Nemolizumab-ilto (NEMLUVIO) in Prurigo Nodularis
National Drug Mini-Monograph

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VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: 1L, first-line; 2L, second-line; AC, active-controlled; CO, crossover; DB, double-blind; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IL-31RA, interleukin-31 receptor antagonist; MC, multicenter; MN, multinational; PC, placebo-controlled; PN, prurigo nodularis; Q, GRADE quality of evidence; RCT, randomized clinical trial

FDA APPROVAL INFORMATION	
Description / MOA	Humanized IgG2 monoclonal antibody that is an interleukin-31 receptor antagonist (IL-31RA). IL-31 is a Th2 cytokine that binds to receptors expressed on dermal small C-fiber sensory neurons that mediate pruritus and induce barrier disruption, skin inflammation, and fibrosis.[1]
Indication Under Review[2]	Treatment of adults with prurigo nodularis (PN)
Dosage Regimen	*Body Weight < 90 kg*: 60 mg (two 30-mg injections) SC then 30 mg every 4 weeks *Body Weight ≥ 90 kg*: 60 mg (two 30-mg injections) SC then 60 mg every 4 weeks
Dosage Forms Under Review	For injection: Single-dose prefilled dual-chamber pen of nemolizumab-ilto lyophilized powder 30 mg and diluent (water for injection)

EFFICACY CONSIDERATIONS	
Phase 3 Trials in NA, EU, KR	**OLYMPIA 1: Unpublished** **OLYMPIA 2: Phase 3 trial of nemolizumab in patients with prurigo nodularis[3]** (conducted in North America, Europe, and South Korea)
Design	OLYMPIA 1: 24-week RCT, otherwise similar in methods to OLYMPIA 2.[1] OLYMPIA 2: 16-week multicenter, double-blind, placebo-controlled, phase 3 RCT (randomized 2:1); stratified by study center and body weight < 90 kg and ≥ 90 kg; primary endpoint: improvement from baseline of ≥ 4 in Peak Pruritus-Numerical Rating Scale (PP-NRS) at Week 16 and Investigator Global Assessment (IGA) success (score of 0 / Clear or 1 / Almost Clear of nodules) at Week 16.[3]
Population	Age ≥ 18 years, clinical diagnosis of PN of ≥ 6 months, severe pruritus (PP-NRS of ≥ 7), ≥ 20 nodules bilaterally distributed; Investigator Global Assessment (IGA) score of 3 or 4 (moderate or severe, respectively). *Major Exclusions:* Chronic pruritus not associated with PN; inadequately controlled asthma; history of chronic obstructive pulmonary disease and/or chronic bronchitis; cutaneous infection within 1 week; infection requiring treatment within 2 weeks; positive serology for hepatitis B or HCV; history of lymphoproliferative disease or malignancy within 5 years except for basal cell carcinoma, squamous cell carcinoma, treated cervical carcinoma in situ, and treated actinic keratoses; active or latent tuberculosis (TB); history of alcohol or substance abuse within 6 months; any medical or psychological condition or any clinically relevant laboratory abnormality that may put the patient at significant risk per investigator discretion or interfere with study assessments. For OLYMPIA 1 | OLYMPIA 2, respectively: Mean age 57.6 | 52.3 years; male 42% | 39%; White 84% | 78%; prior systemic therapy for PN 38% | 60%
Interventions	Body Weight < 90 kg: Nemolizumab 60 mg on Day 1, then 30 mg every 4 weeks Body Weight ≥ 90 kg: Nemolizumab 60 mg every 4 weeks
Comparator	Placebo

