

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761390Orig1s000**

**OTHER REVIEW(S)**

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MEMORANDUM  
REVIEW OF REVISED 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)

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|------------------------------------------|--------------------------------------------------|
| Date of This Review:                     | August 9, 2024                                   |
| Requesting Office or Division:           | Division of Dermatology and Dentistry (DDD)      |
| Application Type and Number:             | BLA 761390                                       |
| Product Name, Dosage Form, and Strength: | Nemluvio (nemolizumab-ilto) for injection, 30 mg |
| Applicant Name:                          | Galderma Laboratories, L.P.                      |
| FDA Received Date:                       | August 9, 2024                                   |
| TTT ID #:                                | 2023-7476-3                                      |
| DMEPA 1 Safety Evaluator:                | Madhuri R. Patel, PharmD                         |
| DMEPA 1 Team Leader:                     | Yevgeniya Kogan, PharmD, BCSCP                   |

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## 1 PURPOSE OF MEMORANDUM

Galderma Laboratories, L.P. submitted revised carton labeling received on August 9, 2024 for Nemluvio. The Division of Dermatology and Dentistry (DDD) requested that we review the revised carton labeling for Nemluvio (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations made by the division to remove (b) (4) on the carton labeling for consistency with the prescribing information.

## 2 CONCLUSION

Galderma Laboratories, L.P. implemented all of our recommendations and we have no additional recommendations at this time.

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/s/  
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MADHURI R PATEL  
08/09/2024 03:42:18 PM

YEVGENIYA M KOGAN  
08/12/2024 09:19:56 AM

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**MEMORANDUM**  
**HUMAN FACTORS STUDY RESULTS 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)

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|                                          |                                                                        |
|------------------------------------------|------------------------------------------------------------------------|
| Date of This Memorandum:                 | July 31, 2024                                                          |
| Requesting Office or Division:           | Division of Dermatology and Dentistry (DDD)                            |
| Application Type and Number:             | BLA 761390                                                             |
| Product Name, Dosage Form, and Strength: | Nemluvio <sup>a</sup> (nemolizumab-ilto) <sup>b</sup> injection, 30 mg |
| Applicant/Sponsor Name:                  | Galderma Laboratories, L.P. (Galderma)                                 |
| TTT ID #:                                | 2024-7724-1                                                            |
| DMEPA 1 Safety Evaluator:                | Maggie Fung, PharmD                                                    |
| DMEPA 1 Team Leader:                     | Murewa Oguntimein, PhD, MHS, CPH, MCHES                                |

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised dual chamber autoinjector (DCC-AI) instructions for use (IFU) received on July 11, 2024 for Nemluvio for the treatment of prurigo nodularis in adults aged 18 years and older. The Division of Dermatology and Dentistry (DDD) requested that we review the IFU for Nemluvio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous human factors study results review.<sup>c</sup>

## 2 DISCUSSION AND CONCLUSION

The Applicant implemented our recommendations to:

- Revise the image in Step 8 and 9 so that users can better identify the dissolved particles
- Change the image for Step 17 to better portray the full image of the sharps container and revise the title to read “*Throw away (dispose of) Nemluvio in a sharps disposal container*”.

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<sup>a</sup> The proposed proprietary name Nemluvio was found conditionally acceptable on March 13, 2024.

<sup>b</sup> The proposed nonproprietary name suffix -ilto was found conditionally acceptable on June 11, 2024.

<sup>c</sup> Huang, L. Human Factors Study Reports Review for Nemluvio (BLA 761390 ). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUL 30. TTT ID No.: 2024-7726; 2024-7724.

The Applicant did not implement our recommendation to increase the prominence of the activation knob. The Applicant provided the following rationale to retain the current design (b) (4)

*“The DCC-AI has been designed to prevent incorrect sequencing of steps and ensures that users cannot remove the gray cap before turning the activation knob. Based on data available to date, the Applicant does not believe that a design change is necessary. Given that priority review status has been granted for this BLA to allow expedited availability of Nemludio to PN patients, (b) (4)*

*. As any modifications to the current user interface can impact the HFE validation, potential changes will be assessed to ensure no unintended use errors are introduced.”* In this specific instance, we find the Applicant's rationale reasonable.

Based on the provided information, we have no additional recommendations for the revised Nemludio DCC-AI IFU at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 11, 2024

Applicant's response to our July 9, 2024, recommendations available via EDR:

<\\CDSESUB1\EVSPROD\bla761390\0037\m1\us\qual-9july24-labeling-hf.pdf>

Revised instructions for use (IFU) available via EDR:

- PDF version: <\\CDSESUB1\EVSPROD\bla761390\0037\m1\us\dcc-ifu-mock-up.pdf>
- Word version: <\\CDSESUB1\EVSPROD\bla761390\0037\m1\us\dcc-ai-ifu-text.doc>

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/s/  
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OLUWAMUREWA OGUNTIMEIN on behalf of MAGGIE FUNG  
07/31/2024 10:02:09 AM

OLUWAMUREWA OGUNTIMEIN  
07/31/2024 10:03:28 AM

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## HUMAN FACTORS STUDY REPORTS 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)

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|-----------------------------------------------|---------------------------------------------------------------------------------------|
| Date of This Review:                          | July 30, 2024                                                                         |
| Requesting Office or Division:                | Division of Dermatology and Dentistry (DDD)                                           |
| Application Type and Number:                  | BLA 761390 (b) (4)                                                                    |
| Product Type:                                 | Combination Product (Biologic-Device)                                                 |
| Product Name, Dosage Form, and Strength:      | Nemluvio <sup>1</sup> (nemolizumab-ilto) <sup>2</sup> injection, 30 mg                |
| Device Constituent:                           | (b) (4) Dual Chamber Autoinjector (AI)                                                |
| Rx or OTC:                                    | Rx                                                                                    |
| Applicant/Sponsor Name:                       | Galderma Laboratories, L.P. (Galderma)                                                |
| Submission Date:                              | December 12, 2023; January 10, 2024; February 6, 2024; March 21, 2024; April 22, 2024 |
| TTT ID #:                                     | 2024-7726; 2024-7724                                                                  |
| DMEPA 1 Human Factors Evaluator:              | Lisa Huang, PharmD, MPH                                                               |
| DMEPA 1 Team Leader:                          | Murewa Oguntimein, PhD, MHS, CPH, MCHES                                               |
| DMEPA 1 Associate Director for Human Factors: | Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP                                         |
| DMEPA 1 Deputy Director:                      | Jason Flint, MBA, PMP                                                                 |
| DMEPA 1 Director:                             | Mishale Mistry, PharmD, MPH                                                           |

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<sup>1</sup> The proposed proprietary name Nemluvio was found conditionally acceptable on March 13, 2024.

<sup>2</sup> The proposed nonproprietary name suffix -ilto was found conditionally acceptable on June 11, 2024.

## 1 REASON FOR REVIEW

This review evaluates the human factors (HF) study results reports submitted under BLA 761390 (b) (4) for Nemludio (nemolizumab-ilto) injection 30 mg, (b) (4) dual chamber autoinjector (AI) for the indications listed in Table 2 below.<sup>3</sup>

We considered the materials listed in Table 1 for this review.

| Table 1. Materials Considered for this Review                                     |                  |
|-----------------------------------------------------------------------------------|------------------|
| Material Reviewed                                                                 | Section/Appendix |
| Product Information/Prescribing Information                                       | Section 1.1      |
| Background Information<br>Previous HF Reviews (DMEPA)                             | Section 1.2      |
| Human Factors Study Reports                                                       | Appendix A       |
| Information Requests Issued During the Review                                     | Appendix B       |
| Labels and Labeling                                                               | Appendix C       |
| Detailed List of Use Errors, Use Difficulties, And<br>Close Calls for Section 3.1 | Appendix D       |

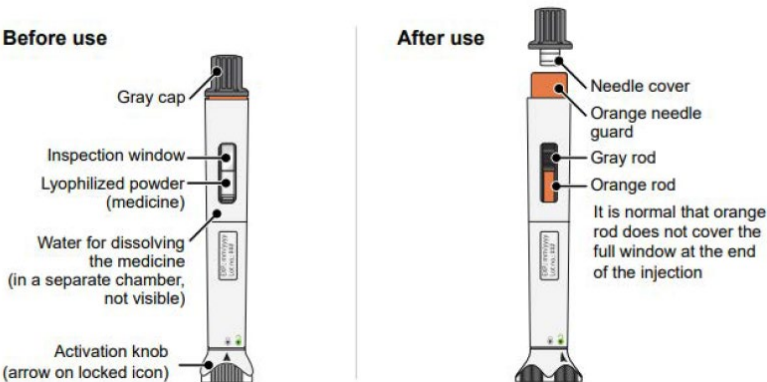
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<sup>3</sup> The Applicant uses the abbreviations (b) (4) dual chamber cartridge autoinjector (DCC AI) throughout their submissions for these device presentations.

## 1.1 PRODUCT DESCRIPTION

| Table 2. Relevant Product Information for Nemluvio |                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Initial Approval Date                              | N/A                                                                                                                                                                                                                                                                                                                                                                                     |
| Active Ingredient                                  | Nemolizumab-ilto (b) (4)                                                                                                                                                                                                                                                                                                                                                                |
| Indication                                         | <div></div> <ul style="list-style-type: none"> <li>Prurigo Nodularis: (PN): Adults aged 18 years and older</li> </ul>                                                                                                                                                                                                                                                                   |
| Route of Administration                            | Subcutaneous                                                                                                                                                                                                                                                                                                                                                                            |
| Dosage Form                                        | Injection                                                                                                                                                                                                                                                                                                                                                                               |
| Strength                                           | <ul style="list-style-type: none"> <li>(b) (4) dual chamber AI: 30 mg</li> </ul>                                                                                                                                                                                                                                                                                                        |
| Dose and Frequency                                 | <div></div> <p><b>PN</b></p> <ul style="list-style-type: none"> <li>Adult patients with a body weight below 90 kg: an initial dose of 60 mg (two 30 mg injections in different injection sites), followed by 30 mg every 4 weeks</li> <li>Adult patients with a body weight <math>\geq</math> 90 kg: 60 mg (two 30 mg injections in different injection sites) every 4 weeks</li> </ul> |
| How Supplied                                       | <div></div> <ul style="list-style-type: none"> <li>Pre-filled, (b) (4) single-dose dual chamber AI             <ul style="list-style-type: none"> <li>30 mg lyophilized powder with 0.49 mL water for injection</li> </ul> </li> </ul>                                                                                                                                                  |
| Storage                                            | Store under refrigerated conditions 2°C to 8°C (36°F to 46°F) in the original carton. Protect from direct sunlight. Can be stored at room temperature up to 25°C (77°F) for up to 90 days.                                                                                                                                                                                              |

(b) (4)

|                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Container Closure/Device Constituent</b></p> | <div style="text-align: right;">(b) (4)</div> <div style="text-align: center;"> <p><b>Dual Chamber AI:</b></p>  <p>The diagram illustrates the 'Before use' and 'After use' states of the Dual Chamber AI device. In the 'Before use' state, the device is shown with a gray cap, an inspection window, lyophilized powder (medicine), water for dissolving the medicine (in a separate chamber, not visible), and an activation knob (arrow on locked icon). In the 'After use' state, the device is shown with a needle cover, orange needle guard, gray rod, and orange rod. A note states: 'It is normal that orange rod does not cover the full window at the end of the injection'.</p> </div> |
| <p><b>Intended Users</b></p>                       | <div style="text-align: right;">(b) (4)</div> <ul style="list-style-type: none"> <li>• PN: adult patients; caregivers; HCP</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <p><b>Intended Use Environment</b></p>             | <ul style="list-style-type: none"> <li>• Home; clinic</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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

On January 15, 2024, we searched previous DMEPA reviews relevant to this current review using the terms, “IND 117122”, “BLA 761390”, (b) (4) and “nemolizumab”. Our search identified six reviews, and we considered our previous recommendations to see if they are applicable for this current review. See details below.

