Dupilumab (DUPIXENT) in Prurigo Nodularis
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Dupilumab is a monoclonal IgG4 antibody to interleukin (IL)-4Rα that thereby inhibits IL-4 and IL-13 signaling.[1] These cytokines have been linked to allergic and atopic diseases.

Indication Under Review in This Document

- Treatment of adult patients with prurigo nodularis (PN).

Dosage Regimen and Dosage Form(s) Under Review

- Initial: 600 mg (two 300-mg injections) SC
- Maintenance: 300 mg SC every 2 weeks.
- Single-dose prefilled syringe or single-dose prefilled pen: 300 mg/2 mL (cartons of 2 syringes or pens)

Efficacy Considerations

- No active-controlled trials have been performed.
- Two published, similarly designed, phase 3 placebo-controlled randomized clinical trials (RCTs), LIBERTY-PN PRIME and PRIME2, showed efficacy of dupilumab in adults who had PN with ≥ 20 nodules and severe itch despite use of topical therapies.[2]

Phase 3 Randomized Clinical Trials

- Table 1 summarizes the methods of the phase 3 RCTs.

Table 1 Methods of Phase 3 RCTs

Topic	PRIME	PRIME2
Study Design	24-wk Phase 3 MN DB PC RCT (1:1) plus 12-wk post-treatment follow-up	24-wk Phase 3 MN DB PC RCT (1:1) plus 12-wk post-treatment follow-up
Major Entry Criteria	*Inclusion:* • 18–80 years of age • Clinical diagnosis of PN for ≥ 3 months • Total of ≥ 20 PN lesions / nodules on both legs and/or both arms and/or trunk (≥ 2 body surface areas) • WI-NRS score ≥ 7 (scale, 0–10) for 7 previous days	Same as in PRIME

Topic	PRIME	PRIME2
	• Inadequate control after a 2-week course of medium–super potency TCS or not medically advisable *Exclusion:* • PN secondary to medications (e.g., opioids, ACEIs) • PN secondary to medical conditions such as neuropathy or psychiatric disease • Documented moderate–severe atopic dermatitis in previous 6 months	
Interventions	For 24 weeks: • Dupilumab 600 mg then 300 mg Q2W • Placebo Allowed co-medications: Stable regimen of low–medium potency topical corticosteroids and topical calcineurin inhibitors	Same as in PRIME
Primary Efficacy Measure(s)	At Week 24: WI-NRS–4 response	At Week 12: WI-NRS–4 response

ACEIs, Angiotensin converting enzyme inhibitors; **WI-NRS–4**, Worst Itch Numeric Rating Scale (range, 0 / No Itch to 10 / Worst imaginable itch) at least 4-point reduction from baseline (considered a clinically meaningful change)

Table 2 Baseline Patient Characteristics

Characteristic	PRIME (N = 151)	PRIME2 (N = 160)
Age, mean, y	50.1	48.8
Male, n (%)	100 (66.2)	103 (64.4)
White, n (%)	80 (53.0)	90 (60.0)
Asian, n (%)	54 (35.8)	52 (32.5)
Black / African American	11 (7.3)	8 (5.0)
Western countries region, n (%)	38 (25.2)	92 (57.5)
History of atopy†	61 (40.4)	74 (46.3)
Prior topical corticosteroid for PN, n (%)	149 (98.7)	157 (98.1)
Prior topical calcineurin inhibitor for PN, n (%)	21 (13.9)	14 (8.8)
Prior systemic medication for PN, n (%)	105 (69.5)	101 (63.1)
Antihistamines	89 (58.9)	76 (47.5)
Corticosteroids	30 (19.9)	24 (15.0)
Nonsteroidal immunosuppressants	26 (17.2)	38 (23.8)
Antidepressants	3 (2.0)	23 (14.4)
Gabapentinoids	7 (4.6)	1 (0.6)
Opioid antagonists	4 (2.6)	3 (1.9)

Source: 2

† Atopy was defined as medical history of atopic dermatitis, allergic rhinitis / rhinoconjunctivitis, asthma, or food allergy

Results

- More patients discontinued the study in the placebo group than the dupilumab group in both studies (16/76 [21.1%] vs 1/75 [1.3%], respectively, in PRIME and 25/82 [30.5%] and 2/78 [2.6%], respectively, in PRIME2).[2] Discontinuations were mainly due to adverse event or lack of efficacy in the placebo groups and lack of efficacy in the dupilumab groups. No discontinuations were due to loss to follow-up.
- Efficacy data are summarized in Table 3 and Table 4.

