09-4000-99

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Subject: Nemolizumab-ilto (Nemluvio) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Nemolizumab-ilto (Nemluvio) is an interleukin-31 (IL-31) receptor antagonist approved in August 2024 by the US Food and Drug Administration (FDA) for the treatment of adults with prurigo nodularis. IL-31 has been identified as a cytokine responsible for stimulating pruritus. Nemolizumab is the first IL-31 receptor antagonist to be approved by the FDA, and it is the second drug to be approved for the treatment of prurigo nodularis. Dupilumab (Dupixent) was the first drug to be approved for prurigo nodularis in September 2022. Nemolizumab is also currently under review by the FDA for the treatment of atopic dermatitis in adolescents and adults. Additionally, nemolizumab is in Phase 3 development for chronic kidney disease-associated pruritus.

Prurigo Nodularis

Prurigo nodularis (PN) is a skin disorder that is defined by the presence of chronic pruritus and multiple elevated, firm, and nodular lesions. PN is more common in older adults but can occur in children. The underlying cause of PN is unknown, but it appears neural and immunologic processes both play a role in its development. The nodules form in a subset of patients that have chronic pruritus, with the nodules forming in areas with continuous scratching over prolonged periods of time. There is significant disease burden associated with PN including sleep disruption, anxiety, and depression. The nodules are typically firm, dome-shaped, and itchy and range in size from millimeters to several centimeters. The nodules can range in color from flesh tones to brown/black and can range in number from a few to hundreds. The pruritis associated with PN can range from sporadic to continuous and generally the underlying cause is unknown. There are a number of conditions, both dermatologic and other diseases, that are associated with PN, such as atopic dermatitis, kidney disease, diabetes, and HIV.

The diagnosis of PN is generally one of exclusion. The American Academy of Dermatology (AAD) indicates that the diagnostic workup should include a clinical examination with a complete review of

systems and assessment of PN severity, which should include both disease burden (e.g., quality of life, sleep disturbances) and pruritis intensity. The ADD notes three core features associated with PN:

- Presence of firm, nodular lesions
- Pruritus that lasts for at least 6 weeks
- History and/or signs of repeated scratching, picking, or rubbing

Management requires a multifaceted approach with a focus on reducing pruritis, interrupting the itch-scratch cycle, and healing lesions. General measures that should be used at baseline include gentle skin care, moisturizers, and antipruritic emollients. Treatment may need to address both the neural and immunologic components of pruritis based on patient signs and symptoms, and often involves the use of topical and systemic therapies. Most therapies for PN have not been adequately studied, and their evidence for use is based on small clinical trials, observational studies, and case reports.

Topical therapies are the initial treatment for limited disease. Topical corticosteroids (TCS) target the immunologic component of PN. The International Forum for the Study of Itch (IFSI) 2020 guideline on chronic prurigo including prurigo nodularis strongly recommends moderate to very potent topical corticosteroids on lesional skin. Intralesional corticosteroids may be directly injected into thicker lesions where required, but use should be limited to patients with less than 10 lesions. Topical calcineurin inhibitors and topical calcipotriol have also been used in patients who failed TCS therapy and a prolonged course of a topical immunomodulator is desired. Topical capsaicin, which targets the neural component of PN, has limited clinical evidence and tends to have short term efficacy.

Systemic therapies are used for widespread disease or disease refractory to topical therapy. Phototherapy is reasonably tolerated and addresses both the immunologic and neural components of PN. However, phototherapy combined with topical therapy will not be adequate for most patients, and the majority will require supplemental systemic therapy. Oral immunosuppressants, such as methotrexate and cyclosporine, have shown to reduce pruritis and heal lesions per limited data available. Methotrexate is generally preferred due to its more favorable side effect profile in comparison to cyclosporine, and cyclosporine should only be considered in more severe cases. Other systemic therapies that have shown to be less efficacious and treat the neural component of PN include thalidomide, gabapentin, pregabalin, antidepressants, aprepitant, and naltrexone. Since PN is a nonhistaminergic condition, antihistamines are unlikely to be effective and are not recommended.

Biologic agents are the first therapies to gain approval from the US Food and Drug Administration (FDA) for the treatment of PN. These immunomodulating drugs are believed to target molecules expressed by specific cell types that release a variety of itching mediators that directly or indirectly stimulate receptors on nerve endings in the skin. Biologic agents disrupt this cycle and have been proven to alleviate both pruritus and PN lesions.

Efficacy

Two randomized, double-blind, placebo-controlled trials (OLYMPIA 1 [NCT04501666] and OLYMPIA 2 [NCT04501679]) enrolled a total of 560 adult subjects with prurigo nodularis (PN). OLYMPIA 1 and OLYMPIA 2 assessed the effect of Nemluvio on the signs and symptoms of PN, targeting improvement in skin lesions and pruritus over 16 weeks. In OLYMPIA 1, subjects were extended up to 24 weeks of treatment. Disease severity was defined using an Investigator's Global Assessment (IGA) in the overall assessment of prurigo nodularis nodules on a severity scale of 0 to 4. 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. The peak pruritus numeric rating scale (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.