Results

Week-16 Efficacy Results for FDA Recommended Primary Endpoint

Outcome	OLYMPIA 1 Nemolizumab	OLYMPIA 1 Placebo	OLYMPIA 1 Q	OLYMPIA 2 Nemolizumab	OLYMPIA 2 Placebo	OLYMPIA 2 Q
Both PP-NRS–4 and IGA-0/1, n/N (%)	**43/190 (23)**	**2/96 (2)**	**ID**	**54/183 (30)**	**5/91 (5)**	**M[α]**
RR (95% CI)	10.9 (2.7, 43.9)	Ref		5.4 (2.2, 13.0)	Ref	
Adj Diff (95% CI)	16 (9, 23)	Ref		26 (17, 35)	Ref	
DLQI–4	—	—	—	**137/183 (74.9)**	**36/91 (39.6)**	**M**
RR (95% CI)				1.9 (1.4, 2.5)	Ref	
Diff (95% CI)				37.4 (25.7, 49.0)	Ref	

Sources: 1,3. **Abbreviations**: DLQI–4, Improvement of ≥ 4 points on the Dermatology Life Quality Index; ID, insufficient data; IGA-0/1, Investigator Global Assessment of 0 / Clear or 1 / Almost Clear of nodules; PP-NRS–4, ≥ 4-point improvement on the Peak Pruritus-Numerical Rating Scale

[α] Downgraded for imprecision (wide CIs and optimal information size not met)

Authors' Conclusions

Nemolizumab therapy for up to 16 weeks resulted in significant improvement in core signs and symptoms of PN in adults with moderate-to-severe disease. Atopic dermatitis developed in more patients on nemolizumab-ilto (5.5% [10/183] than placebo (0% [0/91]).

Phase 2/3 Trial Conducted in JP

Nemolizumab-JP11 Study: Efficacy and safety of nemolizumab and topical corticosteroids for prurigo nodularis: results from a randomized double-blind placebo-controlled phase II/III clinical study in patients aged ≥ 13 years[4,5]

Design

16-week double-blind, double-dummy, dose- and placebo-controlled phase II/III RCT conducted in JP (randomized 1:1:1)

Primary efficacy endpoint: Percentage change from baseline (CFB) to Week 16 in the weekly mean PP-NRS score

Population

Age ≥ 13 years; confirmed diagnosis of PN > 6 months; lesions on upper or lower limbs (minimal requirement); ≥ 20 bilateral PN nodules on the entire body; Investigator Global Assessment (IGA) score of ≥ 3; and inadequate pruritic response despite higher-potency corticosteroids (stable dose for ≥ 4 weeks) and antihistamines (taken as directed for ≥ 2 weeks) or inability to receive these therapies. Itch scores of ≥ 3 on a scale of 0 to 4 and Peak Pruritus Numerical Rating Scale (PP-NRS) score of ≥ 7 on a range of 0 to 10.

Major Exclusions: Body weight < 30 kg; moderate or severe atopic dermatitis; pruritus of atopic dermatitis; hepatitis B or C infection; latent or active tuberculosis (TB); COVID-19; live vaccines within 28 days; inadequately controlled systemic conditions

Baseline Characteristics (N = 229): Median age 51.0 years; male 47%; median duration of disease 4.1 years; concomitant atopic dermatitis 14%; median PP-NRS score 8.6; median number of PN nodules < 100: 44.1% and ≥ 100: 55.9%.

Interventions

Nemolizumab 60 mg SC loading dose then 30 mg every 4 weeks

Nemolizumab 60 mg SC every 4 weeks

Comparator

Placebo

Other Therapy

Medium-potency topical corticosteroids in use prior to randomization were required to be continued at a stable dose except dosage reductions were allowed based on symptom severity.

Lower-potency topical corticosteroids and moisturizers or skin protectants were allowed.

Rescue therapy consisting of higher-potency topical corticosteroids or oral antihistamines (given at investigator's discretion for worsening PN or atopic dermatitis)

