CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	BLA
Application Number	761390
PDUFA Goal Date	August 12, 2024
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Reviewer Name(s)	Donella Fitzgerald, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	August 12, 2024
Subject	Evaluation of Need for a REMS
Established Name	Nemolizumab-ilto
Trade Name	Nemluvio
Name of Applicant	Galderma Laboratories, L.P.
Therapeutic Class	Interleukin-31 receptor antagonist
Formulation(s)	30 mg single-dose prefilled dual chamber pen for subcutaneous injection
Dosing Regimen	Initial dose of 60mg, followed by 30mg every 4 weeks for patients weighing < 90kg, or 60mg every 4 weeks for patients weighing ≥ 90kg

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Nemluvio (nemolizumab-ilto) is necessary to ensure the benefits outweigh its risks. Galderma Laboratories, L.P. (Applicant) submitted a Biologic Licensing Application (BLA 761390) for nemolizumab-ilto with the proposed indication for the treatment of adults with prurigo nodularis. This application is under review in the Division of Dermatology (DDD). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Nemolizumab-ilto, a new molecular entity,[a] is an interleukin-31 (IL-31) receptor antagonist proposed for the treatment of adults with prurigo nodularis (PN). It is a monoclonal antibody that competitively blocks the binding of IL-31 to its receptor and subsequent activation of Janus kinase/signal transducer and activator transcription signaling pathway and transduction of the IL-31 signal into the cell. IL-31 drives inflammatory processes and alters epidermal differentiation and skin barrier integrity. The Applicant reports that inhibition of IL-31 signaling by nemolizumab-ilto helps treat symptoms associated with PN. Nemolizumab-ilto is proposed as a 30 mg single-dose prefilled dual chamber pen for subcutaneous injection. All patients begin with an initial dose of 60 mg. This is followed by 30 mg every 4 weeks for patients weighing < 90 kg or 60 mg every 4 weeks for patients weighing ≥ 90 kg.[b] Nemolizumab-ilto was granted breakthrough therapy designation on November 25, 2019 and priority review on February 9, 2024. Nemolizumab was approved in Japan under the commercial name, Mitchga®, on March 28, 2022 for the treatment of pruritus associated with atopic dermatitis (only when existing treatments are inadequate) in patients aged 13 years and older.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761390 relevant to this review:

- 11/25/2019: Breakthrough therapy designation granted for nemolizumab under IND 117122.
- 12/12/2023: Nemolizumab-ilto BLA 761390 submission for the treatment of adults with prurigo nodularis received.

(b) (4)

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 02/09/2024: Priority review granted for BLA 761390.
- 03/26/2024: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for nemolizumab-ilto.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Prurigo nodularis (PN) is a rare chronic inflammatory skin disease that is characterized by the presence of multiple, intensely pruritic, excoriated nodules that typically develop on the arms, legs, and the upper back and/or abdomen.[1] The nodules can range in size from a few millimeters to several centimeters and can range in number from few to hundreds.[2] Pain, burning, stinging, and other disturbing sensory skin sensations often accompany the intense pruritis and lead to sleep disturbance. The exact cause of PN is unknown; predisposing factors include dermatologic, systemic, neurologic, and psychiatric diseases associated with severe pruritus. Prurigo nodularis primarily affects older adults (median age of 62 years). In the United States the estimated prevalence is 72 per 100,000 persons.[3c] Patients with PN may experience significant psychological distress, as they often suffer embarrassment or shame over the appearance of the skin lesions, which can lead to social isolation. Prurigo nodularis patients are 2.8 times more likely to suffer from depression and anxiety versus healthy individuals.[4d]

3.2. Description of Current Treatment Options

Treatment of PN typically involves a multifaceted approach to interrupt the itch-scratch cycle and flatten the skin lesions. Most of the pharmacologic therapies used to treat PN are used off-label, as there is only one FDA approved treatment (dupilumab). Super-high potency topical and intralesional corticosteroids, such as clobetasol and betamethasone, are considered first-line therapy for patients with a limited number of nodular lesions. Other locally acting options include calcineurin inhibitors, calcipotriene and capsaicin. For patients with widespread disease or those that do not respond to topical corticosteroids, phototherapy used adjunctively with oral antihistamines, tricyclic antidepressants or gabapentin is recommended.[5] Patients with widespread disease, or recalcitrant PN not responsive to phototherapy, are typically prescribed systemic treatments that include dupilumab, conventional immunosuppressants (methotrexate, cyclosporine) and thalidomide. Dupilumab is the only FDA approved treatment for PN. It was approved in 2022 and is an IL-4 receptor antagonist administered as a subcutaneous injection every other week.