Subjects enrolled in these two trials had an IGA score greater than or equal to 3, severe pruritus as defined by a weekly average of the PP-NRS score of greater than or equal to 7 on a scale of 0 to 10, and greater than or equal to 20 nodular lesions. Fifty-eight (58)% of subjects had a baseline IGA score of 3 (moderate PN), and 42% of subjects had a baseline IGA of 4 (severe PN). The baseline weekly average PP-NRS score was a mean of 8.5. Thirty-two (32)% of subjects had a history of atopy. In the OLYMPIA 2 trial, 78.5% of subjects had previously used topical corticosteroids for the treatment of PN.(5) In both trials, patients were prohibited from using other therapies for PN such as topical corticosteroids, topical calcineurin inhibitors, or systemic immunomodulators, unless they were required as a rescue medication at the discretion of the investigator.

Subjects weighing less than 90 kg in the Nemluvio group received subcutaneous injections of Nemluvio 60 mg at Week 0, followed by 30 mg injections every 4 weeks. Subjects weighing 90 kg or more in the Nemluvio group received subcutaneous injections of Nemluvio 60 mg at Week 0 and every 4 weeks.

Efficacy was assessed with the proportion of subjects with an improvement of greater than or equal to 4 from baseline in PP-NRS, the proportion of subjects with an IGA of 0 (Clear) or 1 (Almost Clear) and a greater than or equal to 2-point improvement from baseline, the proportion of subjects who achieved a response in both PP-NRS and IGA per the criteria described above, and the proportion of subjects with PP-NRS less than 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 greater than or equal to 4 from baseline in PP-NRS and IGA 0 or 1	22%	2%	15% (8%, 21%)	25%	4%	22% (14%, 30%)
Proportion of subjects with IGA 0 or 1	26%	7%	15% (7%, 23%)	38%	11%	29% (19%, 38%)
Proportion of subjects with an improvement (reduction) of greater than or equal to 4 from baseline in PP-NRS	56%	16%	38% (27%, 48%)	49%	16%	34% (23%, 45%)
Proportion of subjects with PP-NRS less than 2	32%	4%	28% (20%, 36%)	31%	7%	26% (18%, 34%)

In both OLYMPIA 1 and OLYMPIA 2, statistically significant improvements in itch and PN skin lesions were observed at Week 16, with some subjects achieving this as early as Week 4. Examination of weight,

age, gender, race, history of atopy, and prior treatment did not identify meaningful differences in response to Nemluvio among these subgroups at Week 16.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of nemolizumab-ilto (Nemluvio) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "5"):

1. **ONE** of the following ("a", "b", or "c"):
    a. The member has been treated with nemolizumab (starting on samples is not approvable) within the past 90 days
    b. The prescriber states the member has been treated with nemolizumab (starting on samples is not approvable) within the past 90 days **AND** is at risk if therapy is changed
    c. **BOTH** of the following ('i" and "ii"):
        i. Nemolizumab will be used for the treatment of an indication listed in the Table, and **ALL** of the indication-specific criteria are met
        ii. **EITHER** of the following if the member has an FDA-approved indication ("I" or "II"):
            I. The member's age is within FDA labeling for the requested indication for nemolizumab
            II. The prescriber has provided information in support of using nemolizumab for the member's age for the requested indication
2. The prescriber is a specialist in the area of the member's diagnosis (e.g., dermatologist, allergist, or immunologist for prurigo nodularis), **OR** the prescriber has consulted with a specialist in the area of the member's diagnosis
3. The member does **NOT** have any FDA labeled contraindications to Nemluvio
4. The member will **NOT** be using nemolizumab in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
5. **ONE** of the following ("a", "b", or "c"):
    a. The requested quantity (dose) does **NOT** exceed the following based on the member's weight:
        - 90 kg or greater: 60 mg subcutaneously every 4 weeks (28 days)

- QL: 30 mg prefilled pen – 2 pens per 28 days

- Less than 90 kg: 60 mg subcutaneously for one dose, followed 30 mg subcutaneously every 4 weeks (28 days)
  - QL: 30 mg prefilled pen – 1 pen per 28 days*

  **2 pens are permitted for the initial 28-day supply (i.e., loading dose)*

b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** there is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does **NOT** exceed the program quantity limit

c. The requested indication does **NOT** have a maximum FDA labeled dose, **AND** there is support for therapy with a higher dose for the requested indication

