienced a use error with this task had an injection time (i.e., 5 seconds) of more than 4.58 seconds. Based on this information, these three participants received the full dose. Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and use difficulty and have no recommendations at this time.
- Dispose of PFP
- User does not inject more than one device for maintenance dosing (loading doses require two injections, whereas maintenance doses require one injection): there were four use errors observed with this task. The RCA indicated study artifact (since they could not feel the device puncture through their own skin, as they would at home, one participant believed the medication was not injected), not hearing the clicks (two participants did not hear the second click and believed they had not administered the dose), negative transfer (one participant assumed that based on their past experience of (b) (4) . Our review of the user interface notes that although each participant was provided with (b) (4) a one-PFP

carton. Additionally, along with the auditory cue (2nd click) to confirm injection completion, there is a visual cue (gray plunger becomes visible). Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.

- Store PFP (knowledge task)
- Inspect the PFP for particles/discoloration (knowledge task)
- Inspect for frozen medicine (knowledge task)
- Leave device at room temperature for 45 minutes (knowledge task)
- Rotate injection site (knowledge task)
- Inject on skin and not through clothing (knowledge task)
- Inspect injection site (knowledge task)

4.2 LABELS AND LABELING

Table A below include the identified medication error issues with the submitted IFU based on the HF study results, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. We also provide a PI recommendation. Additionally, we note that the DMEPA 1 primary review team evaluated product specific label and labeling under separate cover and label and labeling comments have been sent to the Applicant based on the outcome of that review.⁷

Table A: Ebgllyss (lebrizumab) Prefilled Pen Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Device			
1.	The prefilled pen (PFP) can be improved to provide understanding and clarification regarding the “Uncap the pen” task.	Per the use-related risk analysis (URRA), if the user does not remove the base cap there is a risk of underdose or no dose delivered and less than full therapeutic effect or delay in therapy if dose replaced within a reasonable time. There were use errors in the human factors (HF) validation study results in which participants did not realize that they must remove the base cap.	Add the statement “ <i>twist to remove cap</i> ” by the “1” on PFP to improve understanding and clarity of the cap removal task.

⁷ Corwin, H. Label and Labeling Review for Ebgllyss (BLA 761306). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 28. RCM No.: 2022-1988.

2.	The PFP can be improved to provide understanding and clarification regarding the needle end.	Per the URRA, if the user touches the needle prior to injecting, there is risk of: • Infection requiring medication intervention and antibiotics • Pain • Temporary and non-debilitating infection not requiring medical intervention There were use errors in the HF validation study results in which participants tried removing the button end of the device instead of the base cap and in the process actuated the injection into the base cap.	Add a “needle end” label to the device to further improve understanding and clarification.

Container label and carton labeling

3.	The expiration date listed on the container label and carton labeling is not large enough for users to read.	Per the URRA, if the user uses an expired PFP there is risk of: • Injection site reaction associated with discomfort • Delivery of drug with less than full potency associated with decreased therapeutic benefit • Hypersensitivity reaction (e.g., anaphylaxis) requiring major medical intervention The HF validation study results identified subjective feedback that indicated that participants could not read the expiration date on the container label and carton labeling.	Increase the expiration date text on the container label and carton labeling.

Table 5: Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The statement, “ <i>For adolescent patients,</i>	There is no HF validation data to support self-administration in	Revise the statement, “ <i>For adolescent patients, caregivers</i>

<i>caregivers may give injections after training in subcutaneous injection technique.” is ambiguous and may imply that it is optional for caregivers to administer the injection to adolescents.</i>	adolescent patients, since the Applicant did not include adolescent patient participants in their HF validation study. Thus, it should be clear that adolescents should not self-administer and that caregivers should administer the injection to adolescents.	<i>may give injections after training in subcutaneous injection technique.” to, “For adolescent patients, caregivers should prepare and inject Ebglyss after training in subcutaneous injection technique.”</i>

5 HUMAN FACTORS VALIDATION STUDY CONCLUSION AND RECOMMENDATION

The results of the HF validation study for the Ebglyss (lebrikizumab) PFP demonstrated several use errors, close calls, and use difficulties with critical tasks that may result in harm. Based on our review of the available participants’ subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. Above, we have provided recommendations in Table A for the Applicant. We ask that the Division of Dermatology and Dentistry convey Table A in its entirety to the Applicant. These changes can be implemented without submitting additional HF validation testing data for Agency review.

5.1 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

Our evaluation of your Ebglyss (lebrikizumab) prefilled pen human factors validation study indicates that there are additional mitigations that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A and we recommend that you implement these recommendations and submit the revised label and labeling for our review. We have determined that in this instance, you may implement these revisions without submitting additional human factors validation data for Agency review.

6 COMPARATIVE ANALYSES FOR EBGLYSS PFS-NSD

The sections below provide our evaluation of the use-related risk analysis (URRA) and comparative analyses.

6.1 USE-RELATED RISK ANALYSIS (URRA)

The URRA was performed to identify intended use, user interface, tasks, potential hazards, and potential harm associated with the use of Ebglyss PFS-NSD. The Applicant assessed the risks associated with the critical tasks in the URRA and determined the risks are mitigated through labeling and device design.

Upon review of the URRA, we did not identify any new, differing, or unique risks associated with the proposed product as compared to the comparator product, Taltz (ixekizumab) prefilled syringe (PFS). We also find that the URRA is comprehensive and is based on the use tasks required for the safe and effective use of the product.

6.2 COMPARATIVE ANALYSES

The following sections provide our evaluation of the comparative analyses conducted by the Applicant.

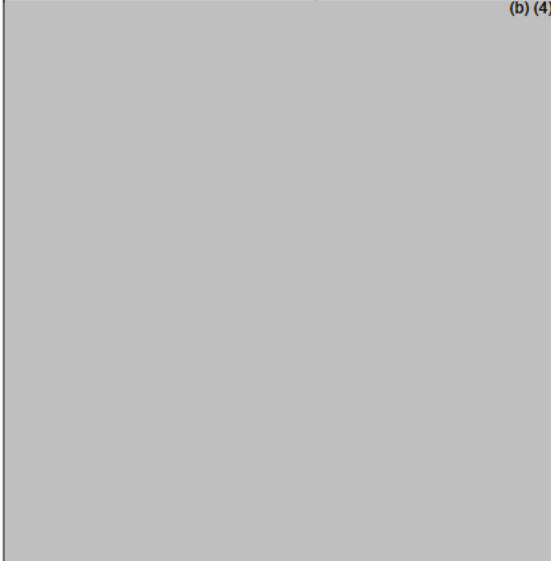
The Applicant conducted the comparative analyses between the proposed, Ebglyss (lebrikizumab) PFS-NSD, and Taltz (ixekizumab) PFS. The Applicant owns Taltz, therefore, it is an appropriate comparator product.