Table 3 Selected efficacy results from phase 3 clinical trials

Outcome	Study	DUP	PBO	Relative Risk (95% CI)	Difference (95% CI)
WI-NRS–4 and IGA-PN-S–0/1 response at Week 24	PRIME	29/75 (38.7)	7/76 (9.2)	4.2 (2.0, 9.0)	29.6 (16.4, 42.8)
	PRIME2	25/78 (32.1)	7/82 (8.5)	3.8 (1.7, 8.2)	25.5 (13.1, 37.9)

Source: 2

CFB, Change from baseline; **DUP**, Dupilumab 300 mg every 2 weeks; **IGA-PN-S–0/1**, Investigator Global Assessment for PN-Stage Score of 0 / Clear (No lesions) or 1 / Almost clear (≤ 5 nodules); **PBO**, Placebo; **WI-NRS–4**, Worst Itch Numeric Rating Scale (range, 0 / No Itch to 10 / Worst imaginable itch) at least 4-point reduction from baseline

Table 4 Absolute Effects for Achieving Combined WI-NRS–4 and IGA-PN-S–0/1 Response With Dupilumab vs Placebo at Week 24

Trial	AAE per 1000 (95% CI)	NNT (95% CI)	Q
PRIME	295 (167, 423)	4 (3, 6)	M[α]
PRIME2	235 (115, 355)	5 (3, 9)	M[α]

AAE, Anticipated absolute effect for achieving the outcome; **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (M = Moderate)

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

- Selected secondary efficacy results:
    - Dupilumab was superior to placebo in changes from baseline to Week 24 in multiplicity-controlled Patient-Reported Outcomes of Dermatology Life Quality Index, Skin Pain Numerical Rating Scale, and total Hospital Anxiety and Depression Scale scores.
- Subgroup Analyses
    - In subgroup analyses by topical corticosteroid or topical calcineurin inhibitor use / non-use and atopic / non-atopic history showed no response predictors.

Safety Considerations

Safety Profile from US Prescribing Information

- **Boxed Warnings, Contraindications, Other Warnings / Precautions:** As for previous indications.
- **Common Adverse Events (≥ 2% of dupilumab group and greater than placebo):** Nasopharyngitis, conjunctivitis, herpes infection, dizziness, myalgia, diarrhea

Safety Results from Clinical Trials

- **Deaths and Serious Adverse Events**: No deaths were reported in either phase 3 trial. Serious adverse events rates were numerically lower on dupilumab than placebo in PRIME (6.7% of 75 patients vs 8.0% of 75 patients, respectively) and similar in PRIME2 (2.6% of 77 patients and 2.4% of 82 patients, respectively).[2]
- **Discontinuations Due to Adverse Events (DAEs)**: DAEs were not reported on dupilumab and were reported in 2.7% and 1.2% of placebo patients in PRIME and PRIME2, respectively.[2]

Evidence Gaps

- Long-term efficacy and safety in PN
- Maintenance of response
- Durability of lesion clearance after treatment discontinuation
- Patient Satisfaction

Network Meta-analyses

- No network meta-analyses including dupilumab studies were found.

Other Considerations

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest significant treatment difference) based on WI-NRS–4 response was 4 weeks in PRIME and 5 weeks in PRIME2. Based on IGA–0/1 response, onset was 4 weeks and 12 weeks in PRIME and PRIME2, respectively.
- The duration of an adequate therapeutic trial based on either WI-NRS–4 response or IGA–0/1 response may not have been reached by Week 24 in both phase 3 trials.
- According to a systematic review, 2 months of dupilumab therapy are required before itch is relieved. Complete remission is rarely observed before 4 months of therapy. Atopic dermatitis-related PN patients need more weeks of treatment than non-atopic dermatitis-related PN patients.[3]

Maintenance and Durability of Response

- No published data.