Results

Primary and Secondary Efficacy Results at Week 16

Outcome	Nemolizumab 30 mg	Nemolizumab 60 mg	Placebo	Q
Percentage CFB in PP-NRS score	**–61.1**	**–56.0**	**–18.6**	**M[α]**
RR (95% CI)	—	—	—	
ARD (95% CI)	–42.5 (–51.9 to –33.1)	–37.4 (–46.7 to –28.1)	Ref	
PP-NRS–4, n (%)	**48/77 (62.3)**	**43/76 (56.6)**	**9/76 (11.8)**	**M[α]**
RR (95% CI)	5.3 (2.8, 10.0)	4.8 (2.5, 9.1)	Ref	
ARD (95% CI)	50.5 (37.5, 63.5)	44.7 (31.4, 58.0)	Ref	
IGA-0/1–2, n (%)	**32/77 (41.6)**	**30/76 (39.5)**	**3/76 (3.9)**	**M[α]**
RR (95% CI)	10.5 (3.4, 32.9)	10.0 (3.2, 31.4)	Ref	
ARD (95% CI)	37.6 (25.8, 49.5)	35.5 (23.7, 47.4)	Ref	
DLQI-4, n (%)	**41/71 (57.7)**	**33/68 (48.5)**	**17/70 (24.3)**	**M[α]**
RR (95% CI)	1.2 (0.89, 1.68)	2.0 (1.2, 3.2)	Ref	
ARD (95% CI)	33.5 (18.2, 48.7)	24.2 (8.7, 39.8)	Ref	

Blue text denotes CI includes the value 1.0.

	DLQI-4, Score of ≤ 4 points on the Dermatology Life Quality Index; IGA-0/1–2, Decrease of ≥ 2 points in the Investigator Global Assessment to a final score of ≤ 1; PP-NRS, Peak pruritus numerical rating scale; PP-NRS–4, Improvement of ≥ 4 points on PP-NRS; [α] Downgraded for imprecision (wide CIs, optimal information size not met)
Authors' Conclusions	In this phase 2/3 study involving patients with PN and moderate-to-severe pruritus despite topical corticosteroids, nemolizumab was better than placebo in reducing both pruritus and PN lesions.
Other Trials	European phase 2a multinational double-blind, placebo-controlled RCT evaluating nemolizumab 0.5 mg/kg every 4 weeks for 3 doses[6] OLYMPIA LTE: 192-week multicenter, open-label, phase 3 long-term extensionError! Bookmark not defined.

SAFETY CONSIDERATIONS: COMPARISON OF SAFETY PROFILES OF NEMOLIZUMAB-ILTO AND DUPILUMAB

Safety Topic	Nemolizumab-Ilto	Dupilumab
Boxed Warnings	None	None
Contraindications	Known hypersensitivity to drug or excipients	Known hypersensitivity to drug or excipients
Other Warnings	Hypersensitivity Avoid use of live vaccines during treatment	Hypersensitivity Conjunctivitis and keratitis – consider ophthalmologic exam for conjunctivitis that persists despite treatment and for signs or symptoms of keratitis Eosinophilic conditions – vasculitis rash, worsening pulmonary symptoms, and/or neuropathy, especially when tapering corticosteroids Taper corticosteroids gradually, if appropriate, when initiating dupilumab. Arthralgia Parasitic / helminth infections – treat existing helminth infections before initiating dupilumab Avoid use of live vaccines
Top 5 AEs	Headache, atopic dermatitis (4% nemolizumab-ilto vs 0.5% placebo), eczema (4% vs 2%, respectively), and eczema nummular (3% vs 0%, respectively)	Nasopharyngitis, conjunctivitis, herpes infection, dizziness, myalgia
Drug Interactions	*CYP450 substrates*: Consider monitoring effect (e.g., warfarin) or drug concentration (e.g., cyclosporine) and consider dosage modification when nemolizumab-ilto is initiated or discontinued.	*CYP450 substrates*: In a study of the effects of dupilumab on CYP450 substrates involving patients with atopic dermatitis, no clinically significant changes in AUC of midazolam (CYP3A4), warfarin (CYP2C9), omeprazole (CYP2C19), metoprolol (CYP2D6), or caffeine (CYP1A2) were observed.
Renal Impairment	Not studied because nemolizumab-ilto is not expected to undergo renal elimination.	—
Hepatic Impairment	Not studied because nemolizumab-ilto is not expected to undergo hepatic elimination.	—
Geriatric Use	Insufficient data to determine whether patients ≥ 65 years old respond differently from younger patients.	Insufficient data to determine whether patients ≥ 65 years old respond differently from younger patients. No overall differences in pharmacokinetics were seen between elderly and younger patients.
Pregnancy	Insufficient human data. Nemolizumab-ilto may cross the placenta and be transferred to the developing fetus. Human IgG antibody crosses the placenta to a greater extent as pregnancy progresses, peaking in the third trimester. In monkey studies, an increase in early postnatal death was observed after high doses (36 times the maximum recommended dose for humans) were given SC during organogenesis to parturition. Risks vs benefits should be considered before giving live vaccines to infants exposed to nemolizumab-ilto in utero	US Prescribing Information[7]: No drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes have been documented in case reports and case series. Dupilumab may be transmitted from the mother to the fetus. In monkey studies, no treatment-related embryofetal toxicity or malformations were observed. Similarly, no adverse morphological,