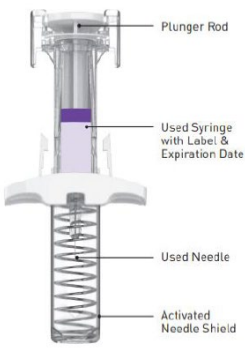
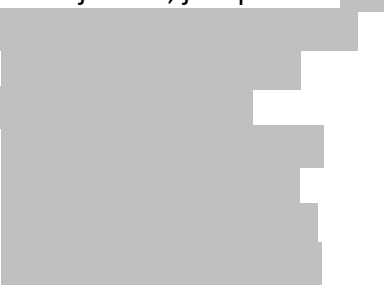
The comparator product, Taltz, is an approved product for the following dermatological conditions (see Table 1 for the complete list of approved indications):

- patients aged 6 years or older with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
- adults with active psoriatic arthritis.

6.2.1 PHYSICAL COMPARISON

The Applicant identified the following physical differences between the Ebglyss PFS-NSD and Taltz PFS:

Device feature	Ebglyss PFS-NSD	Taltz PFS	Applicant's categorization of difference	Applicant's discussion of difference
Plunger rod and thumb pad	Rotatable plunger rod with concave thumbpad incorporating circular rings  (b) (4)	Plunger with concave thumbpad	Minor	Both devices have plunger rods with concave thumbpads to aid in uniform distribution of push force, with lebrikizumab incorporating raised circular rings as an additional ergonomic feature. Additionally, Ebglyss' PFS-NSD plunger rod can be rotated to improve visibility of the device label on the syringe through the viewing window. With the combination of the thumbpad, plunger rod, and finger flanges (see next row), both devices accommodate the three-point pinch grip

	(b) (4)			recommended for safe and proper handling of syringes. This pinch grip complies with push force recommendations (maximum (b) (4) within HF guidance (ANSI/AAMI HE75:2009)).
Finger flanges			Negligible	Both devices' finger flanges provide the appropriate surface area with tactile surfaces for a user's fingers to securely grip the device and ensure stability and control throughout the injection.
Needle safety device	(b) (4) needle safety device 	N/A 	Other	While both products have similar drug delivery mechanisms, the Ebglyss PFS-NSD contains a needle safety device, containing a plastic body, plastic guard, and metal spring. Near the end of the injection, just prior to (b) (4)  results in shielding of the needle to prevent post injection injuries and signals the completion of the injection. This safety feature allows for the lebrizumab PFS-NSD to comply with ISO 23908:2011 – sharps injury protection.

				The Taltz PFS does not contain a needle safety feature within its device constituent, requiring the user to rely on the placement of the gray plunger and green plunger rod to determine the completion of the injection. It also leaves the needle exposed after use until it is disposed properly.
Needle cap		(b) (4)	Negligible	Both devices use a 27G needle 12.7mm in length, suitable for subcutaneous injections. Both devices also contain needle caps that protect the needle before use and are removed by pulling the cap straight off by hand. The Ebglyss PFS-NSD needle cap is widely used among other marketed products and contains a ridged grip area. The Taltz PFS needle cap is designed with a smooth surface and flared design. Both needle cap designs aid in users gripping the cap during removal. Both devices comply with pull force recommendations using either tip pinch grip or palmer pinch grip (maximum (b) (4) N) within HF guidance (Human Factors Ergonomics and Design Handbook, 3rd edition, 2016).

Physical differences between the Ebglyss PFS-NSD and the Taltz PFS include the needle safety device. Specifically, the Ebglyss PFS-NSD is a single-dose PFS with a (b) (4) passive needle safety device as compared to the Taltz PFS, which does not contain a needle

safety device. We find the difference in the type of needle safety device to be an “other” difference because it is likely to impact the critical task of pushing and releasing the plunger. We discuss this “other” difference in more detail in the comparative task analysis section below.

The Applicant categorizes additional physical differences as “negligible” or “minor” and concludes that the differences are not expected to have a negative impact in handling of the Ebglyss PFS-NSD. We disagree that all the physical differences are “minor”, as some differences may impact critical tasks. However, with respect to the plunger rod, thumb pad, finger flanges, and needle cap, we find it unlikely, given the specific magnitude of difference, that these differences will impact critical task performance.

We note the Applicant did not include device specifications in this comparative analyses submission. We defer evaluation regarding the acceptability of device specification and performance to Center for Devices and Radiological Health (CDRH).

6.2.2 COMPARATIVE TASK ANALYSIS

The Applicant identified the following task differences between the Ebglyss PFS-NSD and Taltz PFS:

Table 7. Task Comparison			
Ebglyss PFS-NSD	Taltz PFS	Applicant’s categorization of difference	Applicant’s discussion of difference
N/A	Return the carton with any unused syringes to the refrigerator.	Minor	Taltz PFS provides additional instructions if another, unused syringe is within the carton. This would not apply to the lebrizumab PFS-NSD, which is only available in single syringe cartons (thus, lebrizumab users would not benefit from such a task).
Wait at least 45 minutes to reach room temperature	Wait 30 minutes to reach room temperature	Negligible	Lebrizumab requires 45 minutes to warm up (vs. 30 minutes for Taltz). The difference in warm up time is due to drug characteristics.
Lift thumb to release the plunger rod until the needle	Gently remove needle from skin	Other	Lebrizumab features a needle safety device which automatically activates to

is covered by the needle safety device			cover the needle after administering the injection. Taltz requires the user to remove the needle from the skin after administering the injection.
Dispose PFS-NSD and needle cap in sharps container	Dispose PFS in sharps container and dispose of needle cap	Minor	Taltz does not define how to dispose of needle cap after use, however it is acceptable for the needle cap to be thrown in either a sharps container or household trash. The lebrizumab PFS-NSD provides more guidance to the user to mitigate risk of device part ingestion by children, pets or other ancillary actors.

Regarding the Applicant’s deemed “minor” and “negligible” task differences above, we agree with the Applicant that the Taltz PFS task to return the carton with unused syringes does not apply to Ebglyss PFS-NSD, since each Ebglyss PFS-NSD carton contains one PFS. Although there are differences in the time needed to warm the Ebglyss PFS-NSD and Taltz PFS, both require warming prior to injecting the dose. We also agree with the Applicant that there is more guidance on disposal of the Ebglyss PFS-NSD compared to the Taltz PFS. The differences in the tasks regarding returning the carton with unused syringes and warming time do not impact the performance of the tasks of Ebglyss PFS-NSD when compared to the comparator PFS and are necessary product specific differences. Additionally, the difference in the disposal task provides more information on what to do with the Ebglyss PFS-NSD. As such, we agree with the Applicant’s categorization of the aforementioned three tasks.

Regarding the task difference in needle safety device activation, we agree with the Applicant’s determination that the task difference in activation of the needle safety device is an “other” difference. We note that the Taltz PFS-NSD does not contain a safety device, whereas the Ebglyss PFS-NSD contains a (b) (4) passive needle safety device. The Taltz PFS requires users to push the gray syringe plunger all the way to the needle end of the syringe and the users should see the green plunger rod show through the syringe body when the injection is complete. The Ebglyss PFS-NSD requires users to also push in the plunger all the way down as far as it will go and then lift the thumb to release the plunger rod until the needle shield covers the needle. The entire dose must be administered to automatically activate the needle shield. However, in this instance, we find this “other” difference (inclusion of an automatic needle safety device) is acceptable and this does not raise concerns that require the submission of HF validation data.