(b) (4)

- On June 21, 2021, Galderma submitted an HF validation protocol for their proposed dual chamber AI for (b) (4) prurigo nodularis indications under IND 117122. We reviewed the protocol and provided recommendations.<sup>10</sup>
- On May 20, 2022, Galderma submitted clarifying questions regarding the acceptability of their HF validation study methodology in response to recommendations that we made during the previous HF validation study protocol review for their proposed dual chamber AI. We provided responses to the clarifying

<sup>10</sup> Kumar, N. HF Protocol Review for Nemolizumab (IND 117122). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 NOV 30. RCM No.: 2021-1216.

questions and confirmed our previous recommendations were implemented or considered.<sup>11</sup>

- On December 12, 2023, and on December 13, 2023, respectively, Galderma submitted biological applications (BLA) for (b) (4) dual chamber AI for the treatment of PN under BLA 761390 (b) (4). The submissions included HF validation study results reports, which are the subject of this review.

## 2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 2 presents a summary of the HF validation studies designs. See Appendix A for more details on the study designs.

| Table 2. Study Methodology for the Human Factors (HF) Validation Studies |                                                                                                              |                                                    |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| Study Design Elements                                                    | Details provided by Galderma                                                                                 |                                                    |
| User Groups                                                              |                                                                                                              | Dual-chamber cartridge auto-injector study (b) (4) |
|                                                                          | Adult patients                                                                                               | 35                                                 |
|                                                                          | Lay caregivers                                                                                               | 31                                                 |
|                                                                          | Adolescent patients                                                                                          | 38                                                 |
|                                                                          | Healthcare providers                                                                                         | 15                                                 |
|                                                                          | Total                                                                                                        | 119                                                |
|                                                                          | (b) (4)                                                                                                      |                                                    |
| Training                                                                 | (b) (4)                                                                                                      |                                                    |
|                                                                          | Dual chamber AI study: <ul style="list-style-type: none"><li>Participants did not receive training</li></ul> |                                                    |

<sup>11</sup> Barlow M. HF Protocol Clarifying Questions Review for Nemolizumab (IND 117122). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 AUG 15. RCM No.: 2021-1216-1.

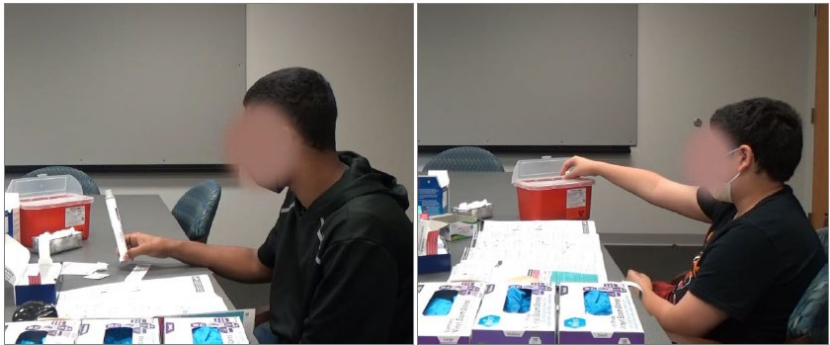
**Test  
Environment &  
Materials**

The study facility test room simulated a home environment or doctor’s office. The following materials were available to the participants:

|                                                                                          |         |
|------------------------------------------------------------------------------------------|---------|
| Dual chamber AI study                                                                    | (b) (4) |
| Hand sanitizer and/or sink, cotton balls, gloves, gauze, alcohol wipes, sharps container |         |
| Did not include refrigerator or small cabinet                                            | (b) (4) |



Dual Chamber AI study:



|                                                                   |                                                                                |                                                                                                                                                    |         |
|-------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Sequence of Study                                                 |                                                                                | Dual chamber AI study                                                                                                                              | (b) (4) |
|                                                                   | Use Scenario 1                                                                 | Deliver 1 <sup>st</sup> dose simulated injection                                                                                                   |         |
|                                                                   | Break                                                                          | 20-minute decay period**                                                                                                                           |         |
|                                                                   | Use Scenario 2                                                                 | Deliver 2 <sup>nd</sup> dose simulated injection<br><br>Adult, Caregiver, & HCPs: simulated 2 injections<br><br>Adolescents: simulated 1 injection |         |
|                                                                   | Use Scenario 3                                                                 | N/A                                                                                                                                                |         |
|                                                                   | Knowledge Tasks                                                                | Knowledge tasks                                                                                                                                    |         |
|                                                                   | Debrief interview to collect subjective feedback for root cause analysis (RCA) |                                                                                                                                                    |         |
| ** Regarding the 20-minute decay period, see Section 2.1.2 below. |                                                                                |                                                                                                                                                    |         |

## 2.1 DISCUSSION OF METHODOLOGY



### 2.1.2 DUAL CHAMBER CARTRIDGE AUTOINJECTOR

During the course of our review, we noted that the Applicant included a 20-minute decay period between Use Scenario 1 (participants delivering their first dose simulated injection) and Use Scenario 2 (participants delivering their second dose simulated injection). Furthermore, we note that in Use Scenario 1, participants delivered one injection whereas in Use Scenario 2, adults, caregivers and HCP user groups simulated two injections and adolescents simulated one injection. The Applicant indicated that the 20-minute break was to simulate the learning decay *“period that would occur between doses during actual use”* based on the *“Ebbinghaus Forgetting Curve.”* We note that in actual use, the initial dose for all patients consists of two 30 mg injections, followed by a maintenance dose of either 30 mg or 60 mg every 4 weeks. Therefore, the simulated Use Scenarios 1 & 2 were not reflective of actual use with respect to the number of injections for administration of an initial dose followed by the maintenance dose. However, we do note that adults, caregivers and HCP user groups simulated a dose requiring two injections.

(b) (4)

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<sup>12</sup> See FDA Guidance for Industry and Food and Drug Administration Staff *Applying Human Factors and Usability Engineering to Medical Devices*, February 2016. Available from <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices>.

### 3 RESULTS AND ANALYSES

In this section, we have carefully reviewed each reported issue (i.e., use error, use difficulty), Galderma's URRAs, the participants' subjective feedback, Galderma's root cause analysis and Galderma's comments to determine if the results indicate that the user interfaces have been appropriately designed to support the safe and effective use of the proposed products. In Table 3 and 4 below, we document our points of dissent with Galderma's findings. Additionally, Appendix D provides the observed use task and knowledge task issues where we agree with Galderma's conclusions and have no further recommendations or comments.

(b) (4)

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| Table 4. Focused Analysis of Use Errors, Use Difficulties and Close Calls and DMEPA's Recommendations for Dual Chamber Autoinjector Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                           |                                                         |                   |                 |           |                           |   |            |                  |   |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|---------------------------------------------------------|-------------------|-----------------|-----------|---------------------------|---|------------|------------------|---|--|
| <p>UE = use error; CC = close call; D = use difficulty; URRRA = use-related risk analysis; RCA = root cause analysis; IFU = instructions for use; HFVS = Human Factors Validation Study</p> <p>Scenario Type: scenario 1 – deliver first simulated injection (all participant groups simulated one injection); scenario 2 – deliver second simulated injection (adult, caregiver, and HCPs: simulated two injections, adolescents: simulated one injection)</p> <p>Participants ID: A = adult participant; T = adolescent participant; C = caregiver participant, H = healthcare provider participant<br/>N = naïve user, X = experienced user</p>                                                                                                                                                                                                                                                                                                                                                              |                           |                                                         |                   |                 |           |                           |   |            |                  |   |  |
| Information Supplied by Applicant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                           | DMEPA's Identified Areas of Dissent and Recommendations |                   |                 |           |                           |   |            |                  |   |  |
| <p>1. <b>Task: Activate the pen</b></p> <table border="1"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th><th>Scenario number</th></tr> </thead> <tbody> <tr> <td>D (n = 5)</td><td>H = 1<br/>TN = 2<br/>TX = 2</td><td>1</td></tr> <tr> <td>CC (n = 2)</td><td>CX = 1<br/>TX = 1</td><td>2</td></tr> </tbody> </table>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                           | Errors:                                                 | Participant Type: | Scenario number | D (n = 5) | H = 1<br>TN = 2<br>TX = 2 | 1 | CC (n = 2) | CX = 1<br>TX = 1 | 2 |  |
| Errors:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Participant Type:         | Scenario number                                         |                   |                 |           |                           |   |            |                  |   |  |
| D (n = 5)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | H = 1<br>TN = 2<br>TX = 2 | 1                                                       |                   |                 |           |                           |   |            |                  |   |  |
| CC (n = 2)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | CX = 1<br>TX = 1          | 2                                                       |                   |                 |           |                           |   |            |                  |   |  |
| <p><b>Observed event(s):</b></p> <ul style="list-style-type: none"> <li>Participants initially did not activate the AI. They shook the AI and began to wait before realizing they had not yet activated it and then proceeded to activate it.</li> <li>Participants experienced difficulty knowing how to activate the AI. They attempted to remove the gray cap for a minute before activating the AI. Eventually, they noticed the activation knob and turned it.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                           |                                                         |                   |                 |           |                           |   |            |                  |   |  |
| <p><b>Relevant RCA/Subjective Feedback/Observation</b></p> <ul style="list-style-type: none"> <li><u>Negative transfer:</u> Three participants assumed the AI would function similarly to an EpiPen, which does not require activation prior to injecting.</li> <li><u>Activation knob appears somewhat inconspicuous due to similar color to AI's body:</u> Participants initially overlooked the activation knob because it is the same color as the rest of the AI. They also assumed they had to remove the gray cap first because it was more noticeable due to its arrows, location at the top of the device, and different color from the rest of the AI.</li> <li><u>Unexpected force required to turn activation knob:</u> Participant initially attempted to twist the activation knob lightly because they thought the device seemed fragile. After attempting to twist the gray cap several times, they decided to try twisting the activation knob again with more force and succeeded.</li> </ul> |                           |                                                         |                   |                 |           |                           |   |            |                  |   |  |
| <p><b>Based on the Applicant's URRRA, performing this task incorrectly or not at all may result in:</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                           |                                                         |                   |                 |           |                           |   |            |                  |   |  |