Other Therapeutic Options

- The goal of therapy in PN is to relieve pruritus and interrupt the itch-scratch cycle.[8] Nodules slowly resolve once itching ceases.
- Since PN is often challenging to treat and involves neural and immune dysregulation, a multimodal approach is suggested. There is wide variability in treatment approaches and nonstandardized dosages for drugs.
- Society treatment guidelines pre-date the FDA approval of dupilumab in PN. The recommendations of a US consensus panel,[4] the International Forum on the Study of Itch (IFSI),[5] and the European Dermatology Forum and European Academy of Dermatology and Venereology (EDF / EADV)[6] are summarized below. Japanese guidelines are not reviewed.[7]
- Note that the guidelines use different terminologies. The US guideline uses PN as an overarching term comprising all variants of the disease.[4] In Europe, the term chronic prurigo is used as the general term, and subclassifications are used for the nodular, papular, plaque, or umbilicated variants (e.g., chronic prurigo of the nodular type).[4,5,8]

US Consensus Panel Approach to Management of PN (2021)

- According to a US consensus panel, treatment should be based on clinical judgment instead of a stepwise approach.[4] The potential treatments are based on small RCTs, intraindividual RCTs, observational studies, case reports / series, or retrospective studies. Table 5 shows the potential drugs for PN available in the US.

Table 5 Potential Treatments for PN Per a US Consensus Panel

Tier		Neuromodulators	Immunomodulators
1	**Mainly Topical Therapies**	Topical capsaicin Topical ketamine / amitriptyline / lidocaine	Intralesional corticosteroids (< 10 lesions) / cryotherapy Topical calcipotriol Topical calcineurin inhibitors Topical corticosteroids
2	**Mainly Widespread Skin-directed or Systemic Therapies with Reasonable Tolerability**	Low-dose gabapentinoids Antidepressants (SNRI > SSRI > TCA) High-dose gabapentinoids NK1 receptor antagonists	Narrowband UVB / PUVA phototherapy Methotrexate Cyclosporine
3	**Less Tolerable, Less Well-established, or Experimental Therapies**	KOR / MOR antagonists Thalidomide	**Dupilumab†** Azathioprine
4	**Therapies that May Prove Useful but Currently Lack Data in PN**	Cannabinoids	Mycophenolate mofetil JAK inhibitors

JAK, Janus kinase; KOR, Kappa-opioid receptor; MOR, Mu-opioid receptor; NK1, Neurokinin-1
† Dupilumab was not FDA approved as of the date of the guideline.

International Forum on the Study of Itch (IFSI) Guideline on Chronic Prurigo (2020)

- The IFSI panel consisted of the European Dermatology Forum and US itch experts. The IFSI used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method for evaluating the quality of evidence.
- The expert panel recommended emollients and an interdisciplinary approach to the management of chronic prurigo.[5] Cognitive behavioral therapy is suggested.
- The IFSI proposed a treatment ladder and recommended a step-wise approach (Table 6).

Table 6 IFSI Guideline on Chronic Prurigo

Step	Strongly Recommended Treatments	Weakly Recommended / Suggested Treatments	Cannot Make a Recommendation
1	Topical Corticosteroids (moderate–very potent)	Topical calcineurin inhibitors Antihistamines (H1)† Cryotherapy‡	—
2	Narrowband 311-nm UVB Broadband UBV PUVA	Topical capsaicin Intralesional corticosteroids‡ Excimer laser‡	—
3	Gabapentin Pregabalin	Antidepressants§ Cyclosporine Methotrexate	—
4	—	**Dupilumab**‡ Mu-opioid antagonists Aprepitant Nemolizumab¶ Thalidomide#	Serlopitant†† Lenalidomide Kappa-opioid receptor agonists Other biologics and small molecules