6.2.3 LABELING COMPARISON

The Applicant identified labeling differences between Ebglyss and Taltz. The Ebglyss PFS-NSD IFU includes information regarding the activation of the needle safety device, which is not included in the Taltz PFS IFU. The Applicant states that there are differences between the Ebglyss PFS-NSD IFU and Taltz IFU related to cues indicating that the injection is complete. These are visual cues of plunger and plunger rod visibility in the Taltz PFS IFU versus the resistance felt at the end of the injection as the needle safety device is activated in the Ebglyss PFS IFU. The Applicant also identified difference in labeling that correspond to the additional task differences, discussed in section 6.2.2., and the Ebglyss PFS-NSD plunger rod rotatability discussed in section 6.2.1. Additionally, the Ebglyss PFS-NSD IFU includes statements, which the Taltz PFS IFU does not, on the handling of the device to ensure that the needle cap and plunger rod are not damaged. These statements include, “*Remove the Tradename Prefilled Syringe from the carton by holding the middle of the Syringe Body and then place the Tradename Prefilled Syringe on a flat surface.*” and “*Hold the Tradename Prefilled Syringe in the middle of the Syringe Body and (b) (4).*”

The Applicant identified one additional “minor” difference in that the Ebglyss PFS-NSD IFU does not include statements to leave the needle cap until the user is ready to inject, whereas the Taltz PFS IFU contains the statement, “*Leave the needle cap on syringe until you are ready to inject*” twice. We consider this an “other” difference, since the URRA states that if the user injects with syringe uncapped for more than 10 minutes then there are multiple risks including that of underdose (5%-100%) and localized or systemic hypersensitivity reaction. We find that the Ebglyss PFS-IFU can be improved to inform the user to leave the needle cap on until the user is ready to inject. **We provide our recommendation in Table B to address this concern.**

Furthermore, regarding the Ebglyss PFS-NSD IFU Step 4. Release the Plunger Rod image (see Figure 1 below) depicting the needle shield covering the needle we note that the image is small and difficult to see. We find that the Ebglyss PFS-NSD IFU Step 4 needle shield covering image can be improved to be more prominent. **We provide our recommendation in Table B to address this concern.**

Figure 1. Ebglyss PFS-NSD IFU Step 4. Release the Plunger Rod image depicting the needle shield covering the needle

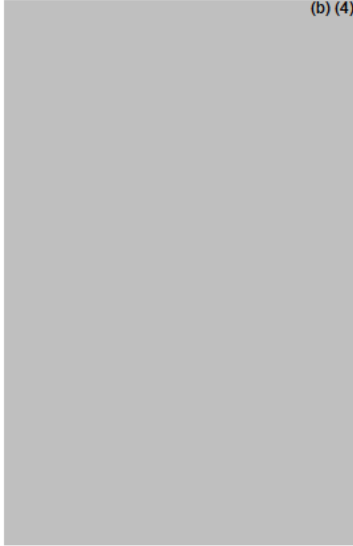


Finally, the Applicant identified all differences as either “minor” or “negligible” with respect to wording, formatting, graphics/illustrations, and location of certain information, as compared to the Taltz PFS. We agree with the Applicant’s determination to categorize the differences in wording, formatting, graphics/illustrations, and location of certain information for certain tasks in the labeling between the Ebglyss PFS-NSD user interface as compared to the Taltz PFS user interface as “minor” or “negligible”. As a general matter, formatting, wording, graphics/illustrations, and location of certain information have the potential to impact the performance of critical tasks. However, we do not think that it is necessary that we request that the Applicant change their PFS-NSD IFU, at this time from a medication error perspective, nor do we think these differences above warrant data from a human factors validation study.

DMEPA 1 primary review team evaluated product specific label and labeling under separate cover and label and labeling comments have been sent to the Applicant based on the outcome of that review.⁷

Table B: Ebglyss (lebrikizumab) Prefilled Syringe Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	The IFU does not instruct users to leave the needle cap on the syringe until they are ready to inject.	Per the use-related risk analysis (URRA), if the user injects with syringe uncapped for more than 10 minutes then there are multiple risks including that of underdose (5%-100%) and localized or systemic hypersensitivity reaction. The comparator product, Taltz (ixekizumab), in your comparative analyses instructs users to “ <i>Leave the needle cap on the syringe until you are ready to inject.</i> ” in Step 1c. Inspect the syringe.	We recommend including the statement, “ <i>Leave the needle cap on the syringe until you are ready to inject.</i> ” in the IFU. For example, consider including the statement in the <i>Inspect the Prefilled Syringe and the medicine</i> section, which is where this statement is located in the Taltz (ixekizumab) PFS IFU.
2.	The image depicting the needle shield covering needle is small and difficult to see in Step 4. Release the Plunger Rod.	User may not be able to see and/or understand the image of the needle shield covering the needle.	Enlarge the image depicting the needle shield covering the needle. For example, include a “close up” image of the needle shield covering the needle, similar to the “close up” images in Steps 2 and 3 (see

			blue arrows pointing to “close-up” images). 

7 USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES CONCLUSION AND RECOMMENDATIONS

Our review of the Applicant’s use-related risk analysis and comparative analyses concluded that no further information or data (e.g., data from a human factors validation study) is needed to support this marketing application for Ebglyss (lebrikizumab) 250 mg/2 mL PFS-NSD. However, we identified areas of vulnerability that may lead to medication errors. We provided recommendations in Table B for the Applicant. We ask that the Division of Dermatology and Dentistry convey Table B in its entirety to the Applicant. These changes can be implemented without submitting HF validation testing data for Agency review.

7.1 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

Our review of your use-related risk analysis and comparative analyses for the Ebglyss (lebrikizumab) prefilled syringe with needle safety device indicates that at this time you do not need to submit results from a comparative use human factors study to support the marketing application. However, we identified areas of vulnerability that may lead to medication errors. We provided recommendations in Table B and we recommend that you implement these recommendations and submit the revised IFU for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On July 13, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, "IND 119866", "BLA 761306" and "lebrikizumab".

B.1.2 Results

Our search identified three previous reviews^{3,5,6} and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761306\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atopicdermatitis\5354-other-stud-rep\hfe\rpt-638213.pdf>

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

Ebglyss prefilled pen HF validation study results report can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761306\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atopicdermatitis\5354-other-stud-rep\hfe\rpt-638213.pdf>

APPENDIX E. COMPARATIVE ANALYSES

Ebglyss prefilled syringe comparative analyses can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761306\0010\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atopicdermatitis\5354-other-stud-rep\hfe\rpt-942872.pdf>

Ebglyss prefilled syringe use-related risk analysis can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761306\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atopicdermatitis\5354-other-stud-rep\hfe\rpt-638213-att-2.pdf>

APPENDIX F. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On February 14, 2023, we issued an information request (IR) to obtain the complete comparative analyses between the proposed Ebglyss prefilled syringe and appropriate comparator.