|            | <p>Delayed injection: loaded spring may lead to potential eye injury; incomplete dose or single injection of low concentration; missed doses</p> <p><b>Applicant Comment and Proposed Mitigations:</b><br/>Based on these use issues related to activating the pen, Galderma updated the device overview image in the IFU to clarify the location of the activation knob, “<i>Activation knob (arrow on unlocked icon)</i>”. Galderma stated that this change does not have any impact on usability and no further validation is needed.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p>Based on subjective feedback, participants initially overlooked the activation knob because it is the same color as the rest of the AI. They also assumed they had to remove the gray cap first because it was more noticeable due to its arrows, location at the top of the device, and different color from the rest of the AI. Based on our overall assessment, we find that the dual chamber AI can be improved to emphasize the activation knob. <b>We provide our recommendation in Table A to address this concern.</b> We have determined that this change can be implemented without submitting additional HF data for Agency review.</p> |                   |                 |            |        |   |        |            |                  |   |            |        |                  |                                                                                                                                                                                                                                     |
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| 2.         | <p><b>Task: Wait 5 minutes for bubbles to decrease</b></p> <table border="1" data-bbox="131 682 821 921"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th><th>Scenario number</th></tr> </thead> <tbody> <tr> <td rowspan="2">UE (n = 5)</td><td>TN = 2</td><td rowspan="2">1</td></tr> <tr> <td>TX = 3</td></tr> <tr> <td>CC (n = 3)</td><td>AN = 1<br/>TX = 2</td><td rowspan="3">2</td></tr> <tr> <td rowspan="2">UE (n = 8)</td><td>CX = 1</td></tr> <tr> <td>TN = 3<br/>TX = 4</td></tr> </tbody> </table> <p><b>Observed event(s):</b></p> <ul style="list-style-type: none"> <li>Participants activated the AI but did not wait for bubbles to decrease before injecting.</li> <li>Participants activated the AI, then shook it, then attempted to inject without waiting for the bubbles to decrease.</li> <li>Participant required assistance to remove gray cap.</li> <li>Participants activated the AI and attempted to inject with the gray cap still attached to AI.</li> </ul> <p><b>Relevant RCA/Subjective Feedback/Observation:</b></p> <ul style="list-style-type: none"> <li><u>Negative transfer</u>: Participants assumed the AI would function like an EpiPen or a typical AI that did not require mixing or waiting.</li> <li>Participant thought the image in IFU Step 8 showing users what to inspect for depicted only bubbles and not particles.</li> <li><u>Relatively inconspicuous IFU Step 9a – located in between similarly formatted text</u>: Participant relied on Step 9 of IFU’s image which they considered depicted the medicine as neither obviously clear nor cloudy despite the image’s intention to depict clear medicine.</li> </ul> <p><b>Based on the Applicant’s URRR, performing this task incorrectly or not at all may result in:</b><br/>Undissolved drug may lead to local or systemic hypersensitivity reaction; underdose; air bubbles may lead to minor pain; degraded drug may lead to local or systemic hypersensitivity reaction; delayed injection.</p> <p><b>Applicant Comment and Proposed Mitigations:</b><br/>None</p> | Errors:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Participant Type: | Scenario number | UE (n = 5) | TN = 2 | 1 | TX = 3 | CC (n = 3) | AN = 1<br>TX = 2 | 2 | UE (n = 8) | CX = 1 | TN = 3<br>TX = 4 | <p>Based on subjective feedback, some participants thought the dual chamber AI did not require mixing or waiting for the medication to be dissolved, similar to their experience with other injection devices like EpiPen. Some</p> |
| Errors:    | Participant Type:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Scenario number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                   |                 |            |        |   |        |            |                  |   |            |        |                  |                                                                                                                                                                                                                                     |
| UE (n = 5) | TN = 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                   |                 |            |        |   |        |            |                  |   |            |        |                  |                                                                                                                                                                                                                                     |
|            | TX = 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                   |                 |            |        |   |        |            |                  |   |            |        |                  |                                                                                                                                                                                                                                     |
| CC (n = 3) | AN = 1<br>TX = 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                   |                 |            |        |   |        |            |                  |   |            |        |                  |                                                                                                                                                                                                                                     |
| UE (n = 8) | CX = 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                   |                 |            |        |   |        |            |                  |   |            |        |                  |                                                                                                                                                                                                                                     |
|            | TN = 3<br>TX = 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                   |                 |            |        |   |        |            |                  |   |            |        |                  |                                                                                                                                                                                                                                     |

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|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-----------------|-------------|---------------------------------------|---|-----------|--------|---|-------------|--------------------------------------|---|--|
| 3.          | <p><b>Task: Throw away (dispose of) the pen and cap</b></p> <table border="1"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th><th>Scenario number</th></tr> </thead> <tbody> <tr> <td>UE (n = 21)</td><td>AX = 3<br/>CX = 2<br/>TN = 12<br/>TX = 4</td><td>1</td></tr> <tr> <td>D (n = 1)</td><td>TX = 1</td><td>1</td></tr> <tr> <td>UE (n = 19)</td><td>AX = 7<br/>CX = 2<br/>TN = 8<br/>TX = 2</td><td>2</td></tr> </tbody> </table> <p><b>Observed Event(s):</b></p> <ul style="list-style-type: none"> <li>Participants discarded the AI in the regular trash can.</li> </ul> <p><b>Relevant RCA/Subjective Feedback/Observation:</b></p> <ul style="list-style-type: none"> <li><u>IFU sharps container graphic appears similar to regular trash can:</u> Participants thought the sharps container graphic in Step 17 of the IFU appeared to look like a regular trash can.</li> <li><u>Vague IFU heading's "throw away" instruction:</u> Participants assumed that they should discard into a regular trash can because "throw away" commonly refers to disposal into a regular trash can. One participant further noted that IFU Step 17's heading instructs users to discard the AI but does not specify where to do so.</li> <li>Participant initially was unsure whether to dispose of used AI in the sharps container; however, after a while and upon referencing the IFU, they correctly disposed of the used AI in the sharps container.</li> <li><u>Separate call to action and caution instruction – "Do not" heading separate from associated instructions:</u> Participants did not see the "Do not" statement ahead of the bullet instructing users not to discard of the AI in household trash because they were skimming the IFU.</li> </ul> <p><b>Based on the Applicant's URRAs, performing this task incorrectly or not at all may result in:</b><br/>Needlestick injury that may lead to local or systemic infection, or infection by blood-borne pathogen.</p> <p><b>Applicant Comment and Proposed Mitigations:</b><br/>Based on these use issues related to throwing away or disposing the pen and cap, Galderma updated Step 9 of the IFU to state, "see Section C Throwing away (Disposing of) NEMLUVIO)". They note that adding the phrase "throwing away" improves readability, account for potential users with low literacy, and is more user friendly. They also updated Step 12 to align with commonly used terminology, from "sharps container" to "sharps disposal container". Galderma stated that these changes do not require further validation.</p> | Errors:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Participant Type: | Scenario number | UE (n = 21) | AX = 3<br>CX = 2<br>TN = 12<br>TX = 4 | 1 | D (n = 1) | TX = 1 | 1 | UE (n = 19) | AX = 7<br>CX = 2<br>TN = 8<br>TX = 2 | 2 |  |
| Errors:     | Participant Type:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Scenario number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                   |                 |             |                                       |   |           |        |   |             |                                      |   |  |
| UE (n = 21) | AX = 3<br>CX = 2<br>TN = 12<br>TX = 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                   |                 |             |                                       |   |           |        |   |             |                                      |   |  |
| D (n = 1)   | TX = 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                   |                 |             |                                       |   |           |        |   |             |                                      |   |  |
| UE (n = 19) | AX = 7<br>CX = 2<br>TN = 8<br>TX = 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                   |                 |             |                                       |   |           |        |   |             |                                      |   |  |
|             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Based on subjective feedback, some participants thought the sharps container graphic looked like a regular trash can in Step 17 of the IFU. Some participants assumed that they should discard into a regular trash can because "throw away" commonly refers to disposal into a regular trash can. One participant noticed the heading instructs users to discard the AI but does not specify where to do so in Step 17. Based on our overall assessment, we find that the disposal instructions can be improved in the IFU. |                   |                 |             |                                       |   |           |        |   |             |                                      |   |  |

|  |  |                                                                                                                                                                                          |
|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  |  | <b>We provide our recommendation in Table A to address this concern.</b> We have determined that this change can be implemented without submitting additional HF data for Agency review. |
|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### **3.1 ANALYSIS OF THE REMAINING IDENTIFIED ISSUES**

The HF validation study reports showed issues with the tasks evaluated by simulated use and knowledge task assessments listed in Appendix D. However, based on our review of the available assessment of these identified issues, the available participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), Galderma's root cause analysis, Galderma's post HF validation studies mitigation, and our evaluation of the residual risks, we did not identify recommendations to address the identified issues with the tasks in Appendix D.

### **3.2 LABELS AND LABELING**

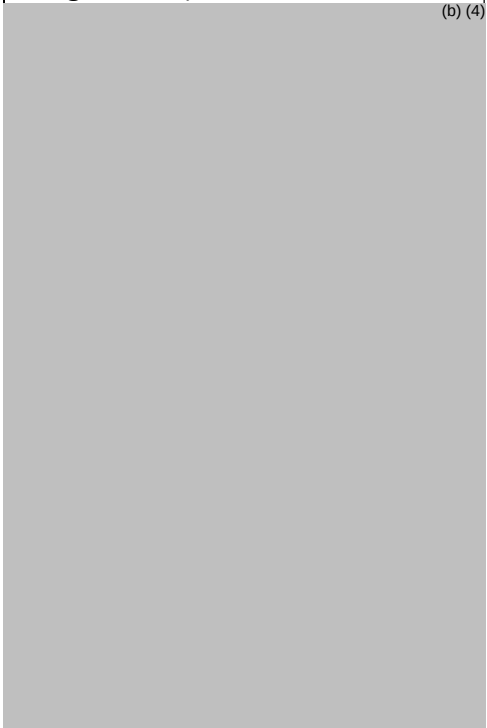
Table A below includes the identified medication error issues with the submitted instructions for use (IFU) based on the HF validation study results, our rationale for concern, and the proposed recommendations to minimize the risk for medication errors. Additionally, we note that the DMEPA 1 nomenclature and labeling review team evaluated product specific label and labeling under a separate cover.<sup>13</sup>

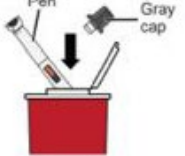
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<sup>13</sup> Patel, M. Labeling Review. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 MAY 10. TTT.: 2023-7476.

| Dual Chamber Cartridge Autoinjector (DCC AI) Product Design |                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                           |
|-------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1.                                                          | The activation knob on the DCC AI required for medication reconstitution lacks prominence as presented. | <p>Per the URRA, if the user does not activate or activates the DCC AI in the incorrect order of steps, there is risk of delayed injection with negligible reduced efficacy or underdose with reduced or no efficacy.</p> <p>The human factors (HF) validation study results identified subjective feedback that indicated participants had difficulty knowing how to activate or initially did not</p> | Increase the prominence of the activation knob. For example, consider using a color different from the body of the DCC AI and/or adding the number "1" on the activation knob and number "2" on the gray cap to indicate the correct order of operations. |

|                                                                                |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                        |
|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
|                                                                                |                                                                                                                                                                                                                    | activate the DCC AI because they overlooked the activation knob as it was the same color as the rest of the DCC AI.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                        |
| <b>Dual Chamber Cartridge Autoinjector (DCC AI) Instructions for Use (IFU)</b> |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                        |
| 1.                                                                             | <p>The image in Step 8 and 9 of the IFU does not depict dissolved medication as presented. (See image below)</p>  <p>(b) (4)</p> | <p>Per the use-related risk analysis (URRA), if the user does not wait 5 minutes for the bubbles to decrease, then there is a risk of undissolved medication, degraded drug, air bubbles, delayed injection or underdose, and they may experience local or systemic hypersensitivity reaction, minor pain, or negligible reduced efficacy.</p> <p>The human factors (HF) validation study results identified subjective feedback that indicated participants considered the image depicting the dissolved medicine as only bubbles and not particles, or neither obviously clear nor cloudy in Step 8 and 9 of the IFU, respectively.</p> | Consider revising the image in Step 8 and 9 so that users can better identify the dissolved particles. |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                 |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2. | <p>The sharps container image in IFU Step 17 is not clearly depicted as presented. (See image below)</p> <p><b>C. Throwing away (disposing of) DRUG NAME</b></p> <p><b>Step 17: Throwing away (dispose of) the pen and cap</b></p> <p>Avoid contact with the needle.</p> <p>Throw away (dispose of) the used pen and the gray cap in a FDA-cleared sharps disposal container right away after use (see Figure Q).</p>  <p>Figure Q</p> | <p>Per the use-related risk analysis (URRA), this results in needlestick injury that may lead to local or systemic infection, or infection by blood-borne pathogen.</p> <p>The human factors (HF) validation study results identified subjective feedback that indicated that participants thought the sharps container image appeared to look like a regular trash can or thought the IFU heading's <i>"throw away"</i> assumed they should discard in a regular trash can.</p> | <p>Consider changing the image for Step 17 to better portray the full image of the sharps container. Additionally, consider revising the title of Step 17 to read <i>"Throw away (dispose of) Nemluvio in a sharps disposal container"</i>.</p> |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## 4 CONCLUSION AND RECOMMENDATIONS

(b) (4)



The results of the dual chamber prefilled autoinjector HF validation study demonstrated several use errors, close calls, and use difficulties with critical tasks. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors with labels and labeling. Above, we have provided recommendations in Table A for Galderma. We ask that the Division of Dermatology and Dentistry (DDD) convey Table A in its entirety to Galderma. These changes can be implemented without submitting additional HF validation testing data for Agency review.