The off-label therapies discussed above have limited evidence to support safe use in PN patients. Immunosuppressants have been associated with significant nephro- and neurotoxicity as well as

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

infections and malignancies. And thalidomide labeling includes a Boxed Warning and is approved with a REMS with elements to assure safe use to mitigate the risk of embryofetal toxicity. In the dupilumab clinical trials for PN, hypersensitivity, conjunctivitis/keratitis, eosinophilic conditions and arthralgia were observed and included as Warnings and Precautions in the prescribing information. Because dupilumab is the only FDA approved product to treat PN, DDD concluded that nemolizumab-ilto would be an important treatment option for patients.[6]

4. Benefit Assessment

The efficacy of nemolizumab-ilto for the treatment of PN was demonstrated in two Phase 3 randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (OLYMPIA 1, NCT04501679; OLYMPIA 2, NCT04501666) conducted in approximately 70 centers in Europe, North America, and Asia Pacific. A total of 560 adult subjects with severe[e] pruritis were randomized 2:1 to receive either 60 mg of nemolizumab-ilto or placebo via two s subcutaneous injections at baseline. Subjects weighing < 90 kg in the nemolizumab-ilto group received subcutaneous injections of nemolizumab-ilto 60 mg at Week 0, followed by 30 mg injections every 4 weeks. Subjects weighing ≥ 90 kg in the nemolizumab-ilto group received subcutaneous injections of nemolizumab-ilto 60 mg at Week 0 and every 4 weeks. For OLYMPIA 2 the study duration was 16 weeks, for OLYMPIA 1 treatment was extended up to 24 weeks. The primary efficacy endpoints for both studies were the proportion of subjects with a ≥ 4-point improvement on the Peak Pruritis Numeric Rating Scale (PP-NRS) from baseline to Week 16 and the proportion of subjects with an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) and a ≥ 2-point improvement from baseline at Week 16.

Nemolizumab-ilto was statistically superior to placebo (p-values <0.0001) for the two primary efficacy endpoints, as well as for the multi-component secondary efficacy endpoint of "Proportion of subjects with both an improvement (reduction) of ≥4 from baseline in PP-NRS and IGA 0 or 1" (not adjusted for multiplicity) at Week 16. This endpoint is currently the FDA-recommended primary endpoint for PN trials.[7] Efficacy results are outlined below in Table 1.

[e] Severe pruritus was defined as an Investigator's Global Assessment score ≥ 3 and a weekly average of the peak pruritus numeric rating scale score of ≥7 on a scale of 0 to 10, and greater than or equal to 20 nodular lesions.

Table 1: Efficacy Results at Week 16 in Adult Subjects with PN in OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1			OLYMPIA 2		
	NEMLUVIO (N=190)	Placebo (N=96)	Difference from Placebo (95% CI)	NEMLUVIO (N=183)	Placebo (N=91)	Difference from Placebo (95% CI)
Proportion of subjects with both an improvement (reduction) of ≥4 from baseline in PP-NRS and IGA 0 or 1[a b]	22%[a]	2%[a]	15% (8%, 21%)[a]	25%[a]	4%[a]	22% (14%, 30%)[a]
Proportion of subjects with IGA 0 or 1[b]	26%	7%	15% (7%, 23%)	38%	11%	29% (19%, 38%)
Proportion of subjects with an improvement (reduction) of ≥4 from baseline in PP-NRS[b]	56%	16%	38% (27%, 48%)	49%	16%	34% (23%, 45%)
Proportion of subjects with PP-NRS <2[b]	32%	4%	28% (20%, 36%)	31%	7%	26% (18%, 34%)

[a] Not adjusted for multiplicity.
[b] Subjects who received rescue therapy or had missing data (fewer than 4 PP-NRS daily diary entries in a 7-day period) were considered non-responders.

