Iowa PDL New Drug Review

Proprietary Name: Nemluvio®
Common Name: nemolizumab-ilto injection, powder
PDL Category: Anti-IgE & Anti-Interleukin Antibodies

Pharmacology/Usage: Nemolizumab-ilto, the active ingredient of Nemluvio®, is an interleukin-31 receptor alpha (IL-31RA) antagonist. It is a humanized IgG2 monoclonal antibody that inhibits IL-31 signaling by binding selectively to IL-31 RA. IL-31 is a naturally occurring cytokine that is involved in pruritus, inflammation, epidermal dysregulation, and fibrosis. Nemolizumab-ilto inhibited IL-31 induced responses including the release of proinflammatory cytokines and chemokines.

Indication: For the treatment of:

- Adults with prurigo nodularis (PN).
- Adults and pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis (AD) in combination with topical corticosteroids and/or calcineurin inhibitors when the disease is not adequately controlled with topical prescription therapies.

There is no pregnancy category for this medication; however, the risk summary indicates that available data on use in pregnant women exposed during clinical trials are not sufficient to assess 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; thus, Nemluvio® may be transferred from the mother to the developing fetus. There are clinical considerations listed; refer to the prescribing information for additional information. The safety and efficacy of use have not been established in the pediatric population when used for the treatment of PN. The safety and efficacy of use have not been established in the pediatric population younger than 12 years of age when used for the treatment of AD

Dosage Form: Lyophilized powder in one chamber and diluent, water for injection, in the other chamber, for injection: Single-dose prefilled dual-chamber pen containing 30mg of nemolizumab-ilto.

Before injection, remove Nemluvio® carton from the refrigerator and allow to reach room temperature (30-45 minutes).

Nemluvio® must be reconstituted prior to administration. Following reconstitution, each prefilled pen delivers 30mg/0.49ml of solution. Use Nemluvio® pens within 4 hours after reconstitution.

Recommended Dosage: Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to treatment with Nemluvio®.

Nemluvio® is administered by subcutaneous (SC) injection. It is intended for use under the guidance of a healthcare provider. Prior to the first injection, provide patients and/or caregivers with proper training on the preparation and administration of Nemluvio®. Patients may self-inject Nemluvio® after receiving training on SC injection techniques. In pediatric patients 12 years of age and older with AD, administer Nemluvio® by or under the supervision of a trained adult or caregiver. Administer SC injection into the front upper thighs or abdomen except for the 2 inches around the navel. Injection in the upper arm should only be performed by a caregiver or healthcare professional. In addition, alternate the injection site with each injection. Do not inject into skin that is tender, inflamed, swollen, damaged, or has bruises or scars or open wounds.

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

Recommended dosage for PN:

Adult patients weighing less than 90kg: The recommended SC dosage of Nemluvio® is an initial dose of 60mg (two 30mg injections), followed by 30mg given every 4 weeks (Q4W).

Adult patients weighing 90kg or more: The recommended SC dosage of Nemluvio® is an initial dose of 60mg (two 30mg injections), followed by 60mg given every 4 weeks (Q4W).

Recommended dosage for AD:

The recommended SC dosage of Nemluvio® in adults and pediatric patients 12 years of age and older is an initial dose of 60mg (two 30mg injections), followed by 30mg given every 4 weeks. After 16 weeks of treatment, for patients who achieve clear or almost clear skin, a SC dosage of 30mg every 8 weeks is recommended.

For AD, use Nemluvio® with topical corticosteroids and/or topical calcineurin inhibitors. When the disease has sufficiently improved, discontinue use of topical therapies.

Drug Interactions: *Only included in the Nemluvio® prescribing information discussing the PN indication*. The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNF alpha) during chronic inflammation. Treatment with Nemluvio® may modulate serum levels of some cytokines and influence the formation of CYP450 enzymes. Thus, upon initiation or discontinuation of Nemluvio® in patients who are receiving concomitant drugs which are CYP450 substrates, especially those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modifications of the CYP450 substrate.

There are no drug interactions listed in the Nemluvio® prescribing information discussing the AD indication.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Nemluvio®) minus reported % incidence for placebo in adults with PN. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included headache (3%), dermatitis atopic (3.5%), eczema (2%), and eczema nummular (3%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (Nemluvio®) minus reported % incidence for placebo in adults and pediatric patients 12 years of age and older with AD. Please note that an incidence of 0% means the incidence was the same as or less than placebo. The most frequently reported adverse events included headache (including migraine; 1%), arthralgia (0.8%), urticaria (0.7%), and myalgia (0.8%).

Hypersensitivity reactions, such as facial angioedema, have been reported with use of Nemluvio®. Nemluvio® is contraindicated in patients with a known hypersensitivity to nemolizumab-ilto or to any of the excipients of the product. If a clinically significant hypersensitivity reaction occurs, immediately start appropriate therapy and discontinue Nemluvio®.

Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to Nemluvio® treatment. Avoid use of live vaccines in patients during treatment with Nemluvio®. It is not known if administration of live vaccines during Nemluvio® treatment will impact the safety or efficacy of these vaccines. No data are available on the response to non-live vaccines.

Contraindications: In patients who have known hypersensitivity to nemolizumab-ilto or to any of the excipients of the product.

Manufacturer: Galderma Laboratories, L.P.

Analysis: *The following information is regarding the PN studies***.** The efficacy of Nemluvio® was assessed in two randomized, double-blind, placebo-controlled trials (OLYMPIA 1 and OLYMPIA 2) that included adult subjects (N=560) with prurigo nodularis (PN). Disease severity was defined using an Investigator's Global Assessment (IGA) in the overall assessment of PN nodules on a severity scale of 0 to 4. Subjects enrolled in the two trials had an IGA score ≥3, severe pruritus as defined by a weekly average of the peak pruritus numeric rating scale (PP-NRS) score of ≥7 on a scale of 0 to 10, and ≥20 nodular lesions.

In the trials, at baseline, 60% of subjects were female, 81% were white, and 25% of subjects were older than 65 years of age. In addition, 32% had a history of atopy, the baseline weekly average PP-NRS score was a mean of 8.5, 58% of subjects had a baseline IGA score of 3 (moderate PN), and 42% had a baseline IGA of 4 (severe PN).

The PP-NRS score is a weekly average of daily PP-NRS scores on an 11-point scale from 0-10 that assesses the maximal intensity of pruritus in the last 24 hours with 0 being no itch and 10 being worst itch imaginable. The IGA is a 5-category scale, including 0=clear, 1=almost clear, 2=mild, 3=moderate, or 4=severe, indicating the investigator's overall assessment of the pruriginous nodules.

Efficacy was assessed with the proportion of subjects with an improvement of ≥4 from baseline in PP-NRS, the proportion of subjects with an IGA of 0 (clear) or 1 (almost clear) and a ≥2-point improvement from baseline, the proportion who achieved a response in both PP-NRS and IGA per the criteria described above, and the proportion of subjects with PP-NRS <2. Results are presented in the table below, which was adapted from the prescribing information.

	OLYMPIA 1			OLYMPIA 2		
	Nemluvio® (N=190)	**Placebo (N=96)**	**Difference from placebo**	**Nemluvio® (N=183)**	**Placebo (N=91)**	**Difference from placebo**
Proportion with both an improvement (reduction) of ≥4 from baseline in PP-NRS & IGA 0 or 1	22%[1]	2%[1]	15%	25%[1]	4%[1]	22%
NNT *calculated by Optum Rx*	7			5		
Proportion with IGA 0 or 1	26%	7%	15%	38%	11%	29%
NNT *calculated by Optum Rx*	7			4		
Proportion with an improvement (reduction) of ≥4 from baseline in PP-NRS	56%	16%	38%	49%	16%	34%
NNT *calculated by Optum Rx*	3			3		
Proportion with PP-NRS <2	32%	4%	28%	31%	7%	26%
NNT *calculated by Optum Rx*	4			4		

[1]Not adjusted for multiplicity.

*The following information is regarding the AD studies***.** The efficacy of Nemluvio® was assessed in two randomized, double-blind, placebo-controlled trials (ARCADIA 1 and ARCADIA 2) that included subjects 12 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical treatments (N=1728). Disease severity was defined by an Investigator's Global Assessment (IGA) score of 3 (moderate) and 4 (severe) in the overall assessment of AD, an Eczema Area and Severity Index (EASI) score of ≥16, a minimum body surface area (BSA) involvement of ≥10%, and a Peak Pruritus Numeric Rating Scale (PP-NRS) score of ≥4.

Subjects in the Nemluvio® group received an initial injection followed by injections every 4 weeks. Concomitant low and/or medium potency topical corticosteroid (TCS) and/or topical calcineurin inhibitors (TCI) were administered for at least 14 days prior to baseline and continued during the trial. Based on disease activity, these concomitant therapies could be tapered and/or discontinued at investigator discretion. After 16 weeks, subjects achieving either EASI-75 or

IGA success continued into the trial maintenance period for another 32 weeks to assess the maintenance of response achieved at week 16. Nemluvio® responders were re-randomized to either Nemluvio® 30mgevery 4 weeks, Nemluvio® 30mgevery 8 weeks, or placebo every 4 weeks (all groups continued background TCS/TCI). Subjects randomized to placebo in the initial treatment period who achieved the same clinical response at week 16 continued to receive placebo every 4 weeks.

At baseline, included patients were 51% male, 80% white, and 15% were 12-17 years of age. In addition, 70% had a baseline IGA score of 3 (moderate AD) and 30% had a baseline IGA score of 4 (severe AD). The baseline mean EASI score was 27.5 and the baseline mean weekly average PP-NRS was 7.1. Overall, 63% received other previous systemic treatments for AD.