### 4.1 RECOMMENDATIONS FOR GALDERMA LABORATORIES, L.P

(b) (4)



### **Dual Chambered Cartridge Autoinjector**

The results of your human factors (HF) validation studies for Nemluvio 30 mg dual chamber cartridge autoinjector user interface indicate that there are additional mitigations that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A. We recommend that you implement these recommendations and submit the revised instructions for use for our review, prior to the approval of this application. We have determined that in this instance, you may implement these revisions without submitting additional human factors testing data for Agency review.

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<sup>14</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>15</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. HUMAN FACTORS STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:



Dual Chamber Autoinjector:

<\\CDSESUB1\EVSPROD\bla761390\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\prurigo-nodularis\5354-other-stud-rep\dcc-reports\report-body-dcc-ai-hfer.pdf>

### APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On January 5, 2024, we issued an information request (IR) requesting Galderma to submit 5 placebo only-intend-to-market samples of the products. On January 10, 2024, Galderma provided a response that can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761390\0003\m1\us\cover.pdf>

On February 2, 2024, we issued an information request (IR) requesting Galderma to submit the following:

- Confirm that the HF validation study results for the proposed  (b) (4)  dual chamber autoinjector user interface you submitted on December 12, 2023, under BLA 761390  (b) (4)



On February 6, 2024, Galderma provided an acceptable response that can be accessible in EDR via: <\\CDSESUB1\EVSPROD\bla761390\0006\m1\us\quality-info-resp-02feb2024.pdf> and <\\CDSESUB1\EVSPROD\bla761390\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\prurigo-nodularis\5354-other-stud-rep\dcc-reports\dcc-ai-urra-5feb24.pdf>

On March 20, 2024, we issued an information request (IR) requesting Galderma to submit the moderator script. On March 21, 2024, Galderma provided a response that can be accessible in EDR via: <\\CDSESUB1\EVSPROD\bla761390\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\prurigo-nodularis\5354-other-stud-rep\dcc-reports\dcc-ai-hf-val-mod-script.pdf>

On April 18, 2024, we issued an information request (IR) requesting Galderma to clarify the steps they took to mitigate the use error of participants losing their grip on the dual chamber AI that resulted in the device slipping and their commercial intend- to- market labeling. On April 22, 2024, Galderma provided a response that can be accessible in EDR via: <\\CDSESUB1\EVSPROD\bla761390\0021\m1\us\qual-cmc-ir6-18apr24.pdf>

## APPENDIX C. LABELS AND LABELING

### C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>16</sup> along with postmarket medication error data, we reviewed the following Nemluvio labels and labeling submitted by Galderma on December 12, 2023.

- Carton labeling
- Container labels
- Prescribing information (images not shown) is available from: <\\CDSESUB1\EVSPROD\bla761390\0001\m1\us\annotated-draft-labeling-text.pdf>
-  (b) (4)
- Autoinjector IFU (image not shown): <\\CDSESUB1\EVSPROD\bla761390\0001\m1\us\dcc-ai-ifu.pdf>

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<sup>16</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

### Dual Chamber AI

- Use tasks:
  - Wash your hands
  - Hold AI
  - Check the pen
  - Check the medicine in the inspection window
  - Select one injection site
  - Clean the injection site
  - Twist the gray cap
  - Place the pen
  - Start injection and hold pen on the skin: There were eight use errors observed for this task. The root cause analysis indicated that the use errors were due to negative transfer and habit. 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.

- Inject for 15 seconds: There were 36 use errors observed for this task. The root cause analysis indicated that the use errors were due to negative transfer, high information density of the IFU, and the dual chamber AI's smooth body might not provide sufficient grip traction. We issued an information request (IR) to Galderma to clarify the steps they took to mitigate these use errors observed of participants losing their grip on the dual chamber AI that resulted in the device slipping and information regarding commercial intend- to- market labeling. Galderma provided a response indicated that the errors related to the dual chamber AI's smooth body were due to participant being distracted during injection, excessive pressure on the injection pad, nervousness, or holding the dual chamber AI with three fingers instead of holding it as shown in the IFU. Galderma indicated that the average injection time observed in dual chamber AI functional testing during the stability study was 2.96 seconds and the participants that repositioned their hands did so approximately 5 seconds after the start of the injection, which means all these participants received a complete dose. Additionally, we note that the intend- to- market label for the dual chamber AI includes raised lettering that may mitigate the slipperiness compared to the glossy label that was used for the validation study. 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.
- Lift the pen up
- Throw away (dispose of) the pen and cap
- Knowledge task assessments:
  - "Is there anyone who should not have access to this pen? If so, who?" Correct answer: "Keep DRUG NAME pen and all medicines out of the reach of children."
  - "Where should you keep the pen when you return from the pharmacy?" Correct answer: "Store DRUG NAME pen in the refrigerator between 36°F and 46°F (2°C and 8°C)."
  - [If participants state only that they would store it in the fridge] "How long can you store it at room temperature?" Correct answer: "DRUG NAME can be stored at room temperature up to 77°F (25°C) for a single period up to 90 days."
  - "Would you remove the pen from its box before storing it, or leave the pen in its box?" Correct answer: "Store DRUG NAME pen in the original carton to protect it from light."
  - "Should you freeze the medicine or not?" Correct answer: "Do not freeze the DRUG NAME pen."
  - "Is it OK if the pen gets wet, or not?" Correct answer: "Do not: directly expose the pen to liquids."
  - "What would you do after removing it from the refrigerator?" Correct answer: "Take the DRUG NAME carton out of the refrigerator and let it come to room temperature for 30-45 minutes before starting Step 2."

- “Is it OK or not OK to do something to warm up the pen?” Correct answer: “Do not heat the DRUG NAME pen.”
- “How do you know if the pen is OK to use or not?” Correct answer: “Check the pen for the following: The pen has not been dropped and is not damaged or cracked. The lyophilized powder is white and not dissolved.”
- “What should you check the mixed medicine for?” Correct answer: “Check to see if the dissolved medicine is clear and colorless to slightly yellow and does not contain particles.”
- “How long after mixing the medicine do you need to use it?” Correct answer: “After the medicine has dissolved, it should be used within 4 hours. During this time, it should be kept at room temperature (up to 77°F (25°C)). If you have not used it within 4 hours, throw it away (dispose of it).”
- “Imagine you just pushed the pen down to start an injection, but the orange rod did not appear fully or at all. What does this mean?” Correct answer: “Check inspection window to make sure orange rod and gray rod have stopped. This means the injection has completed. After removing the pen, look for the orange rod in the window as a way to tell that the dose has not been given. If the orange rod does not appear, contact [helpline number].” There were 11 use errors observed in the knowledge check task. The root cause analysis indicated that the use errors were due to confusion and misinterpreting IFU Step 15’s note because it first says, “*It is normal that the orange rod does not cover the whole inspection window...*” but then says, “*In case the orange rod is not visible throw away the pen and use a new one*”. Based on the use errors and subjective feedback, Galderma changed the phrase, “*In case*” to “*If the*” in the abovementioned step 15 instruction to clarify the meaning and language. We acknowledge Galderma’s mitigation strategies and based on review of the user interface, we did not identify any additional mitigations to address these use issues and have no recommendations at this time.
- “What should you avoid doing with your used sharps container?” Correct answer: “Do not: recycle your used sharps container.”
- “Imagine you just injected your dose. How should you track when to take your next dose?” Correct answer: “Mark your calendar ahead of time to remember when to take DRUG NAME.”
- “What is the product name?”

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OLUWAMUREWA OGUNTIMEIN on behalf of LISA HUANG  
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07/30/2024 10:21:49 AM

JASON A FLINT on behalf of ARIANE O CONRAD  
07/30/2024 11:45:33 AM

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07/30/2024 12:55:14 PM

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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\*\*\*

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|                                          |                                                  |
|------------------------------------------|--------------------------------------------------|
| Date of This Review:                     | July 3, 2024                                     |
| Requesting Office or Division:           | Division of Dermatology and Dentistry (DDD)      |
| Application Type and Number:             | BLA 761390                                       |
| Product Name, Dosage Form, and Strength: | Nemludio (nemolizumab-ilto) for injection, 30 mg |
| Applicant Name:                          | Galderma Laboratories, L.P.                      |
| FDA Received Date:                       | June 26, 2024                                    |
| TTT ID #:                                | 2023-7476-2                                      |
| DMEPA 1 Safety Evaluator:                | Madhuri R. Patel, PharmD                         |
| DMEPA 1 Team Leader:                     | Yevgeniya Kogan, PharmD, BCSCP                   |

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## 1 PURPOSE OF MEMORANDUM

Galderma Laboratories, L.P. submitted revised container labels and carton labeling received on June 26, 2024 for Nemluvio. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Nemluvio (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.<sup>a</sup>

## 2 CONCLUSION

Galderma Laboratories, L.P. implemented all of our recommendations and we have no additional recommendations at this time.

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

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<sup>a</sup> Patel, M. Label and Labeling Review Memo for Nemluvio (BLA 761390). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUN 11. TTT ID: 2023-7476-1.

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MADHURI R PATEL  
07/03/2024 01:47:55 PM

YEVGENIYA M KOGAN  
07/05/2024 08:02:24 AM

## Clinical Inspection Summary

|                                   |                                                                                                                                                                                                                                                        |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Date</b>                       | 6/27/2024                                                                                                                                                                                                                                              |
| <b>From</b>                       | Stephanie Coquia, MD<br>Michele Fedowitz, MD, Team Leader<br>Jenn Sellers, MD, PhD, Branch Chief<br>Good Clinical Practice Assessment Branch (GCPAB)<br>Division of Clinical Compliance Evaluation (DCCE)<br>Office of Scientific Investigations (OSI) |
| <b>To</b>                         | Hamid Tabatabai, MD, Clinical Reviewer<br>David Kettl, MD, Clinical Team Leader<br>Kimberle Searcy, Regulatory Project Manager<br>Division of Dermatology and Dentistry (DDD)                                                                          |
| <b>BLA #</b>                      | 761390                                                                                                                                                                                                                                                 |
| <b>Applicant</b>                  | Galderma Laboratories, L.P.                                                                                                                                                                                                                            |
| <b>Drug</b>                       | Nemolizumab                                                                                                                                                                                                                                            |
| <b>NME (Yes/No)</b>               | Yes                                                                                                                                                                                                                                                    |
| <b>Therapeutic Classification</b> | Interleukin-31 receptor alpha antagonist                                                                                                                                                                                                               |
| <b>Proposed Indication</b>        | For the treatment of prurigo nodularis                                                                                                                                                                                                                 |
| <b>Consultation Request Date</b>  | 1/31/2024                                                                                                                                                                                                                                              |
| <b>Summary Goal Date</b>          | 6/30/2024                                                                                                                                                                                                                                              |
| <b>Action Goal Date</b>           | 8/12/2024                                                                                                                                                                                                                                              |
| <b>PDUFA Date</b>                 | 8/12/2024                                                                                                                                                                                                                                              |

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Galderma Laboratories, L.P., submitted clinical data for nemolizumab injection for the treatment of prurigo nodularis (PN) from Studies SPR.202685 (NCT04501666) and SPR.203065 (NCT04501679).