The medical officer concluded that nemolizumab-ilto demonstrated efficacy in patients with PN in two adequate and well-controlled Phase 3 clinical trials.[f]

5. Risk Assessment & Safe-Use Conditions

The primary safety analysis consists of data from 556 subjects (370 nemolizumab-ilto, 186 placebo) from the two Phase 3 trials with supportive data from the Phase 3, long-term extension study (SPR.202699, NCT04204616) of 184 weeks duration.

Deaths and Serious Adverse Events

No deaths were reported in any subject treated with nemolizumab during the phase 3 trials. Serious adverse events (SAEs) were reported with a similar frequency for the nemolizumab-ilto group compared to the placebo group during Weeks 0-16 and the overall treatment period.

Table 2: Serious Adverse Events reported in > 1 subject in the nemolizumab-ilto pooled analyses for OLYMPIA 1 and OLYMPIA 2 Trials

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

SAEs in > 1 subject in nemolizumab-ilto treated groups (OLYMPIA 1, OLYMPIA 2)	Nemolizumab-ilto N=370 n (%)	Placebo N=186 n (%)
Neurodermatitis	4 (1.1%)	2 (1.1%)
Pemphigoid bullous	3 (0.8%)	0 (0.0%)
Osteoarthritis	2 (0.5%)	1 (0.5%)
Acrodermatitis	2 (0.5%)	0 (0.0%)

Neurodermatitis, osteoarthritis and acrodermatitis were assessed as not being related to nemolizumab. Pemphigoid bullous was determined to be possibly related. The subject discontinued nemolizumab treatment and subsequently recovered. The condition was resolved with sequalae. The DDD agreed with the Applicant's assessment that nemolizumab could possibly to related to the subject's condition.

Adverse Events of Special Interest

5.1. Hypersensitivity

Hypersensitivity AEs are associated with biological agents and have the potential to be serious and life-threatening.[8] In the Phase 3 trials, hypersensitivity reactions were reported for 61 (16.5%) nemolizumab-ilto subjects versus 36 (19.4%) placebo treated subjects.[g] Facial edema was reported for 4 (1.1%) nemolizumab-treated subjects (including 1 AE of periocular angioedema in one subject) compared to no placebo-treated subjects. None of the hypersensitivity reactions were reported as serious or severe, and there were no reports of anaphylactic shock or serum-sickness. The draft prescribing information (PI) includes a contraindication for known hypersensitivity to nemolizumab-ilto or to any of the excipients in the formulation. Additionally, there is a Warning and Precaution that hypersensitivity reactions have been reported with use and if a clinically significant hypersensitivity reaction occurs, nemolizumab should be discontinued and appropriate therapy instituted immediately. Language regarding the possibility of allergic reactions is also included in the draft Patient Information sheet that is part of the proposed labeling.

5.2. Malignancy

Prurigo nodularis has been associated with an increased risk of malignancies.[9] SAEs of malignancy were not reported during the nemolizumab overall treatment period, but there were reports of moderate severity malignancies. Two (0.6%) subjects in the nemolizumab-ilto group, compared to one (0.5%) subject in the placebo group were reported with nonmelanoma skin cancers. An 82-year-old male with

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

history of actinic keratosis (AK) and basal cell carcinoma (BCC) was reported with both a BCC and a squamous cell carcinoma (SCC) of moderate severity on Day 145. He underwent surgical excisions while still on study drug; the outcome was reported as resolved. A 66-year-old male with history of AK and BCC was reported with a SCC of moderate severity on Day 35. He also had surgical excision, but discontinued nemolizumab-ilto and withdrew from the trial. Malignancies reported for nemolizumab-ilto-treated subjects during the PN long-term extension study SPR.202699 (up to the data cut-off point for interim analysis) included BCC (1), Hodgkin's disease stage IV (1), rectal adenocarcinoma (1), SCC (1), and uterine cancer (1).[10]

DDD concluded that a potential relationship of the reported malignancies to the study drug is unknown. The pharmacology toxicology reviewer reported that there was no evidence of tissue proliferation (i.e., hyperplasia, preneoplastic lesions) in the 6-month repeat-dose subcutaneous toxicity study in monkeys. Nemolizumab-ilto prescribing information will include a statement that animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of nemolizumab-ilto.