The Applicant provided an acceptable response on February 21, 2023 that can be accessible in EDR via: <\\CDSESUB1\EVSPROD\bla761306\0010\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atopicdermatitis\5354-other-stud-rep\hfe\rpt-942872.pdf>

On February 23, 2023, we issued an IR to request the Applicant's human factors validation study protocol.

The Applicant provided a response on February 24, 2023 that can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761306\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atopicdermatitis\5354-other-stud-rep\hfe\prt-225983.pdf> and

<\\CDSESUB1\EVSPROD\bla761306\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atopicdermatitis\5354-other-stud-rep\hfe\prt-225983-att-1.pdf>

On May 12, 2023, we issued an IR to request the average injection completion time for the lot of autoinjectors tested in the HF validation study.

The Applicant provided a response on May 15, 2023 that can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761306\0024\m1\us\leb-us-bla761306-rtq-09may2023--q1-.pdf>

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁸ along with postmarket medication error data, we reviewed the following Ebglyss labels and labeling submitted by Eli Lilly and Company on September 29, 2022.

- Prefilled pen carton (1 count) labeling
-  (b) (4)
- Prefilled pen container label
- Prefilled syringe with needle shield carton labeling
- Prefilled with needle shield container label
- Prefilled pen instructions for use (image not shown). Available from: <\\CDSESUB1\EVSPROD\bla761306\0001\m1\us\proposed-ifu-pen.docx>
- Prefilled syringe instructions for Use (image not shown). Available from: <\\CDSESUB1\EVSPROD\bla761306\0001\m1\us\proposed-ifu-pfs.docx>

⁸ 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/

NEHA KUMAR
06/13/2023 03:40:17 PM

OLUWAMUREWA OGUNTIMEIN
06/20/2023 07:36:14 PM

JASON A FLINT
06/21/2023 05:22:21 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 5/18/2023 **Date consulted:** 5/1/2023

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Dermatology and Dentistry (DDD)

Drug: Ebglyss (lebrikizumab) injection, for subcutaneous use

BLA: 761306

Applicant: Eli Lilly and Company

Subject: Pregnancy and Lactation Labeling

**Proposed
Indication:** for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

**Materials
Reviewed:**

- Applicant’s submitted background package and proposed labeling for BLA 761306
- DDD consult form for DPMH, DARRTS Reference ID 5166844

Consult Question:

- The review team requests DPMH’s assist with the Pregnancy and Lactation subsections of labeling.

INTRODUCTION AND BACKGROUND

On September 28, 2022, the applicant (Eli Lilly and Company) submitted an original BLA for Ebglyss (lebrikizumab) injection, BLA 761306, for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DDD consulted DPMH on May 1, 2023, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Lebrikizumab is an interleukin-13 antagonist. It was developed by Eli Lilly and Company for the treatment of moderate to severe atopic dermatitis. It has not been approved or marketed in any countries.
- On December 6, 2019, FDA granted Fast Track Designation for lebrikizumab acknowledging both the seriousness of moderate to severe atopic dermatitis and the potential for lebrikizumab to demonstrate substantial improvement of the disease.
- The Sponsor, Eli Lilly and Company, submitted an original BLA for Ebglyss (lebrikizumab) injection, BLA 761306, under 21 CFR 601.2, on September 28, 2022 with proposed indication for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
- On May 1, 2023, DDD consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.
- On May 10, 2023, FDA sent an Information Request (IR) to the applicant for narratives of all pregnancies reported during the clinical trials.
- On May 15, 2023, the Sponsor responded to the IR.

Drug Characteristics

Lebrikizumab Characteristics¹

Drug Class	Recombinant monoclonal IgG4, interleukin-13 antagonist
Mechanism of action	Lebrikizumab is a monoclonal antibody (MAB) that binds with high affinity and slow off-rate to interleukin (IL)-13 and inhibits its interaction with the IL-4 receptor alpha (IL-4R α), but not the IL-13 receptor α 1 and α 2 subunits (IL-13R α 1 and IL-13R α 2). Lebrikizumab-bound IL-13 can still bind IL-13R α 2 allowing subsequent internalization and natural clearance of IL-13. IL-13 is a naturally occurring cytokine of the Type 2 immune response. Lebrikizumab-xxxx inhibits the bioactivity of IL-13 by blocking IL-13 interaction with IL-13R α 1/IL-4R α receptor complex. Lebrikizumab-xxxx inhibits IL-13-induced responses including the release of proinflammatory cytokines, chemokines and IgE.
Molecular weight	145,285 D
Half-life	24.5 days
Bioavailability	86%

¹ Based on applicant proposed labeling and discussion with DDD review team.

Elimination	degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Ebglyss (lebrikizumab) is recombinant immunoglobulin G4 (IgG4) monoclonal antibody (MAb) (b) (4) a mutated Fc region. Lebrikizumab binds to interleukin (IL)-13 and inhibits IL-13 signaling. The proposed dosage of Ebglyss is 500 mg (two 250 mg injections) at Week 0 and Week 2, followed by 250 mg (one injection) every 2 weeks (b) (4) Week 16 or later, when adequate clinical response is achieved. The proposed maintenance dose is Ebglyss 250 mg every 4 weeks.

Serious adverse reactions²

- Hypersensitivity: Hypersensitivity reactions, including urticaria and angioedema, have occurred after administration of EBGLYSS. Discontinue EBGLYSS in the event of a hypersensitivity reaction.
- Conjunctivitis and Keratitis: Patients should report new onset or worsening eye symptoms to their healthcare provider
- Parasitic (Helminth) Infections: Treat patients with pre-existing helminth infections before initiating treatment with EBGLYSS. If patients become infected while receiving EBGLYSS and do not respond to anti-helminth treatment, discontinue treatment with EBGLYSS until the infection resolves.
- Risk of Infection with Live Vaccines: Avoid use of live vaccines.

PREGNANCY

Atopic Dermatitis and Pregnancy³

It is estimated up to 10% of adults in the United States are affected by AD though prevalence estimates are limited and vary because AD is a clinical diagnosis.⁴ Approximately half of the AD population are females, and AD affects all age groups including females of reproductive potential.⁵ It is estimated that 44-57% of adult patients with AD have moderate disease and 12-21% have severe disease based on the Patient Oriented Scoring of Atopic Dermatitis. Systemic immunomodulating therapies may be needed in those with moderate-severe AD.⁶

Eczema is the most common dermatosis of pregnancy. Approximately 20-40% of patients with eczema during pregnancy have a pre-existing history of eczema. Of those, approximately 25 % improve, and more than half of cases deteriorate.⁷ Pre-existing eczema may deteriorate during pregnancy, and 10% of cases flare postpartum. Secondary skin infection causing eczema

² Based on applicant proposed labeling and discussion with the Clinical Review Team on 5/12/2023.