Approval duration: 12 months

Table 1

Indications and Specific Criteria	
Indication	**Specific Criteria**
Prurigo nodularis (PN)	When **ALL** of the following are met ("1", "2". and "3"): 1. The member has **ALL** of the following features associated with PN: a. Presence of greater than or equal to 20 firm, nodular lesions **AND** b. Pruritus that has lasted for at least 6 weeks **AND** c. History and/or signs of repeated scratching, picking, or rubbing **AND** 2. **ONE** of the following: a. The member has tried and had an inadequate response to at least a medium-potency topical corticosteroid used in the treatment of PN after at least a 2-week duration of therapy **OR** b. The member has an intolerance or hypersensitivity to therapy with at least a medium-potency topical corticosteroid used in the treatment of PN **OR**

	c. The member has an FDA-labeled contraindication to **ALL** medium-, high-, and super-potency topical corticosteroid used in the treatment of PN **OR** d. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PN **AND** 3. **ANY** of the following (submitted medical records/chart notes are required for confirmation): a. The member has tried and had an inadequate response to treatment with dupilumab (Dupixent) for the treatment of PN after at least a 3-month duration of therapy **OR** b. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to dupilumab (Dupixent) **OR** c. The member has an FDA-labeled contraindication to dupilumab (Dupixent)

Continuation of nemolizumab-ilto (Nemluvio) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "6"):

1. An authorization or reauthorization for nemolizumab has been previously approved by Florida Blue [Note: members not previously approved for the requested agent will require initial evaluation review]
2. The member has had clinical benefit with nemolizumab
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., dermatologist, allergist, or immunologist for prurigo nodularis), **OR** the prescriber has consulted with a specialist in the area of the member's diagnosis
4. The member does **NOT** have any FDA labeled contraindications to Nemluvio
5. The member will **NOT** be using nemolizumab in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
6. **ONE** of the following ("a", "b", or "c"):
    a. The requested quantity (dose) does **NOT** exceed the following based on the member's weight:

- 90 kg or greater: 60 mg subcutaneously every 4 weeks
    - QL: 30 mg prefilled pen – 2 pens per 28 days
- Less than 90 kg: 30 mg subcutaneously every 4 weeks
    - QL: 30 mg prefilled pen – 1 pen per 28 days

b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** there is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does **NOT** exceed the program quantity limit

c. The requested indication does **NOT** have a maximum FDA labeled dose, **AND** there is support for therapy with a higher dose for the requested indication

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Indicated for the treatment of adults with prurigo nodularis
    - Adult patients weighing <90 kg: The recommended subcutaneous dosage is an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks.
    - Adult patients weighing ≥90 kg: The recommended subcutaneous dosage is an initial dose of 60 mg (two 30 mg injections), followed by 60 mg given every 4 weeks.
- Nemluvio 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 preparation and administration. Patients may self-inject after receiving training on subcutaneous injection techniques. For the initial dose, administer each of the two injections at different injection sites. Administer subcutaneous injection into the front upper thighs or abdomen except for the 2 inches around the navel. Injection in upper arm should only be performed by a caregiver or healthcare professional.
- Nemluvio is supplied in a single-dose prefilled dual-chamber pen with white powder in one chamber and a clear diluent in the other chamber. Nemluvio must be reconstituted prior to administration. Use Nemluvio pens within 4 hours after reconstitution. Refer to the product labeling for more information.

Dose Adjustments

- Hepatic impairment – Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.
- Renal impairment - Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

- Available in a single-dose, dual chamber prefilled pen containing 30 mg of nemolizumab in one chamber and the diluent, water for injection, in the other chamber. Following reconstitution, each prefilled pen delivers 30 mg/0.49 mL of nemolizumab.
- Store the dual chamber prefilled pen in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light until the expiration date. Do not freeze. Do NOT expose to heat or direct sunlight. Alternatively, the carton containing the unused dual chamber prefilled pen may be stored at room temperature [up to 77°F (25°C)] for up to 90 days.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Known hypersensitivity to nemolizumab or to any of the excipients in Nemluvio

Precautions/Warnings

- **Hypersensitivity**: Hypersensitivity reactions, such as facial angioedema, have been reported with Nemluvio use. If a clinically significant hypersensitivity reaction occurs, immediately institute appropriate therapy and discontinue Nemluvio.
- **Vaccinations**: Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to treatment with Nemluvio. Avoid use of live vaccines in patients during treatment with Nemluvio. It is unknown if administration of live vaccines during Nemluvio treatment will impact the safety or effectiveness of these vaccines. No data are available on the response to non-live vaccines.

BILLING/CODING INFORMATION:

HCPCS Coding

J3590	Unclassified biologics

ICD-10 Diagnosis Codes That Support Medical Necessity

L28.1	Prurigo nodularis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

Thalidomide (Thalomid) Capsules, 09-J1000-56

Dupilumab (Dupixent) Injection, 09-J2000-80

OTHER:

NOTE: The list of biologic immunomodulator agents not permitted as concomitant therapy can be found at Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.

REFERENCES:

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8. Stander S, Yosipovitch G, Legat F, et al. Nemolizumab monotherapy improves itch and skin lesions in patients with moderate-to-severe prurigo nodularis: Results from a global phase 3 trial (OLYMPIA 1). European Academy of Dermatology and Venereology; 2023. https://s3.eu-central-1.amazonaws.com/m-anage.com.storage.eadv/abstracts_congress2023/39434.pdf
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/09/24.

GUIDELINE UPDATE INFORMATION:

01/01/25	New Medical Coverage Guideline.