Safety Topic	Nemolizumab-Ilto	Dupilumab
	because the drug may impair immune response to infections. Based on the drug's half-life, a minimum of 3 months after birth should be considered to delay live virus immunizations in infants exposed to nemolizumab-ilto in utero, although the optimal timeframe is unknown.[2] The US prescribing information provides no other clinical recommendations regarding use of nemolizumab-ilto during pregnancy.	functional, or immunological effects were seen in infants (birth through 6 months old).
Lactation	Insufficient human data. Endogenous maternal IgG and monoclonal antibodies are transferred in human milk. The effects of gastrointestinal and limited systemic exposure to nemolizumab-ilto in breastfed infants are unknown. Weigh risks vs benefits. In monkey studies, nemolizumab-ilto was detected in breast milk.	Same as for nemolizumab-ilto.

OTHER CONSIDERATIONS	
Onset of Treatment Benefit	Week 4 based on PP-NRS–4 and IGA-0/1 responder rates
Duration of an Adequate Therapeutic Trial	A peak responder rate was not reached by Week 16 based on PP-NRS–4 and IGA-0/1

THERAPEUTIC OPTIONS: PLACE IN THERAPY

DRUG	VANF	CFU	FDA	GUIDELINES	COMMENTS
Nemolizumab-ilto	TBD	TBD	Treatment of adult patients with PN	All guidelines pre-dated approval of nemolizumab-ilto and dupilumab. *US Consensus Panel Recommendations on PN (2021)*: Dupilumab was considered a 3rd-tier therapy (less tolerable, less well-established, or experimental).[8] *International Forum on the Study of Itch (IFSI) Guidelines on Chronic Prurigo (2020):* Weakly recommended / suggested dupilumab and nemolizumab as step-4 therapies.[9]	Dupilumab and nemolizumab-ilto are the only therapies shown to be effective for PN in placebo-controlled RCTs.
Dupilumab	NonF	No	Treatment of adult patients with PN		

POTENTIAL PLACE IN THERAPY

1L: Topical / Intralesional Therapy

2L: Dupilumab or nemolizumab-ilto

1. Nemolizumab-ilto may be used for the treatment of patients with a documented clinical diagnosis of PN and ≥ 20 nodules who have an inadequate response (after ≥ 2 weeks per therapy) or intolerance to either (1) two topical therapies (e.g., corticosteroids, calcipotriene, or calcineurin inhibitor) or (2) one topical therapy and an intralesional corticosteroid, unless these therapies are medically inadvisable.
2. There are no head-to-head trials to inform the place in therapy of nemolizumab-ilto relative to dupilumab. Potential safety advantages of nemolizumab-ilto over dupilumab include a lack of conjunctivitis and keratitis, arthralgia, herpes infection, and helminth infection. A potential safety disadvantage of nemolizumab-ilto is a small increased risk of atopic dermatitis, whereas dupilumab is indicated for that condition. In addition, nemolizumab-ilto lacks published long-term safety data and the OLYMPIA LTE study is ongoing, whereas dupilumab has an established record of safety during chronic use.
3. The relative costs of these agents depend on patient weight, with nemolizumab-ilto having a more favorable cost than dupilumab in patients weighing < 90 kg and a less favorable cost in patients ≥ 90 kg.

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