Four clinical investigators (Drs. Staender, Legat, Reich, and Paul) were inspected. The inspections did not find significant concerns regarding the study conduct or oversight of the clinical trials or Good Clinical Practice (GCP) or regulatory compliance, and based on the results of these inspections, the data generated by the inspected clinical investigators appear acceptable in support of the proposed indication.

### II. BACKGROUND

Galderma Laboratories, L.P. seeks approval of a biologics license application (BLA) for nemolizumab injection. In support of the BLA, the Applicant submitted clinical data from two phase 3 studies, SPR.202685 and SPR.203065. The following is a summary of the study protocols and key study information relevant to the clinical inspections.

## Study Design

These were phase 3, multicenter, double-blind, placebo-controlled, randomized, parallel-group studies designed to evaluate the safety and efficacy of nemolizumab in subjects with PN. Subjects were treated for 16 weeks (SPR.203065) or 24 weeks (SPR.202685).

## Objectives and Endpoints

The primary objective of each study was to assess the efficacy of nemolizumab compared to placebo in adult subjects with PN after 16 weeks of treatment.

The primary efficacy endpoints were:

- The proportion of subjects with an improvement of  $\geq 4$  from baseline in the Peak Pruritus Numeric Rating Scale (PP NRS) at Week 16
- The proportion of subjects with an Investigator's Global Assessment (IGA) success at Week 16, with success defined as IGA of 0 [clear] or 1 [almost clear] and a  $\geq 2$ -point improvement from baseline.

## Key Eligibility Criteria

- $\geq 18$  years of age
- Clinical diagnosis of PN for at least 6 months
- Severe pruritus based on the PP NRS
- None of the following:
  - Body weight  $< 30$  kg
  - Chronic pruritus from another active condition other than PN not adequately treated
  - Unilateral lesions of PN
  - History of or current confounding skin condition
  - Requiring rescue therapy for PN during the screening period or expected to require rescue therapy within 4 weeks following the baseline visit
  - Active atopic dermatitis within the past 3 months
  - Receipt of restricted prior treatments within a specific timeframe before the baseline visit
  - Neuropathic or psychogenic pruritus
  - Previous participation in a clinical study with nemolizumab

## Study Conduct

For Study SPR.202685, 77 sites enrolled at least one subject. The first subject was randomized October 21, 2020, and the last subject visit was February 21, 2023. A total of 286 subjects were randomized (190 nemolizumab subjects and 96 placebo subjects).

For Study SPR.203065, 55 sites enrolled at least one subject. The first subject was randomized October 29, 2020, and the last subject visit was March 30, 2022. A total of 274 subjects were randomized (183 nemolizumab subjects and 91 placebo subjects).

## RESULTS

### 1. **Dr. Franz J. Legat (SPR.202685, Site 5471)**

Medizinische Universität Graz Universitätsklinik,  
Auenbruggerplatz 8  
Graz, Styria, 8036 Austria

Inspection Dates: May 13 – 16, 2024

This investigator was inspected as a routine PDUFA inspection for Study SPR.202685. This was the first FDA inspection for this investigator.

Subject-related paper and electronic records for the 19 screened subjects (15 enrolled subjects) were reviewed and included: medical records, progress notes, laboratory reports, informed consent forms (ICFs), IGA questionnaire forms, subject PDFs, case report forms (CRFs), investigational product (IP) accountability records, and documentation of concomitant medications, eligibility, and adverse events (AEs). The records were also reviewed for protocol adherence and AE reporting.

Study-related documents reviewed included: the protocol and amendments, investigator brochures, ethics committee approvals and correspondence, sponsor correspondence, monitoring reports, financial disclosures, signed investigator agreements, site signature and responsibility logs, IP accountability records, notes to file, and site and rater training documentation.

Information in the source records, including data for the primary efficacy endpoints IGA and PP NRS, was consistent with the data submitted in the BLA. There was no underreporting of concomitant or rescue medications, AEs, or protocol deviations.

Due to scheduling issues, six of 16 subjects had the same evaluator for the baseline and Week 16 assessments. While it was preferred to have the same evaluator for all timepoints, it was not specifically required. All evaluators underwent the same required study-related rater training and met the required qualifications.

### 2. **Dr. Sonja Staender (SPR.202685, Site 5307)**

University Hospital Munster, Von-Esmarch-Str. 58  
Munster, North Rhine-Westphalia, 48149 Germany

Inspection Dates: May 13 – 17, 2024

This investigator was inspected as a routine PDUFA inspection for Study SPR.202685. This was the first FDA inspection for this investigator.

Subject-related paper and electronic records for the 21 subjects screened (18 subjects randomized) were reviewed and included: CRFs, IP accountability records, eligibility

checklists, source IGA worksheets and PP NRS data, laboratory reports, progress notes, and documentation of randomization assignments, informed consent, subject visits, procedures, concomitant medications, vital sign and ECG measurement, medical history, and AEs.

Study-related documents reviewed included: IP accountability records, signed investigator agreements, sponsor correspondence, ethics committee correspondence, training records, the site delegation of authority and screening and enrollment logs, the site-level informed consent and protocol deviation logs, financial disclosure forms, and monitoring records.

Information in the source records, including data for the primary efficacy endpoints of IGA and PP NRS, was consistent with the data submitted in the BLA. There was no underreporting of AEs or protocol deviations.

It was observed that one evaluator performed IGA assessments before receiving study-specific training and certification. The affected baseline and Week 16 IGA assessments provided by the evaluator are listed below.

| Subject ID | Arm         | Timepoint Affected | Responder Status |
|------------|-------------|--------------------|------------------|
| (b) (6)    | Placebo     | Week 16            | No               |
|            | Nemolizumab | Week 16            | No               |
|            | Nemolizumab | Week 16            | No               |
|            | Placebo     | Week 16            | No               |
|            | Placebo     | Baseline           | No               |
|            | Nemolizumab | Baseline           | Yes              |
|            | Placebo     | Baseline           | No               |
|            | Nemolizumab | Baseline           | No               |
|            | Nemolizumab | Week 16            | No               |
|            | Placebo     | Baseline           | No               |

*Reviewer's Comment: The issue of evaluators performing assessments without meeting study certification requirements was observed study-wide and was reported in the clinical study report for Study SPR.202685 (pages 70-71). At this site, the rater in question provided a training certificate for IGA for PN for a previous study, and Dr. Staender provided a note-to-file stating that the rater had previous clinical experience applying IGA to PN.*

Only two out of 18 subjects had the same evaluator for the baseline and Week 16 assessments. While it was preferred to have the same evaluator for all timepoints, it was not specifically required. Aside for the issue described above, all other evaluators at the site underwent the same required study-related training and met the required qualifications.

### 3. Dr. Adam Reich (SPR.203065, Site 5495)

Kliniczny Szpital Wojewodzki Nr 1 Im, Fryderyka Chopina W  
Rzeszowie, Klinka Dermatologii, Ul. Fryderyka Szopena 2  
Rzeszoz, Podkarpackie, 35-055 Poland

Inspection Dates: May 6 – 10, 2024

This investigator was inspected as a routine PDUFA inspection for Study SPR.203065. This was the first FDA inspection for this investigator.

Subject-related paper and electronic records for the 19 screened (14 enrolled) subjects were reviewed and included: IP accountability records, ICFs, CRFs, eligibility criteria checklists, laboratory reports, medical records, patient-reported outcome data, progress notes, study and IGA worksheets, and documentation of randomization assignments, AEs, discontinuations, and concomitant medications.

Study-related documents reviewed included: signed investigator agreements, site delegation and screening and enrollment logs, training records, sponsor and ethics committee correspondence, pharmacy and laboratory manuals, financial disclosure forms, IP accountability logs, and monitoring reports.

Information in the source records, including data for the primary efficacy endpoints of IGA and PP NRS, was consistent with the data submitted in the BLA. There was no underreporting of AEs or protocol deviations.

Due to rater availability, eight of the 14 enrolled subjects had the same evaluator for the baseline and Week 16 IGA assessments. Both evaluators underwent the study-required training.

**4. Dr. Carle Paul (SPR.203065, Site 5525)**

Hopital Larrey – Chu De Toulouse – Service de Dermatologie, 24  
Chemin de Pouvoirville  
Toulouse, 31059 France  
France

Inspection Dates: May 21 – 24, 2024

This investigator was inspected as a routine PDUFA inspection for Study SPR.203065. This was the first FDA inspection for this investigator.

Subject-related paper and electronic records for all nine enrolled subjects and one screen-failure subject were reviewed and included: signed ICFs, primary efficacy endpoint source data (IGA and PP NRS), and documentation of eligibility, AEs, concomitant medications, safety assessments, IP accountability, and protocol deviations.

Study-related documents reviewed included: the protocol, screening and enrollment log, subject identification log, sponsor correspondence, ethics committee correspondence, financial disclosure forms, training records, pharmacy records, monitoring records, signed investigator agreements, and regulatory approvals.

Information in the source records, including those for the primary efficacy endpoints IGA and PP NRS, was consistent with the data submitted in the BLA. There was no underreporting of

concomitant medications, AEs, or significant protocol deviations.

Due to scheduling issues, only five out of the nine enrolled subjects had the same evaluator for the baseline and Week 16 assessments. While it was preferred to have the same evaluator for all timepoints, it was not specifically required. All evaluators were dermatologists who underwent the same required study-related training, testing, and certification process.

{ 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/Jill Lindstrom  
Review Division/Project Manager/Kimberle Searcy  
Review Division/Cross Discipline Team Lead/David Kettl  
Review Division/Clinical Reviewer/Hamid Tabatabai  
OSI/Office Director/David Burrow  
OSI/GCP Program Analysts/Yolanda Patague

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MICHELE B FEDOWITZ  
06/27/2024 09:14:17 AM

JENN W SELLERS  
06/27/2024 09:16:31 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: June 21, 2024

To: Kim Searcy  
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)**

From: Maria Nguyen, MSHS, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Montherson Saint Juste, PharmD, MS  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

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

Drug Name (established name): NEMLUVIO (nemolizumab-xxxx)

Dosage Form and Route: for injection, for subcutaneous use

Application Type/Number: BLA 761390

Applicant: Galderma Laboratories, L.P.

## 1 INTRODUCTION

On December 12, 2023, Galderma Laboratories, L.P., submitted for the Agency's review an original Biologics License Application (BLA) 761390 NEMLUVIO (nemolizumab-xxxx) lyophilized powder solution for injection. The proposed indication is treatment of prurigo nodularis.

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 February 8, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for NEMLUVIO (nemolizumab-xxxx) lyophilized powder solution for injection, for subcutaneous use.

## 2 MATERIAL REVIEWED

- Draft NEMLUVIO (nemolizumab-xxxx) PPI received on December 12, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 11, 2024.
- Draft NEMLUVIO (nemolizumab-xxxx) Prescribing Information (PI) received on December 12, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 11, 2024.
- Approved DUPIXENT (dupilumab) comparator labeling dated April 12, 2024.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%.

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 and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU 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 IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022).
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The PPI and IFU 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 IFU are 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 IFU.

Please let us know if you have any questions.

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MARIA T NGUYEN

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DMPP-OPDP review of nemolizumab-xxxx (NEMLUVIO) BLA 761390 PPI and IFU

MONTHERSON L SAINT JUSTE

06/21/2024 02:44:25 PM

LASHAWN M GRIFFITHS

06/21/2024 03:34:30 PM

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

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

## Memorandum

**Date:** June 20, 2024

**To:** Kimberle Searcy, Regulatory Project Manager, Division of  
Dermatology and Dentistry (DDD)

Hamid Tabatabai, Clinical Reviewer, DDD

Matthew White, Associate Director for Labeling, DDD

**From:** Montherson L. Saint Juste, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** James Dvorsky, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for NEMLUVIO® (nemolizumab-xxxx) for  
injection, for subcutaneous use

**BLA:** 761390

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**Background:**

In response to DDD's consult request dated February 8, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original BLA submission for NEMLUVIO® (nemolizumab-xxxx).