³ DPMH review of Atopic Dermatitis and Pregnancy from Integrated Pregnancy Study Protocol Review on 7/29/2022. DARRTS Reference ID 5025927. The tralokinumab integrated review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

⁴ Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: a cross-sectional study examining the prevalence and disease burden of atopic dermatitis in the US adult population. *J Invest Dermatol.* 2019;139(3):583-590.

⁵ Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* 10, 1215–1228 (2020).

⁶ Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* 10, 1215–1228 (2020).

⁷ Weatherhead S, Robson SC, Reynolds NJ. Eczema in pregnancy. *BMJ.* 2007;335(7611):152-154.

herpeticum, may be associated with preterm delivery, intrauterine growth restriction, and miscarriage.^{8,9}

There is little evidence that AD increases the risk of adverse pregnancy outcomes. Some atopic diseases are associated with decreased fertility, but the relationship for AD and reduced fertility is less clear.^{10,11}

Initial therapies for AD include topical treatments and phototherapy. Currently approved topical therapies include topical corticosteroids, topical calcineurin inhibitors (e.g., tacrolimus ointment, pimecrolimus cream), and topical phosphodiesterase 4 inhibitor (e.g., crisaborole). Topical corticosteroids with low potency are typically first-line treatment for AD during pregnancy. Systemic therapies are recommended when AD is not adequately controlled by these initial therapies. There are currently two approved systemic therapies for patients with moderate-severe AD (i.e., systemic corticosteroids and dupilumab). Systemic corticosteroids can be effective for severe acute exacerbations but are not recommended for long-term use. Dupilumab is an injectable systemic IgG4 monoclonal antibody that binds to the IL-4 R α subunit and inhibits IL-4 and IL-13. Current data in pregnancy are limited to one case report and limited cases in clinical trials, but there are no known safety issues for use during pregnancy.^{12,13,14}

REVIEW

Nonclinical Experience

In an embryofetal development study, no malformations or embryofetal toxicity were observed in fetuses from pregnant cynomolgus monkeys administered lebrikizumab-xxxx during organogenesis at doses up to 150 mg/kg initial dose followed by 50 mg/kg per week by subcutaneous injection, which was associated with plasma exposure (C_{avg,ss}) approximately 18 times the human exposure at the maximum recommended human dose (MRHD). Lebrikizumab-xxxx crossed the placenta in monkeys.

In a prenatal and postnatal development study, pregnant cynomolgus monkeys were administered lebrikizumab-xxxx during organogenesis to parturition at doses up to 150 mg/kg initial followed by 50 mg/kg per week by subcutaneous injection, which was associated with plasma exposure (C_{avg,ss}) approximately 18 times the human exposure at the MRHD. No embryofetal toxicity or malformations, or effects on morphological, functional, or

⁸ Napolitano M, Ruggiero A, Fontanella G, Fabbrocini G, Patruno C. New emergent therapies for atopic dermatitis: A review of safety profile with respect to female fertility, pregnancy, and breastfeeding. *Dermatol Ther*. 2021 Jan;34(1):e14475.

⁹ Weatherhead S, Robson SC, Reynolds NJ. Eczema in pregnancy. *BMJ*. 2007;335(7611):152-154.

¹⁰ Langan, S.M.; Irvine, A.D.; Weidinger, S. Atopic dermatitis. *Lancet* 2020, 396, 345–360.

¹¹ Napolitano M, Ruggiero A, Fontanella G, Fabbrocini G, Patruno C. New emergent therapies for atopic dermatitis: A review of safety profile with respect to female fertility, pregnancy, and breastfeeding. *Dermatol Ther*. 2021 Jan;34(1):e14475.

¹² Kage P, Simon JC, Treudler R. A case of atopic eczema treated safely with dupilumab during pregnancy and lactation. *J Eur Acad Dermatol Venereol*. 2020;34(6):e256–7.

¹³ Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* 10, 1215–1228 (2020).

¹⁴ DPMH labeling review for Dupixent, BLA 761055, January 13, 2017, Christos Mastroyannis, MD, Medical Officer, DARRTs reference ID: 4041992

immunological development were observed in the infants from birth through 6 months of age.

The reader is referred to full Pharmacology/Toxicology report by Renqin Duan, Ph.D. and Barbara Hill, Ph.D. under Section 19.3 of the Multi-Disciplinary Review and Evaluation for BLA 761306.

Review of Clinical Trials

Pregnant women were excluded from the clinical trials. During the development, there were 26 pregnancies across all lebrikizumab indications cumulatively as of June 6, 2022 among 1,421 subjects. Of the 26 pregnancies, 6 were from paternal exposures and 20 were maternal exposures.

Of the maternally exposed pregnancies, the exposure occurred mostly during the first trimester. The outcomes are:

- 6 livebirths (one case of fetal growth restriction, one case of neonatal jaundice)
- 7 spontaneous abortions or terminations due to anembryonic pregnancy
- 4 elective terminations (reasons not included)
- 1 ectopic pregnancy
- 2 lost to follow-up

There are no cases of congenital birth defects reported during the clinical trials. A summary of the pregnancies outcomes from maternal exposures are listed under Appendix A.

Reviewer comment:

This reviewer notes that the majority of exposures also occurred during early pregnancy where IgGs are not typically transferred across the placenta in large quantities.

One additional pregnancy was identified through the narrative portion of the submission which was not included in the table submitted from the Sponsor. Patient (b) (6) from study J2T-DM-KGAF for the treatment of atopic dermatitis. on 150mg dose of lebrikizumab had an exposure during first trimester and terminated pregnancy electively for unknown reasons at 11 weeks.

Review of Literature

DPMH Review of Literature

DPMH performed a search of published literature using PubMed, Embase, and reference sites (Micromedex,¹⁵ ReproTox,¹⁶ Shepard's)¹⁷ regarding lebrikizumab use in pregnancy.

- There are no published data on the use of lebrikizumab in pregnancy.

Reviewer comment:

Pregnant women were excluded from the clinical trials with lebrikizumab. Limited cases of accidental exposure during pregnancy within the clinical trials are not adequate to inform labeling. As lebrikizumab is a new molecular entity (NME) and not previously approved anywhere, there are no published studies regarding the use of lebrikizumab during pregnancy.

¹⁵ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 5/8/2023.

¹⁶ ReproTox Website: www.Reprotox.org. REPROTOX was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 5/8/23.

¹⁷ 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 5/8/2023.

According to animal pre and postnatal developmental studies, no effects on immunological development were observed in the F1 monkeys from birth through 6 months of age. Although proposed labeling for lebrikizumab and labeling for other IL-13 inhibitors, including tralokinumab and dupilumab, have a Warning and Precaution to avoid live vaccines during treatment due to the potential for the biologic to alter a patient's immunity and increase the risk of infection following administration of live vaccines, this warning is based on a theoretical risk, and these adverse effects were not observed during the clinical trial. Subsection 8.1 of approved labeling for tralokinumab and dupilumab does not contain any language regarding the avoidance of live vaccines in infants exposed to these IL-13 inhibitors in utero. Therefore, labeling for lebrikizumab will be consistent with labeling for other IL-13 inhibitors. The approach to subsection 8.1 of labeling regarding live vaccines was discussed with the Clinical Team, and they agree with this approach.