6. Expected Postmarket Use

Nemolizumab-ilto is proposed as a single-dose prefilled dual chamber pen for subcutaneous injection. It will likely be prescribed and self-administered in the outpatient setting. Draft labeling includes Instructions for Use (IFU) to educate patients on how to administer the injection and also a Patient Information sheet that highlights possible side effects and product storage information.

The most likely prescribers of nemolizumab will be dermatologists who are experienced with managing patients with inflammatory dermatologic conditions such as PN. These prescribers are likely familiar with the risks associated with IL receptor antagonist use in PN, given use of dupilumab for the same indication.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for nemolizumab beyond routine pharmacovigilance and labeling. Draft labeling includes the Prescribing Information, IFU, and Patient Information sheet.

8. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of nemolizumab-ilto for the treatment of adults with prurigo nodularis. Prurigo nodularis (PN) is a rare chronic inflammatory skin disease that is characterized by the presence of multiple, intensely pruritic, excoriated nodules that typically develop on the arms, legs, and the upper back and/or abdomen. Multiple pharmacologic agents are used off-label to treat PN but there is only one FDA-approved treatment (dupilumab). The DDD stated that there is a significant unmet medical need for additional treatment options.

Efficacy of nemolizumab-ilto was demonstrated in two Phase 3 randomized, double-blind, placebo-controlled, multicenter, parallel-group trials by meeting the primary endpoints of the proportion of subjects with a ≥ 4-point improvement on the PP-NRS from baseline to Week 16 and the proportion of subjects with an IGA score of 0 or 1 and a ≥ 2-point improvement from baseline at Week 16. The adverse events of special interest observed with nemolizumab were hypersensitivity and malignancy. Because nemolizumab is a biologic agent, the risk of hypersensitivity was expected; none of the hypersensitivity reactions were serious or severe. Like dupilumab, labeling for nemolizumab will include a contraindication for known hypersensitivity to nemolizumab-ilto, as well as a Warning and Precaution that hypersensitivity reactions have been reported with use and that nemolizumab should be discontinued and appropriate therapy instituted immediately if a clinically significant hypersensitivity reaction occurs. Language regarding the possibility of allergic reactions is also included in the draft Patient Information sheet. Patients should be able to identify symptoms of hypersensitivity and contact their prescriber or seek emergency help if necessary.

The reports of malignancy in the clinical trials were moderate in severity. The DDD concluded that the potential relationship of the reported malignancies to the study drug is unknown. The nemolizumab-ilto label will include a statement that animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of nemolizumab-ilto.

Per the medical officer, review of the clinical trial data did not identify any safety issues that would require risk management beyond standard pharmacovigilance. And Japanese postmarketing safety data for nemolizumab has not identified any new risks since marketing initiated in 2022. Based on the information currently available, this reviewer agrees that risk mitigation beyond labeling is not necessary at this time.

9. Conclusion & Recommendations

Based on the available data, a REMS for nemolizumab-ilto is not necessary to ensure the benefits outweigh the risks. The hypersensitivity safety concerns associated with nemolizumab are known to prescribers and the symptoms can be identified by patients. The lack of data concerning animal malignancy studies will be communicated in labeling. Should DDD have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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[6] Division of Dermatology and Dentistry. Draft Integrated Review for nemolizumab-ilto BLA 761390. July 2, 2024.

[7] Division of Dermatology and Dentistry. Draft Integrated Review for nemolizumab-ilto BLA 761390. July 2, 2024.

[8] Pintea I, Petricau C, Dumitrascu D, et al. Hypersensitivity reactions to monoclonal antibodies: Classification and treatment approach. Exp Ther Med, 2021 Sep; 22(3): 949

[9] Larsen VA, Tang O, Stander S, et al. Association between pririgo nodularis and malignancy in middle-age adults. J AM ACAD Dermatol, 2019 Nov; 81(5)

[10] Division of Dermatology and Dentistry. Draft Integrated Review for nemolizumab-ilto BLA 761390. July 20, 2024.

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/s/

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