The IGA is a 5-category score, including 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), or 4 (severe) indicating the investigator's overall assessment of the AD. EASI scores range from 0 to 72 points and reflect the severity and extent of AD. EASI-75 indicates at least a 75% improvement in EASI score from baseline. The PP-NRS score is a weekly average of daily PP NRS scores on an 11-point scale from 0-10 that assesses the maximal intensity of pruritus in the last 24 hours with 0 being no itch and 10 being worst itch imaginable.

The co-primary endpoints for both studies include:

- Proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥2-point reduction from baseline) at week 16.
- Proportion of subjects with EASI-75 (≥75% improvement in EASI from baseline) at week 16.

PP-NRS improvement ≥4 from baseline at week 16 was a key secondary outcome in both trials.

Results of both studies evaluating the initial treatment period with Nemluvio® over 16 weeks are presented in the table below, which was adapted from the prescribing information.

	ARCADIA 1			ARCADIA 2		
	Nemluvio® + TCS/TCI	Placebo + TCS/TCI	Difference from placebo	Nemluvio® + TCS/TCI	Placebo + TCS/TCI	Difference from placebo
Number of subjects randomized	620	321		522	265	
Proportion of subjects with IGA 0 or 1	36%	25%	12%	38%	26%	12%
NNT *calculated by Optum Rx*	9			9		
Proportion of subjects with EASI-75	44%	29%	15%	42%	30%	12%
NNT *calculated by Optum Rx*	7			9		
Proportion with an improvement (reduction) of ≥4 from baseline in PP-NRS	33%	15%	18%	36%	15%	21%
NNT *calculated by Optum Rx*	6			5		

The maintenance and durability of response (week 16 to week 48) was assessed. The clinical response in Nemluvio® responders (IGA 0/1 or EASI-75 at week 16) was assessed between week 16 and week 48 in both ARCADIA studies. For the maintenance treatment period, Nemluvio® responders were re-randomized to Nemluvio® 30mgevery 4 weeks, Nemluvio® 30mgevery 8 weeks, or placebo every 4 weeks (Nemluvio® withdrawal) with concomitant TCS/TCI. The results are presented in the table below, which was adapted from the prescribing information.

	Nemluvio® Q4W + TCS/TCI	Nemluvio Q8W + TCS/TCI	Placebo + TCS/TCI
Number of subjects who were IGA Responders at week 16	142	142	131
Proportion of subjects with IGA 0 or 1 at week 48	63%	64%	55%
Number of subjects who were EASI-75 Responders at week 16	163	163	157
Proportion of subjects with EASI-75 at week 48	75%	77%	65%

Place in Therapy: Nemluvio® is an interleukin-31 receptor antagonist indicated for the treatment of adults with prurigo nodularis. It is also indicated for the treatment of adults and pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis in combination with topical corticosteroids and/or calcineurin inhibitors when the disease is not adequately controlled with topical prescription therapies. Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to treatment with Nemluvio®. Two randomized, double-blind, placebo-controlled trials assessed the efficacy of Nemluvio® in adults with prurigo nodularis. Efficacy was assessed with the proportion of subjects with an improvement of ≥4 from baseline in PP-NRS and the proportion of subjects with an IGA of 0 (clear) or 1 (almost clear) and a ≥2-point improvement from baseline. Nemluvio® was more effective than placebo for the endpoints assessed. Per the full-text study by Kwatra et al[2] (OLYMPIA 2), nemolizumab was significantly more effective than placebo for the primary endpoints at week 16 ($p<0.001$ for both comparisons). Two randomized, double-blind, placebo-controlled trials assessed the efficacy of Nemluvio® in adult and pediatric patients 12 years of age and older with moderate-to-severe AD not adequately controlled by topical treatments. The co-primary endpoints included the proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥2-point reduction from baseline) at week 16 and the proportion of subjects with EASI-75 (≥75% improvement in EASI from baseline) at week 16. Nemluvio® was more effective than placebo for the co-primary endpoints assessed. Per the full-text by Silverberg et al[3], nemolizumab was significantly more effective than placebo for the primary endpoints. Head-to-head active comparator trials were not currently found.

Summary

There is some evidence from two phase 3 studies to suggest that Nemluvio® plus topical corticosteroid/topical calcineurin inhibitor may be more effective than placebo plus topical corticosteroid/topical calcineurin inhibitor for the primary endpoints of the study when used in patients with atopic dermatitis; however, there is no evidence at this time to support that Nemluvio® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Nemluvio® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred with Conditions**

References

[1] Nemluvio [package insert]. Dallas, TX: Galderma Laboratories; 2024.

[2] Kwatra SG, Yosipovitch G, Legat FJ, et al. Phase 3 trial of nemolizumab in patients with prurigo nodularis. *NEJM*. 2023; 389(17): 1579-1589.

[3] Silverberg JI, Wollenberg A, Reich A, et al. Nemolizumab with concomitant topical therapy in adolescents and adults with moderate-to-severe atopic dermatitis (ARCADIA 1 and ARCADIA 2): results from two replicate, double-blind, randomized controlled phase 3 trials. *Lancet*. 2024; 404(10451): 445-460.

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