**PI/Medication Guide/IFU:**

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on June 11, 2024, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide/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 emailed to OPDP on June 18, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Montherson L. Saint Juste at 301-796-1200 or Montherson.SaintJuste@fda.hhs.gov.

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MONTHERSON L SAINT JUSTE  
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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\*\*\*

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|                                          |                                                               |
|------------------------------------------|---------------------------------------------------------------|
| Date of This Review:                     | June 11, 2024                                                 |
| Requesting Office or Division:           | Division of Dermatology and Dentistry (DDD)                   |
| Application Type and Number:             | BLA 761390                                                    |
| Product Name, Dosage Form, and Strength: | Nemluvio (nemolizumab-xxxx) <sup>a</sup> for injection, 30 mg |
| Applicant Name:                          | Galderma Laboratories, L.P.                                   |
| FDA Received Date:                       | May 22, 2024                                                  |
| TTT ID #:                                | 2023-7476-1                                                   |
| DMEPA 1 Safety Evaluator:                | Madhuri R. Patel, PharmD                                      |
| DMEPA 1 Team Leader:                     | Yevgeniya Kogan, PharmD, BCSCP                                |

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<sup>a</sup> The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder nemolizumab-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

## 1 PURPOSE OF MEMORANDUM

Galderma Laboratories, L.P. submitted revised container labels and carton labeling received on May 22, 2024 for Nemluvio. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Nemluvio (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.<sup>b</sup>

## 2 CONCLUSION

The container labels and carton labeling are unacceptable from a medication error perspective. Per Applicant, “The format “YY/MM” for the expiration date has been included in all packaging components”. We continue to recommend 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. (b) (4)



## 3 RECOMMENDATIONS FOR GALDERMA LABORATORIES, L.P.

### A. General Comments (Container Label(s) & Carton Labeling)

1. As currently presented, the container labels and carton labeling show the expiration date format as YYYY/MM. However, you indicate in your response the expiration date format is “YY/MM”. Please note FDA recommends the expiration date appear in a four-digit year ‘YYYY’ and 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.

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<sup>b</sup> Patel, M. Label and Labeling Review for Nemluvio (BLA 761390). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAY 10. TTT ID: 2023.

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MADHURI R PATEL  
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YEVGENIYA M KOGAN  
06/12/2024 08:56:21 AM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

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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 Pediatrics and Maternal Health Review**

**Date:** 6/5/2024                                      **Date consulted:** 3/26/24

**From:** Kristie Baisden, DO, Medical Officer, Maternal Health  
Division of Pediatrics and Maternal Health (DPMH)

**Through:** Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH  
  
Lynne P. Yao, MD, OND, Division Director, DPMH

**To:** Division of Dermatology and Dentistry (DDD)

**Drug:** Nemluvio (nemolizumab-ilto)

**BLA:** 761390 (b) (4)

**Applicant:** Galderma Laboratories

**Subject:** Pregnancy and Lactation Labeling and Postmarketing Requirements

**Proposed  
Indication:**

- BLA 761390: Treatment of adult patients with prurigo nodularis

(b) (4)

**Materials Reviewed:**

- BLA 761390 submitted on 12/12/2023

(b) (4)

- DPMH PLLR Review of Bimzelx (bimekizumab) BLA 761151 by Kristie Baisden, DO, dated 2/3/21, DARRTs Reference ID: 4741087.<sup>1</sup>
- Addendum DPMH PLLR and PMR Review of Bimzelx (bimekizumab) BLA 761151 resubmission by Kristie Baisden, DO, dated 4/25/23, DARRTs Reference ID: 5163918.<sup>1</sup>
- DPMH PLLR review of Dupixent (dupilumab) BLA 761055 by Christos Mastroyannis, MD, dated 1/13/17, DARRTs Reference ID: 4041992.<sup>1</sup>

**Consult Question:** “DDD requests Maternal Health Team review of subsections 8.1 and 8.2 of Nemluvio (nemolizumab-ilto) labeling”

## INTRODUCTION

On December 12, 2023, the applicant, Galderma Laboratories, submitted an original BLA (761390) for nemolizumab-ilto for the treatment of adult patients with prurigo nodularis. (b) (4)

On January 30, 2024 and March 26, 2024, the Division of Dermatology and Dentistry (DDD) consulted the Division of Pediatrics and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections and to provide recommendations for postmarketing requirements (PMRs).

## BACKGROUND

### Drug Characteristics (based on currently proposed labeling)

- *Mechanism of action:* humanized IgG2 monoclonal antibody that inhibits IL-31 signaling by binding selectively to IL-31 RA. IL-31 is a cytokine that is involved in pruritis, inflammation, epidermal dysregulation, and fibrosis.
- *Dosage and administration:*
  - Prurigo Nodularis
    - Adult patients weighing less than 90 kg: initial dose of 60 mg followed by 30 mg every 4 weeks.
    - Adult patients weighing 90 kg or more: initial dose of 60 mg followed by 60 mg every 4 weeks.

- *Molecular weight:* 144,000 Daltons
- *Half-life:* 18.9 days

<sup>1</sup> DPMH consults for Bimzelx (bimekizumab) BLA (b) (4) and Dupixent (dupilumab) BLA 761055 were reviewed as background and are not being relied upon for any decisions regarding approval of Nemluvio, including its labeling. DPMH’s recommendations for Nemluvio labeling discussed below are based on Nemluvio development program and information from the published literature that is not specific to a particular product.

### Identified safety concerns (based on currently proposed labeling)

- *Contraindications*: known hypersensitivity to nemolizumab-ilto
- *Warnings and Precautions*: hypersensitivity reactions; complete all age-appropriate vaccinations and avoid use of live vaccines in patients treated with nemolizumab-ilto
- *Adverse reactions*: dermatitis atopic, eczema, eczema nummular, and headache.

### Epidemiology of (b) (4) Prurigo Nodularis (PN)<sup>2</sup>

(b) (4)

- *Prurigo Nodularis*: In the US, the estimated prevalence of PN is 72 per 100,000 persons.<sup>5</sup> PN can occur in all age groups without sex predilection but primarily affects older adults.

## **REVIEW**

### ***PREGNANCY***

#### Nonclinical Experience

In an enhanced pre- and postnatal development study, subcutaneous doses up to 25 mg/kg nemolizumab-ilto were administered to pregnant cynomolgus monkeys once every two weeks during organogenesis to parturition. No maternal or embryofetal toxicities were observed at doses up to 25 mg/kg (36 times the MRHD, based on AUC comparison). Early postnatal death occurred in the offspring of one control monkey and 3 monkeys at 25 mg/kg (36 times the MRHD, based on AUC comparison). The clinical significance of this nonclinical finding is unknown.

Nemolizumab-ilto was administered subcutaneously to the offspring at doses up to 25 mg/kg (122 times the MRHD, based on AUC comparison), once every 2 weeks for 6 months, starting from postnatal day 35. No adverse effects were noted in the remaining offspring. For additional details, refer to the Nonclinical Review by Jianyong Wang, PhD.

#### Clinical Trials

Pregnant women were excluded from clinical trials during the development program for nemolizumab-ilto. A total of 10 pregnancies have occurred in female participants during any nemolizumab-ilto study participation. Nemolizumab-ilto was discontinued at identification of pregnancy as per the study protocol. Pregnancy outcomes included: normal livebirth (n=3), unknown (n=3), spontaneous abortion (n=2), and pregnancy termination (n=2). No congenital anomalies were reported and the indications for the pregnancy terminations were not specified.

#### Review of Literature

##### *Applicant's Review of Literature*

The applicant did not perform a literature search related to nemolizumab-ilto use and pregnancy.

<sup>2</sup> UpToDate topics "Prurigo Nodularis" (b) (4) accessed 5/15/2024.

(b) (4)

<sup>5</sup> Huang AH, et al. Real-world Prevalence of Prurigo Nodularis and Burden of Associated Diseases. J Invest Dermatol. 202; 140(2). 2019.

### *DPMH Review of Literature*

This Reviewer performed a search in PubMed, Embase, Micromedex<sup>6</sup>, TERIS<sup>7</sup>, Reprotox<sup>8</sup>, and Briggs<sup>9</sup> to find relevant articles related to the use of nemolizumab-ilto during pregnancy. Search terms included “nemolizumab-ilto” AND “pregnancy,” “pregnant women,” “birth defects,” “congenital malformations,” “stillbirth,” “spontaneous abortion,” and “miscarriage.” No relevant articles were identified.

### ***LACTATION***

#### Nonclinical Experience

Nemolizumab-ilto was detected in breast milk of monkeys in the enhanced pre- and postnatal development study mean nemolizumab-ilto concentrations in milk were approximately 0.3 – 0.5% of the maternal plasma levels from lactation day 7 to 63. For additional details, refer to the Nonclinical Review by Jianyong Wang, PhD.

#### Clinical Trials

Lactating women were excluded from clinical trials during the development program for nemolizumab-ilto. No lactation exposure cases were reported during clinical development.

#### Review of Literature

##### *Applicant's Review of Literature*

The applicant did not perform a literature search related to nemolizumab-ilto use and lactation.

### *DPMH Review of Literature*

This Reviewer performed a search in PubMed, Embase, Micromedex<sup>6</sup>, TERIS<sup>7</sup>, Reprotox<sup>8</sup>, and Briggs<sup>9</sup>, *Medications and Mothers' Milk*<sup>10</sup>, and LactMed<sup>11</sup> to find relevant articles related to the use of nemolizumab-ilto during lactation. Search terms included “nemolizumab-ilto” AND “breastfeeding” or “lactation.” No relevant articles were identified.

### ***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

#### Nonclinical Experience

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of nemolizumab-ilto. No effects on fertility parameters as reproductive organ morphology, menstrual cycle length, or sperm/testicular analysis were observed in male or female sexually mature cynomolgus monkeys that were administered nemolizumab-ilto at subcutaneous doses up to 25 mg/kg once every two weeks for 6 months (53 times the MRHD, based on AUC comparison). The

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<sup>6</sup> Truven Health Analytics information, <http://www.micromedexsolutions.com/> Accessed 4/17/24.

<sup>7</sup> TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 4/17/24.

<sup>8</sup> Reprotox® Website: [www.Reprotox.org](http://www.Reprotox.org). REPROTOX® system Accessed 4/17/24.

<sup>9</sup> Briggs, GG, Freeman, RK, & Yaffe, SJ. (2017). *Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk*. Philadelphia, Pa, Lippincott Williams & Wilkins.

<sup>10</sup> Hale, Thomas (2020) *Medications and Mothers' Milk* online. Accessed 4/17/24.

<sup>11</sup> <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. LactMed is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 4/17/24.

monkeys were not mated to evaluate fertility. For additional details, refer to the Nonclinical Review by Jianyong Wang, PhD.

### Review of Literature

#### *Applicant's Review of Literature*

The applicant did not perform a literature search related to nemolizumab-ilto use and fertility.

#### *DPMH Review of Literature*

This Reviewer performed a search in PubMed, Embase, Reprotox<sup>8</sup> to find relevant articles related to the use of nemolizumab-ilto and effects on fertility. Search terms included “nemolizumab-ilto” AND “fertility,” “infertility,” “contraception,” and “oral contraceptives.” No relevant articles were identified.

## **DISCUSSION AND CONCLUSIONS**

### Pregnancy

Pregnant women were excluded from clinical trials with nemolizumab-ilto during the clinical development program. A total of 10 pregnancy exposure cases were reported with outcomes including: normal livebirth n=3, unknown n=3, pregnancy termination n=2, and spontaneous abortion n=2. Overall, these limited available human data are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Therefore, DPMH recommends subsection 8.1 of Nemluvio labeling include a Risk Summary statement to summarize the limited available human pregnancy exposure data from case reports during the clinical development program.