The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION

Nonclinical Experience

It is not known if lebrikizumab is present in animal milk.

Review of Clinical Trials

Lactating women were excluded from the clinical trials. There were no lactating women in the clinical trials.

DPMH Review of Literature

DPMH performed a search of published literature using PubMed, Embase, and reference sites (Micromedex,¹⁸ LactMed,¹⁹ Brigg's,²⁰ or Hales²¹) regarding lebrikizumab use in lactation, and no information was found.

Reviewer comment:

There are no data on the presence of lebrikizumab in human or animal milk and the effect of lebrikizumab on the breastfed infant and on milk production. Lebrikizumab is a monoclonal IgG. The oral bioavailability of lebrikizumab is likely to be low; however, the effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to lebrikizumab are unknown. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

¹⁸ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 5/8/2023.

¹⁹ <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The lactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Access 5/8/23.

²⁰ Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 5/8/2023.

²¹ Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY. Accessed 5/8/2023.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of lebrikizumab-xxxx.

No effects on fertility parameters such as reproductive organs or menstrual cycle length were observed in sexually mature female cynomolgus monkeys that were administered intravenous doses of lebrikizumab-xxxx up to 25 mg/kg/week for 37 weeks, which was associated with plasma exposure (C_{avg,ss}) approximately 15 times the human exposure at the MRHD. No effects on reproductive organs or sperm analysis were observed in sexually mature male cynomolgus monkeys that were administered subcutaneous doses of lebrikizumab-xxxx up to 25 mg/kg/week for 13 weeks, which was associated with plasma exposure (C_{avg,ss}) approximately 11 times the human exposure at the MRHD.

The reader is referred to full Pharmacology/Toxicology report by Renqin Duan, Ph.D. and Barbara Hill, Ph.D. under Section 19.3 of the Multi-Disciplinary Review and Evaluation for BLA 761306.

DPMH Review of Literature

DPMH performed a search of published literature using PubMed, Embase, and the reference sites regarding adverse effect of lebrikizumab on fertility. No information was found.

Reviewer comment:

There are no data regarding the effect of lebrikizumab on human fertility. Animal reproductive studies did not show lebrikizumab adversely affecting fertility in monkeys. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

Twenty-one human pregnancies have been described in the clinical development program for lebrikizumab. The available human data are insufficient to assess a drug-related risk of congenital malformations, miscarriage, or adverse maternal or fetal outcomes. There are no available human data regarding the amount of lebrikizumab that is transferred through the placenta, lebrikizumab levels at birth in infants exposed in utero, or the duration of persistence of lebrikizumab in infant serum after delivery. Since lebrikizumab is a monoclonal IgG, it is expected to be transferred through the placenta during pregnancy based on published literature for other monoclonal antibodies.²² Developmental toxicity studies in pregnant monkeys at doses up to 18 times the human exposure at the MRHD revealed no evidence of harm to the developing fetus.

Moderate to severe atopic dermatitis effects females of reproductive potential, and therefore, exposures to lebrikizumab during pregnancy are likely to occur. The current human data are

²²Soh MC, et al. The Use of Biologics for Autoimmune Rheumatic Diseases in Fertility and Pregnancy. *Obstetric Medicine* 2020, Vol. 13 (1) 5-13.

insufficient to inform lebrikizumab use during pregnancy. Therefore, DPMH recommends issuing postmarketing requirement (PMR) for a pregnancy registry and a complementary study of a different design to collect pregnancy safety information. DPMH also recommends including language regarding the planned postapproval pregnancy exposure registry in subsection 8.1 and section 17 of labeling. See below for DPMH suggested PMR language.

Lactation

There are no data on the presence of lebrikizumab in human or animal milk, the effects of lebrikizumab on the breastfed infant and the effects on milk production. Endogenous monoclonal antibodies are known to be present in milk. Lebrikizumab is a monoclonal antibody, and therefore, is expected to be transferred through milk. Since lebrikizumab is a monoclonal antibody, DPMH recommends including language in 8.2 that is consistent with the approach used for other approved monoclonal antibodies. Labeling will note that “The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to lebrikizumab are unknown.” The following risk/benefit statement will also be included in labeling: “The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Ebglyss and any potential adverse effects on the breastfed infant from Ebglyss or from the underlying maternal condition.”

Based on the lack of available lactation data and the anticipated use of Ebglyss in females of reproductive potential, including lactating women, DPMH recommends issuing a PMR for a milk-only clinical lactation study to inform labeling regarding the concentration of lebrikizumab in human milk and effects on the breastfed infant. If there is evidence that lebrikizumab is transferred into breastmilk, additional studies (i.e., mother-infant pair study) may be required to further evaluate infant exposure through breast milk. See below for DPMH PMR language for monoclonal antibody products.

Females and Males of Reproductive Potential

There are no human data regarding lebrikizumab and effects on male or female fertility. Animal reproduction studies do not show any adverse effects of lebrikizumab on fertility. There is no anticipated drug-to-drug interaction between lebrikizumab and hormonal contraceptives. There are no available data to suggest Ebglyss use is associated with embryo-fetal toxicity. DPMH recommends omitting subsection 8.3 from the labeling.

RECOMMENDATIONS

Postmarketing Requirements (PMRs)

DPMH recommends the following PMR language for the pregnancy registry and complementary study and clinical lactation study:

1. DPMH recommends issuing a PMR for the applicant to conduct a pregnancy exposure registry in order to inform the pregnancy section of labeling. The following PMR language is suggested:

A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Ebglyss during pregnancy to an unexposed control population. The registry should be designed to

detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, neonatal deaths, and infections, will be assessed through at least the first year of life.

2. DPMH recommends issuing a PMR for the applicant to conduct a retrospective cohort study in order to inform the pregnancy section of labeling. The following PMR language is suggested:

An additional pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to Ebglyss during pregnancy compared to an unexposed control population.

3. DPMH recommends issuing a PMR for the applicant to conduct a lactation study in order to inform the lactation subsection of labeling. The following PMR language is suggested:

Perform a lactation study (milk only) in lactating women who have received therapeutic doses of Ebglyss to assess concentrations of lebrikizumab in breastmilk using a validated assay and to assess the effects on the breastfed infant. A mother-infant pair study may be required in the future depending on the results of this milk-only study.

4. DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

APPENDIX A. Pregnancy Outcomes of Maternally Exposed Pregnancies from the Clinical Trials²³

Table 4.1. Maternal Exposures Pregnancy Outcomes

Patient Identifier	Indication	Dose (mg) Interval (weeks)	Pregnancy Trimester of Exposure	Last Menstrual Period	Pregnancy Outcomes Neonate Outcomes (when available / applicable)	Updates from Initial Submission	Neonate Follow-up
(b) (6)	Asthma	Not provided Q4W	First	(b) (6)	Spontaneous abortion	None	Not applicable
(b) (6)	Asthma	Not provided Q4W	First	(b) (6)	Elective termination due to ectopic pregnancy	None	Not applicable
(b) (6)	Asthma	Not provided dose or frequency	Not reported	(b) (6)	In-utero (lost to follow-up)	None	Lost to follow-up
(b) (6)	Asthma	Not provided Q4W	First	(b) (6)	Abortion due to anembryonic pregnancy	None	Not applicable
(b) (6)	Asthma	Not provided Q4W	First	(b) (6)	Full-term and live birth Perinatal complication (fetal growth restriction)	None	Last update received (b) (6) (approx. 2 years after birth)
(b) (6)	Asthma	Not provided Q4W	First	(b) (6)	Spontaneous abortion	None	Not applicable

²³ Table 4.1 of sponsor’s response to FDA IR, submitted on 5/15/2023.

Patient Identifier	Indication	Dose (mg) Interval (weeks)	Pregnancy Trimester of Exposure	Last Menstrual Period	Pregnancy Outcomes Neonate Outcomes (when available / applicable)	Updates from Initial Submission	Neonate Follow-up
(b) (6)	Asthma	Not provided Q4W	First, Second, and Third	(b) (6)	Full-term and live birth Normal neonate	None	Last update received (b) (6) (approx. 5 weeks after birth)
	Asthma	Not provided Q4W	First		Spontaneous abortion	None	Not applicable
	Asthma	Not provided Q4W	First		Elective termination	None	Not applicable
	Asthma	Not provided Q4W	First		Spontaneous abortion	None	Not applicable
	Asthma	Not provided Q4W	Not reported		Full-term and live birth Normal neonate	None	Last update received (b) (6) (approx. 8 weeks after birth)
	Asthma	Not provided Q4W	First		Spontaneous abortion	None	Not applicable
	Asthma	Not provided Q4W	First		Full-term and live birth Perinatal complication (jaundice neonatal)	None	Last update received (b) (6) (approx. 7 weeks after birth)

Patient Identifier	Indication	Dose (mg) Interval (weeks)	Pregnancy Trimester of Exposure	Last Menstrual Period	Pregnancy Outcomes Neonate Outcomes (when available / applicable)	Updates from Initial Submission	Neonate Follow-up
(b) (6)	AD	L250 Q2W	First	(b) (6)	Elective termination due to anembryonic pregnancy	None	Not applicable
(b) (6)	AD	L250 Q2W	First	(b) (6)	Full-term and live birth Normal neonate	None	Lost to follow-up
(b) (6)	AD	Pregnancy occurred during the follow-up period / L250mg Q4W prior to follow-up	First	(b) (6)	Elective termination	None	Not applicable
(b) (6)	AD	Pregnancy occurred during the follow-up period / L250mg Q4W prior to follow-up	First	(b) (6)	Full-term and live birth Normal neonate	None	Lost to follow-up
(b) (6)	AD	L250mg Q2W	First	(b) (6)	Elective termination	None	Not applicable
(b) (6)	AD	L250mg Q2W	First	(b) (6)	Elective termination	None	Not applicable
(b) (6)	AD	L250mg Q2W	First	(b) (6)	In-utero (lost to follow-up)	None	Lost to follow-up

Abbreviations: AD = atopic dermatitis; L250mg = lebrikizumab 250 mg; Q2W = every 2 weeks; Q4W = every 4 weeks.

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/

WENJIE SUN
05/18/2023 09:43:04 AM

MIRIAM C DINATALE
05/18/2023 09:54:41 AM

LYNNE P YAO
05/18/2023 10:11:13 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 1, 2023

To: Qianyiren Song, PharmD
Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Ruth Mayrosh, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

David Foss, PharmD, MPH, BCPS, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFUs)

Drug Name (established name): EBGLYSS (lebrikizumab-xxxx)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761306

Applicant: Eli Lilly and Company

1 INTRODUCTION

On September 28, 2022, Eli Lilly and Company submitted for the Agency's review an original Biologics License Application (BLA) 761306 for EBGLYSS (lebrikizumab-xxxx) injection with the proposed indication for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on November 28, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFUs) for EBGLYSS (lebrikizumab-xxxx) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFUs will be forthcoming.

2 MATERIAL REVIEWED

- Draft EBGLYSS (lebrikizumab-xxxx) injection PPI and IFUs received on September 28, 2022, and received by DMPP and OPDP on April 20, 2023.
- Draft EBGLYSS (lebrikizumab-xxxx) injection Prescribing Information (PI) received on September 28, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 20, 2023.

-  (b) (4)

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI and IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFUs are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFUs are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFUs is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFUs.

Please let us know if you have any questions.

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/

RUTH I MAYROSH
05/01/2023 03:36:26 PM

DAVID F FOSS
05/02/2023 08:40:38 AM

SHARON R MILLS
05/02/2023 09:00:04 AM

LASHAWN M GRIFFITHS
05/02/2023 09:12:46 AM

LABEL ALABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	April 28, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761306
Product Name, Dosage Form, and Strength:	Ebglyss (lebrikizumab-lbkz,) injection, 250 mg/2 mL (125 mg/mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company
FDA Received Date:	September 28, 2022, and March 3, 2023
TTT ID #:	2022-1988
DMEPA 1 Safety Evaluator:	Corwin D. Howard, PharmD, RPh
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ebglyss (lebrikizumab-lbkz.) injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Ebglyss Prescribing information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling 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 – N/A
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 CONCLUSION AND RECOMMENDATIONS

The proposed Prescribing information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container labels 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 in Section 4 for the Division and in Section 5 for Eli Lilly and Company. Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

Table 2. Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information, Instructions for Use – General Issues			
1.	As currently presented, the package type term, “single-dose prefilled pen” and “single-dose prefilled syringe”, are inconsistent throughout the PI, IFU, container labels and carton labeling.	Consistent use of the correct package type term will promote proper use of the drug product. The lack of this information may lead to wrong technique medication errors during preparation or administration of the product.	We defer to OPQ on the appropriate package type term. We recommend revising the PI, IFU, container labels, and carton labeling the appropriate package type term for consistency[(e.g., Single-dose prefilled pen and Single-dose prefilled syringe)].
2.	As currently presented, the labels and labeling contain the nonproprietary name suffix placeholder “xxxx”.	We refer to our General Advice Letter dated April 26, 2023, which states we found the nonproprietary name suffix ‘-lbkz’ conditionally acceptable.	We recommend revising the nonproprietary name on all labels and labeling to incorporate the FDA-designated nonproprietary name suffix, -lbkz, appended to the core name, lebrikizumab, so that the proper name appears as lebrikizumab-lbkz throughout the labels and labeling.
Highlights of Prescribing Information			
1.	As currently presented, the strength is presented as “250 mg/2-mL” which is not consistent with the rest of the Prescribing Information that expresses the strength as “250 mg/2 mL”.	Inconsistent strength presentation may increase the risk for wrong dose medication errors.	To ensure consistency with the Prescribing Information, we recommend removing the “-” from “2-mL”.