There are no available pregnancy pharmacokinetic (PK) data for nemolizumab-ilto to inform evidence-based dosing recommendations during pregnancy. There are also no available human data regarding the amount of nemolizumab-ilto placental transfer, nemolizumab-ilto levels at birth in infants exposed in utero, or the duration of persistence of nemolizumab-ilto in infant serum after delivery. Considering nemolizumab-ilto is an IgG2 monoclonal antibody, placental transfer is presumed based on published literature for other monoclonal antibodies.<sup>12</sup> Published literature for other monoclonal antibodies indicate the amount of placental transfer varies widely and the half-life observed in adults may not be predictive of the half-life or the duration of pharmacodynamic effects in the in utero exposed infant.<sup>12</sup>

Given the lack of available human PK and placental transfer data specific to nemolizumab-ilto use in pregnancy, DPMH recommends including language in subsection 8.1 similar to the Agency's approach to PLLR labeling for other monoclonal antibodies. Pregnancy labeling should include information under Risk Summary and Clinical Considerations about the active transport of monoclonal antibodies across the placenta, the potential for immunosuppression in the *in utero* exposed infant, and the risks and benefits that should be considered prior to administration of live vaccines. The labeling should include a statement that a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown, however, a minimum of 3 months after birth should be considered based on the half-life of the product. DPMH confirmed with the DDD Clinical Team the appropriateness of including this language in

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<sup>12</sup> Soh MC, et al. The Use of Biologics for Autoimmune Rheumatic Diseases in Fertility and Pregnancy. *Obstetric Medicine* 2020, Vol. 13 (1) 5-13.

labeling for nemolizumab-ilto considering the related Warning and Precaution regarding live vaccine administration in adults prior to treatment.<sup>13</sup>

Nemolizumab-ilto is proposed for treatment of conditions that affect females of reproductive potential (including during pregnancy), and current data are insufficient to inform women regarding nemolizumab-ilto use during pregnancy. There is a potential safety risk in fetuses exposed to nemolizumab-ilto because fetuses would not otherwise be exposed to this product except through maternal exposure. Data in animal studies are unclear about the risk to human fetuses. Therefore, DPMH recommends a postmarketing requirement (PMR) for the applicant to conduct a pregnancy exposure registry and a complementary study of a different design (such as a claims database study). Refer to the FDA draft Guidance for Industry Postapproval Pregnancy Safety Studies, published May 2019. DPMH also recommends including language regarding the planned postapproval pregnancy exposure registry in subsection 8.1 and section 17 of labeling along with the applicant's pharmacovigilance contact information. After the pregnancy registry study protocol has been finalized, the applicant should submit a prior approval supplement (PAS) to update PLLR labeling with the established pregnancy registry contact information.

#### Lactation

Lactating women were excluded from clinical trials with nemolizumab-ilto and no lactation exposure cases were reported during clinical development. There are no available data on the presence of nemolizumab-ilto in human milk, the effects on the breastfed infant, or the effects on milk production. The molecular weight for nemolizumab-ilto is 144,000 Daltons, and according to breastfeeding experts, the amount of monoclonal antibody in human milk, if any, is expected to be low. Considering nemolizumab-ilto is an IgG2 monoclonal antibody, DPMH recommends including language in subsection 8.2 of Nemluvio labeling similar to the Agency's approach to PLLR labeling for other monoclonal antibodies. Lactation labeling should include information under Risk Summary that "maternal IgG and monoclonal antibodies are known to be present in human milk" as well as the "the effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to nemolizumab-ilto are unknown." The following risk/benefit statement should also be included: "the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Nemluvio and any potential adverse effects on the breastfed infant from Nemluvio or from the underlying maternal condition."

Nemolizumab-ilto is proposed for treatment of conditions that would be expected to be seen in females of reproductive potential (including during lactation), and there are no available data to inform women regarding nemolizumab-ilto use during lactation. Therefore, DPMH recommends issuing a PMR for the applicant to conduct a clinical lactation study with nemolizumab-ilto to inform labeling. Refer to the FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design, published May 2019.

#### Females and Males of Reproductive Potential

There are no available human data on the effects of nemolizumab-ilto on male or female fertility. Animal fertility studies do not indicate any adverse effects. Therefore, DPMH recommends omitting subsection 8.3 from labeling for Nemluvio.

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<sup>13</sup> DPMH personal communication with DDD Clinical Team Leader, David Kettl, MD, dated 6/5/24.

## PMR RECOMMENDATIONS

(b) (4)

### *Reviewer's Comment*

*Regarding issuing PMRs for transplacental transfer studies, DPMH is planning a workshop and aims to establish a policy which will be developed based on the results of the workshop.*

## **LABELING RECOMMENDATIONS**

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

### **DPMH Proposed Nemluvio (nemolizumab-ilto) Pregnancy and Lactation Labeling**

#### **FULL PRESCRIBING INFORMATION**

#### **8 USE IN SPECIFIC POPULATIONS**

##### **8.1 Pregnancy**

(b) (4)

### Risk Summary

Available data on nemolizumab-ilto use in pregnant women exposed during clinical trials are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Transport of human IgG antibody across the placenta increases as pregnancy progresses and peaks during the third trimester; therefore, Nemludio may be transferred from the mother to the developing fetus (*see Clinical Considerations*). In an enhanced pre- and postnatal development study in cynomolgus monkeys, when nemolizumab-ilto was administered subcutaneously during organogenesis to parturition, an increase in early postnatal death was observed at a dose 36 times the maximum recommended human dose (MRHD) (*see Data*). The clinical significance of this nonclinical finding is unknown.

The background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20% respectively.

### Clinical Considerations

#### *Fetal/Neonatal Adverse Reactions*

Because nemolizumab-ilto may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants exposed to Nemludio in utero. There are no data regarding infant serum levels of nemolizumab-ilto at birth and the duration of persistence of nemolizumab-ilto in infant serum after birth. Although a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown, a minimum of 3 months after birth should be considered because of the half-life of the product.

### Data

#### *Animal Data*

In an enhanced pre- and postnatal development study, subcutaneous doses up to 25 mg/kg nemolizumab-ilto were administered to pregnant cynomolgus monkeys once every two weeks during organogenesis to parturition. No maternal or embryofetal toxicities were observed at doses up to 25 mg/kg (36 times the MRHD, based on AUC comparison). Early postnatal death occurred in the offspring of one control monkey and 3 monkeys at 25 mg/kg (36 times the MRHD, based on AUC comparison). The clinical significance of this nonclinical finding is unknown. Nemolizumab-ilto was administered subcutaneously to the offspring at doses up to 25 mg/kg (122 times the MRHD, based on AUC comparison), once every 2 weeks for 6 months, starting from postnatal day 35. No adverse effects were noted in the remaining offspring.

## 8.2 Lactation

### Risk Summary

There are no data on the presence of nemolizumab-ilto in human milk, the effects on the breastfed infant, or the effects on milk production. Nemolizumab-ilto was detected in breast milk of monkeys (*see Data*). Endogenous maternal IgG and monoclonal antibodies are transferred in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to nemolizumab-ilto are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Nemluvio and any potential adverse effects on the breastfed infant from Nemluvio or from the underlying maternal condition.

### Data

Nemolizumab-ilto was detected in breast milk of monkeys in the enhanced pre- and postnatal development study following subcutaneous doses of up to 25 mg/kg once every two weeks during organogenesis to parturition. The mean nemolizumab-ilto concentrations in milk were approximately 0.3 – 0.5% of the maternal plasma levels from lactation day 7 to 63. The concentration of nemolizumab-ilto in animal milk does not necessarily predict the concentration of drug in human milk.

## 17 PATIENT COUNSELING INFORMATION

(b) (4)



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**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.**  
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/s/  
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KRISTIE W BAISDEN  
06/05/2024 05:17:50 PM

TAMARA N JOHNSON  
06/06/2024 10:33:51 AM

LYNNE P YAO  
06/06/2024 10:43:42 AM

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## 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\*\*\*

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|                                          |                                                               |
|------------------------------------------|---------------------------------------------------------------|
| Date of This Review:                     | May 10, 2024                                                  |
| Requesting Office or Division:           | Division of Dermatology and Dentistry (DDD)                   |
| Application Type and Number:             | BLA 761390                                                    |
| Product Name, Dosage Form, and Strength: | Nemludio (nemolizumab-xxxx) <sup>a</sup> for injection, 30 mg |
| Product Type:                            | Combination Product (Biologic-Device)                         |
| Rx or OTC:                               | Prescription (Rx)                                             |
| Applicant Name:                          | Galderma Laboratories, L.P.                                   |
| FDA Received Date:                       | December 12, 2023 and March 20, 2024                          |
| TTT ID #:                                | 2023-7476                                                     |
| DMEPA 1 Safety Evaluator:                | Madhuri R. Patel, PharmD                                      |
| DMEPA 1 Team Leader:                     | Yevgeniya Kogan, PharmD, BCSCP                                |

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<sup>a</sup> The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder nemolizumab-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

## 1 INTRODUCTION

As part of the approval process for Nemluvio (nemolizumab-xxxx) for injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Nemluvio 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

This section lists the materials considered for our review of BLA 761390.

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

## 3 CONCLUSION

The proposed Nemluvio Prescribing Information (PI), Patient Package Insert (PPI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling may be improved to promote 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 2 and for Galderma Laboratories, L.P. in Section 3. 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 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                                                                                                                                                            |
| Prescribing Information, Medication Guide, Patient Package Inset, Instructions for Use – General Issues |                                                                       |                                                                                                                                               |                                                                                                                                                                           |
| 1.                                                                                                      | The nonproprietary name suffix is denoted by the placeholder ‘-ilto’. | A distinguishable nonproprietary name will facilitate accurate identification of the biological product by healthcare providers and patients. | We recommend replacing ‘-ilto-’ with the placeholder ‘-xxxx’. Replace the placeholder with the conditionally acceptable nonproprietary name suffix when it is determined. |

| Table 2. Identified Issues and Recommendations for the Division of Dermatology and Dentistry (DDD) |                                                                                                          |                                                                                              |                                                                      |
|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
|                                                                                                    | IDENTIFIED ISSUE                                                                                         | RATIONALE FOR CONCERN                                                                        | RECOMMENDATION                                                       |
| Highlights and Full Prescribing Information – Section 2 Dosage and Administration                  |                                                                                                          |                                                                                              |                                                                      |
| 1.                                                                                                 | The dosage and administration section, includes the abbreviation “(Q4W)”.                                | Abbreviations such as “Q4W” can be misinterpreted and pose risk of medication dosing errors. | We recommend removing the “(Q4W)” to avoid confusion.                |
| Full Prescribing Information – Section 16 How Supplied/Storage and Handling                        |                                                                                                          |                                                                                              |                                                                      |
| 1.                                                                                                 | The statement “Each carton contains: 1 single-dose prefilled pen, (b) (4)” may be misleading due (b) (4) | Lack of clarity on the package presentation may lead to confusion on the total contents.     | Consider removing the statement “Each carton contains...” statement. |

## 5 RECOMMENDATIONS FOR GALDERMA LABORATORIES, L.P.

Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors validation study results.

| Table 3. Identified Issues and Recommendations for Galderma Laboratories, L.P.<br>(entire table to be conveyed to Applicant) |                                                                                                                                                   |                                                                                                                                               |                                                                                                                                                                                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                              | IDENTIFIED ISSUE                                                                                                                                  | RATIONALE FOR CONCERN                                                                                                                         | RECOMMENDATION                                                                                                                                                                                                                                                   |
| Container Label(s) and Carton Labeling                                                                                       |                                                                                                                                                   |                                                                                                                                               |                                                                                                                                                                                                                                                                  |
| 1.                                                                                                                           | As currently presented, the placeholder ‘ilto’ for the suffix is present as part of the nonproprietary name on the principal display panel (PDP). | A distinguishable nonproprietary name will facilitate accurate identification of the biological product by healthcare providers and patients. | We note a conditionally acceptable nonproprietary name suffix has not been determined. We recommend replacing ‘-ilto-’ with the placeholder ‘-xxxx’. Replace the placeholder with the conditionally acceptable nonproprietary name suffix when it is determined. |
| 2.                                                                                                                           | As currently presented, the format for the                                                                                                        | We are unable to assess the proposed expiration date                                                                                          | To minimize confusion and reduce the risk for deteriorated                                                                                                                                                                                                       |

Table 3. Identified Issues and Recommendations for Galderma Laboratories, L.P.  
(entire table to be conveyed to Applicant)

|    | IDENTIFIED ISSUE                                                                                       | RATIONALE FOR CONCERN                                                                                                                                                                  | RECOMMENDATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    | expiration date is not defined.                                                                        | format from a medication safety perspective.                                                                                                                                           | drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See <i>Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)</i> . |
| 3. | The linear barcode is missing on the container labels, blister label, and some of the carton labeling. | The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a | Add the product's linear barcode to each individual container label and carton labeling in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

Table 3. Identified Issues and Recommendations for Galderma Laboratories, L.P.  
(entire table to be conveyed to Applicant)

|    | IDENTIFIED ISSUE                                                                                                                                       | RATIONALE FOR CONCERN                                                                                                                                                                                                                                                                                          | RECOMMENDATION                                                                                                                                                                                                       |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                                                                                                                                        | requirement per 21 CFR 201.25(c)(2).                                                                                                                                                                                                                                                                           | will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation). |
| 4. | As currently presented, the container labels, blister labeling, and some of the carton labeling do not include the assigned NDC number or placeholder. | The human-readable NDC is often used for product verification and identification prior to dispensing or administering a drug. It is an important safety feature that is recommended to be prominently displayed on the principal display panel of the container labels, blister labeling, and carton labeling. | We request that you include the NDC number or placeholder on the principal display panel of the container labels, blister labeling, and carton labeling per 21 CFR 201.2.                                            |
| 5. | The route of administration statement contains the word “(b) (4)”.                                                                                     | We reserve the use of the word “(b) (4)” when there is a safety concern or data that supports the product must be given by a specific route.                                                                                                                                                                   | We recommend revising the route of administration statement so that it reads “For subcutaneous use”.<br>(b) (4)                                                                                                      |
| 6. | We were unable to locate the professional sample container labels (b) (4).                                                                             | Not indicating that this is a sample may lead to dispensing errors.                                                                                                                                                                                                                                            |                                                                                                                                                                                                                      |

Table 3. Identified Issues and Recommendations for Galderma Laboratories, L.P.  
(entire table to be conveyed to Applicant)

|                    | IDENTIFIED ISSUE                                                                            | RATIONALE FOR CONCERN                                                                                                                                                          | RECOMMENDATION                                                                                                                                                           |
|--------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Container Label(s) |                                                                                             |                                                                                                                                                                                |                                                                                                                                                                          |
| 1.                 | The prefilled pen container label does not include storage information post reconstitution. | Including information on post-reconstitution storage will inform healthcare providers during product preparation and minimize the risk of administering deteriorated products. | We recommend including post reconstitution (e.g. "Discard unused reconstituted pen after 4 hours." or "After reconstitution, must be used within 4 hours or discarded.") |
| Carton Labeling    |                                                                                             |                                                                                                                                                                                |                                                                                                                                                                          |
| 1.                 |                                                                                             |                                                                                                                                                                                |                                                                                                                                                                          |
|                    |                                                                                             |                                                                                                                                                                                |                                                                                                                                                                          |

(b) (4)

Table 3. Identified Issues and Recommendations for Galderma Laboratories, L.P.  
(entire table to be conveyed to Applicant)

|    | IDENTIFIED ISSUE                                                                                                                                                                                       | RATIONALE FOR CONCERN                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | RECOMMENDATION                                                                                                                                                                                                                                                                                                                                                                                                     |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2. | The product identifier is missing.                                                                                                                                                                     | In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. | We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling. |
| 3. | The terminology within the statement of dosage statement "package insert" is inconsistent with the terminology in the Prescribing Information.                                                         | To ensure consistency with the terminology in the Prescribing Information.                                                                                                                                                                                                                                                                                                                                                                                                                                                | We recommend revising the statement of dosage statement to read, "Recommended Dosage: see Prescribing Information." or "Dosage: see Prescribing Information."                                                                                                                                                                                                                                                      |
| 4. | The space for users to write in the date removed from refrigerator is not located near the room temperature storage information. Additionally, there is no space for end-users to write the beyond-use | Clarity on the storage information will minimize the risk of administering deteriorated products. Additionally, since the product has a different beyond-use date after reconstitution, the container label should have a designated space and                                                                                                                                                                                                                                                                            | Ensure that the line to write the date removed from the refrigerator is located near the room temperature storage instructions.<br><br>Additionally, we recommend including space for end users to write beyond-use date on the container labels (if space                                                                                                                                                         |

| Table 3. Identified Issues and Recommendations for Galderma Laboratories, L.P.<br>(entire table to be conveyed to Applicant) |                                                                              |                                                                                                                   |                                                                                            |
|------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
|                                                                                                                              | IDENTIFIED ISSUE                                                             | RATIONALE FOR CONCERN                                                                                             | RECOMMENDATION                                                                             |
|                                                                                                                              | date which is the date and time the reconstituted product must be discarded. | format for the end-user to write the beyond-use date to minimize the risk of deteriorated drug medication errors. | permits) and carton labeling.<br>For example:<br>Discard after ____/____/____<br>Time_____ |

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Nemluvio received on December 12, 2023 from Galderma Laboratories, L.P..

| Table 4. Relevant Product Information for Nemluvio |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |              |              |           |       |                    |  |  |                |               |              |                    |  |  |
|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------|-----------|-------|--------------------|--|--|----------------|---------------|--------------|--------------------|--|--|
| Initial Approval Date                              | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |              |              |           |       |                    |  |  |                |               |              |                    |  |  |
| Nonproprietary Name                                | nemolizumab-xxxx                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |              |              |           |       |                    |  |  |                |               |              |                    |  |  |
| Indication                                         | treatment of prurigo nodularis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |              |              |           |       |                    |  |  |                |               |              |                    |  |  |
| Dosage Form                                        | for injection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |              |              |           |       |                    |  |  |                |               |              |                    |  |  |
| Strength                                           | 30 mg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |              |              |           |       |                    |  |  |                |               |              |                    |  |  |
| Route of Administration                            | subcutaneous                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |              |              |           |       |                    |  |  |                |               |              |                    |  |  |
| Dose and Frequency                                 | <p>patients aged 18 years and older weighing less than 90 kg is an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (Q4W).</p> <p>patients aged 18 years and older weighing 90 kg or more is an initial dose of 60 mg dose (two 30 mg injections), followed by 60 mg given every 4 weeks (Q4W).</p> <div>(b) (4)</div>                                                                                                                                                                                                                                                                                                                                                                                      |              |              |           |       |                    |  |  |                |               |              |                    |  |  |
| How Supplied                                       | <p>for injection is a sterile, preservative-free, white lyophilized powder available in single-dose, prefilled pen <div>(b) (4)</div> containing nemolizumab-xxxx in one chamber and the diluent, Water for Injection, in the other chamber. The pen <div>(b) (4)</div> <div></div> designed to deliver 30 mg of NEMLUVIO in 0.49 mL of solution.</p> <p>Each carton contains:</p> <ul style="list-style-type: none"><li>1 single-dose prefilled pen, or <div>(b) (4)</div></li></ul> <table><tr><td>Presentation</td><td>Pack size</td><td>NDC #</td></tr><tr><td colspan="3"><div>(b) (4)</div></td></tr><tr><td>Pre-filled Pen</td><td>Pack of 1 pen</td><td>0299-6220-15</td></tr><tr><td colspan="3"><div>(b) (4)</div></td></tr></table> |              | Presentation | Pack size | NDC # | <div>(b) (4)</div> |  |  | Pre-filled Pen | Pack of 1 pen | 0299-6220-15 | <div>(b) (4)</div> |  |  |
| Presentation                                       | Pack size                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | NDC #        |              |           |       |                    |  |  |                |               |              |                    |  |  |
| <div>(b) (4)</div>                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |              |              |           |       |                    |  |  |                |               |              |                    |  |  |
| Pre-filled Pen                                     | Pack of 1 pen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 0299-6220-15 |              |           |       |                    |  |  |                |               |              |                    |  |  |
| <div>(b) (4)</div>                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |              |              |           |       |                    |  |  |                |               |              |                    |  |  |

| Table 4. Relevant Product Information for Nemluvio |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Storage                                            | <p>Refrigerate NEMLUVIO at 36°F to 46°F (2°C to 8°C) in the original package to protect from light until the expiration date. Do not freeze. Alternatively, NEMLUVIO carton containing pens (b) (4) may be stored at room temperature [up to 77°F (25°C)] for up to 90 days. Write the date NEMLUVIO is first removed from the refrigerator in the space provided on the inner partition for the pen (b) (4). Do not use NEMLUVIO beyond the expiration date or 90 days after the date it was first removed from the refrigerator (whichever is earlier).</p> <p>NEMLUVIO must be removed from the refrigerator for 30-45 min before reconstitution. Once reconstitution steps are completed, NEMLUVIO must be used within 4 hours or discarded.</p> <p>Do NOT shake. Do NOT expose to heat or direct sunlight.</p> |
| Container Closure                                  | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

## APPENDIX B. LABELS AND LABELING

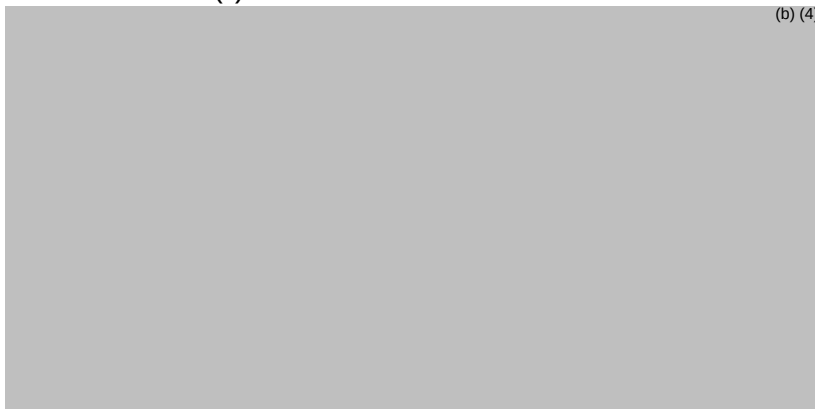
### B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>b</sup> along with postmarket medication error data, we reviewed the following Nemluvio labels and labeling submitted by Galderma Laboratories, L.P..

- Prescribing Information received on March 20, 2024, available from <\\CDSESUB1\EVSPROD\bla761390\0011\m1\us\uspi-draft-text-tc.doc>
- Patient Package Insert received on December 12, 2023, available from <\\CDSESUB1\EVSPROD\bla761390\0001\m1\us\draft-labeling-text-ppi.pdf>
- Instructions for Use received on March 20, 2024, available from <\\CDSESUB1\EVSPROD\bla761390\0011\m1\us\dcx-ifu-text.doc> and <\\CDSESUB1\EVSPROD\bla761390\0011\m1\us\dcc-ai-ifu-text.doc>
- Container label(s) received on December 12, 2023
- Carton labeling received on December 12, 2023
- Professional Sample Carton Labeling received on December 12, 2023

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

Container label(s)



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

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<sup>b</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**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.**  
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/s/  
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MADHURI R PATEL  
05/10/2024 01:27:39 PM

YEVGENIYA M KOGAN  
05/10/2024 01:45:10 PM