5 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

Table 3. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The strength statement lacks prominence. As currently presented, the '2 mL' portion of the strength is not displayed in with the same size as '250', affecting prominence.	Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(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.	Revise the product to appear as '250 mg/2 mL', where the numbers '250' and '2' are displayed with the same size.
2.	As currently presented, the labels and labeling contain the nonproprietary name suffix placeholder "xxxx".	We refer to our General Advice Letter dated April 26, 2023, which states we found the nonproprietary name suffix '-lbkz' conditionally acceptable.	Should your BLA be approved during this review cycle, (lebrikizumab-lbkz) will be the proper name designated in the license. Revise the nonproprietary name on all labels and labeling to incorporate the FDA-designated nonproprietary name suffix, -lbkz, appended to the core name, lebrikizumab, so that the proper name appears as lebrikizumab-lbkz

Table 3. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			throughout the labels and labeling.
3.	The format for 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 a space be used to separate the portions of the expiration date. See <i>Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)</i> .
Container Label(s)			

Table 3. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	It is unclear if the linear barcodes on the pen container label and syringe container labels are scannable.	The drug barcode is often used as an additional verification before drug administration; therefore, it is an important safety feature that should be part of the label whenever possible.	Verify that the linear barcode on the container labels are scannable when placed around the curvature of the pen or syringe. Please note the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i). Ensure the linear barcode on the container label is surrounded by enough white space to facilitate proper scanning.
2.	As currently proposed, the prefilled syringe container label may be difficult to read and reduces its visibility.	Color contrast may be improved.	For the prefilled syringe container label, ensure there is sufficient contrast between the black text and the gray background color for readability. Consider changing the background color to a lighter color (one that has sufficient contrast) or using other means to improve the readability.
Carton Labeling			
1.	As currently presented, the proposed carton labeling contains the statement “ (b) (4) ”	The terminology “ (b) (4) ” and “ (b) (4) ” is inconsistent with the terminology used in the Prescribing Information.	To ensure consistency with the Prescribing Information, we recommend revising the statement, “ (b) (4) ” to read “Dosage: See Prescribing Information.”
2.	The storage statement lacks prominence.	Lack of prominence of the storage statement may lead to important storage	Revise and bold the statement “Store refrigerated at 36°F to 46°F (2°C to 8°C) in original

Table 3. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		information being overlooked, resulting in incorrect storage medication errors.	carton to protect from light until use." We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
3.	It is unclear where the machine-readable product identifier and human-readable identifier are located on the label.	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.	The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. Include the machine-readable data matrix barcode to the carton labeling. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] SERIAL: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date] We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-

Table 3. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			gen/documents/document/ucm621044.pdf .
4.	(b) (4)	Inconsistency with the images on the PDP may lead to the selection errors.	Consider depicting (b) (4) one pen on the PDP for the carton (b) (4).

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Ebglyss that Eli Lilly and Company submitted on March 3, 2023.

Table 4. Relevant Product Information for Ebglyss																
Initial Approval Date	N/A															
Active Ingredient	lebrikizumab-lbkz															
Indication	Treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. EBGLYSS can be used with or without topical corticosteroids.															
Route of Administration	Subcutaneous															
Dosage Form	Injection															
Strength	250 mg/2 mL (125 mg/mL)															
Dose and Frequency	The recommended dosage of EBGLYSS is 500 mg (two 250 mg injections) at Week 0 and Week 2, followed by 250 mg (one injection) every 2 weeks (b) (4) Week 16 or later, when adequate clinical response is achieved. The maintenance dose is EBGLYSS 250 mg every 4 weeks; (b) (4) .															
How Supplied	EBGLYSS (lebrikizumab-xxxx) injection is a sterile, preservative free, clear, colorless to slightly yellow solution, (b) (4) available in a single-dose prefilled pen or a single-dose prefilled syringe with needle shield. Each prefilled pen and prefilled syringe with needle shield is designed to deliver 250 mg of EBGLYSS in 2 mL.. EBGLYSS is supplied as: <table border="1"> <thead> <tr> <th></th> <th>Pack Size</th> <th>NDC</th> </tr> </thead> <tbody> <tr> <td colspan="3">Prefilled Pen</td> </tr> <tr> <td>250 mg/2 mL single-dose</td> <td>Carton of 1</td> <td>0002-7772-11 (b) (4)</td> </tr> <tr> <td colspan="3">Prefilled syringe with needle shield</td> </tr> <tr> <td>250 mg/2 mL single-dose</td> <td>Carton of 1</td> <td>0002-7797-11</td> </tr> </tbody> </table>		Pack Size	NDC	Prefilled Pen			250 mg/2 mL single-dose	Carton of 1	0002-7772-11 (b) (4)	Prefilled syringe with needle shield			250 mg/2 mL single-dose	Carton of 1	0002-7797-11
	Pack Size	NDC														
Prefilled Pen																
250 mg/2 mL single-dose	Carton of 1	0002-7772-11 (b) (4)														
Prefilled syringe with needle shield																
250 mg/2 mL single-dose	Carton of 1	0002-7797-11														
Storage	EBGLYSS is sterile and preservative-free.															

	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. If necessary, EBGLYSS may be kept at room temperature up to 30°C (86°F) for up to 7 days in the original carton. Throw away EBGLYSS if not used within 7 days at room temperature. Do not freeze. Do not use EBGLYSS if it has been frozen. Do not shake. Discard the EBGLYSS single-dose prefilled pen or prefilled syringe with needle shield after use in a puncture-resistant container.
Container Closure	single-dose prefilled pen or prefilled syringe

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 Ebglyss labels and labeling submitted by Eli Lilly and Company.

- Container label(s) received on September 28, 2022
- Carton labeling received on September 28, 2022
- Instructions for Use (Image not shown) received on September 28, 2022, available from <\\CDSESUB1\EVSPROD\bla761306\0001\m1\us\proposed-ifu-pfs.docx> (Single-Dose Prefilled Syringe with Needle Shield)
- <\\CDSESUB1\EVSPROD\bla761306\0001\m1\us\proposed-ifu-pen.docx> (Single-Dose Prefilled Pen)
- Prescribing Information (Image not shown) received on March 3, 2023, available from <\\CDSESUB1\EVSPROD\bla761306\0013\m1\us\proposed-uspi.docx>
- Patient Package Insert (PPI) (Image not shown) received on September 28, 2022, available from <\\CDSESUB1\EVSPROD\bla761306\0001\m1\us\proposed-ppi.docx>

F.2 Label and Labeling Images

Container label(s)

Pen



^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/

CORWIN D HOWARD
04/28/2023 01:30:16 PM

MADHURI R PATEL
04/28/2023 02:25:03 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: April 27, 2023

To: Qianyiren Song, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)
Shera Schreiber, Clinical Reviewer, DDD

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for EBGLYSS (lebrikizumab-xxxx), injection, for subcutaneous use

BLA: 761306

Background:

In response to DDD's consult request dated November 28, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original BLA submission for Ebglyss.

PI/PPI/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 20, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI/IFU, and comments will be sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on September 28, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

DAVID F FOSS
04/27/2023 11:26:03 AM