† Antihistamines (H1) have only low evidence of antipruritic effects. Histamine may be an itch mediator in chronic prurigo.
‡ Cryotherapy and/or intralesional corticosteroids, excimer laser, and dupilumab are suggested in selected patients.
§ Antidepressants (examples): serotonin reuptake inhibitors, mirtazapine (at a non-antidepressant dose of 15 mg).
¶ Nemolizumab pending availability (currently investigational)
# Thalidomide is suggested only in very exceptional cases of chronic prurigo refractory to safer therapies and prescribed by physicians experienced in the use of the drug.
†† Serlopitant, a neurokinin-1 receptor antagonist, showed efficacy in a phase 2 RCT[9] but failed to show PN anti-itch efficacy in two phase 3 RCTs.[10,11]

European Guidelines on Chronic Pruritus Including Chronic Prurigo (2019)

- Treatments recommended for PN by the European Dermatology Forum and European Academy of Dermatology and Venereology (EADV) were topical corticosteroids and systemic cyclosporin, methotrexate, azathioprine, neurokinin-1 (NK-1) receptor antagonists (e.g., the investigational agent serlopitant), and phototherapy.[6,8]

Potential Treatment Modalities for PN

- Evidence for pharmacotherapies in PN are limited.[12,13] Dupilumab is the only agent shown to be effective in placebo-controlled RCTs.[2]
- In a large, US prescription claims database, ambulatory cohort study (N = 86,855; 7095 with PN), the three most commonly prescribed treatments in patients with a diagnosis of PN (International Classification of Diseases, 10th revision–Clinical Modification [ICD-10-CM] code: L28.1) were all corticosteroids given via different routes of administration: intralesional (36%), topical (26%), and systemic (19%). Of the other systemic agents, gabapentin (7%) was most frequently used.[14]
- Individual therapies for PN are summarized in Table 7.

Table 7 Pharmacotherapies for PN

Treatment Modality	Alternatives	Comments
Local Therapies	*Neuromodulators*	
	Topical capsaicin	Use is limited by minimal effectiveness, frequent dosing (6x/d), and skin irritation.
	Topical ketamine / amitriptyline / lidocaine	Off-label, compounded. Retrospective study in chronic pruritus[15] (not prurigo).
	Immunomodulators	
	Topical corticosteroids	Limited, active-controlled RCTs.[16,17] High-potency agents are considered first-line topical therapy. Occlusion may improve effectiveness and discourage scratching the skin.
	Topical calcineurin inhibitors	Limited, active-controlled RCT with pimecrolimus cream.[18] No RCTs with tacrolimus.
	Topical calcipotriene (aka calcipotriol)	Limited, active-controlled RCT suggested better lesion count/size efficacy with calcipotriene ointment 0.005% than betamethasone valerate ointment 0.1%.[19]
	Intralesional corticosteroids	For patients with < 10 lesions. Can relieve pruritus and flatten nodules. E.g.: triamcinolone (initially 10 mg/mL).
	Topical anesthetics	Moderately antipruritic; may be useful in mild PN. Not mentioned by US consensus panel.[4] E.g.: pramoxine lotion 1%, lidocaine spray.
Phototherapy	Narrow-band UVB (nbUVB)	Phototherapy may be useful in patients with comorbidities and drug-drug interactions. nbUVB is considered first-line therapy. Adjunctive systemic therapies are often needed to obtain an adequate response. Evidence for phototherapy in PN consists of case series.[20,21]
	Psoralens + UVA (PUVA)	
Systemic Therapies	*Neuromodulators*	
	Gabapentinoids (e.g., gabapentin, pregabalin)	Case reports / series in PN.[22,23] Gabapentin (300–900 mg/d) is considered useful for reducing the "emotional dysregulation" associated with development of PN.[22] Use is limited by sedation because of the higher doses often needed to relieve itching.
	Antidepressants	E.g., SSRIs / paroxetine, fluvoxamine; SNRIs / duloxetine; TCAs / amitriptyline
	Aprepitant	Ineffective in a phase 2 RCT.[24]

Treatment Modality	Alternatives	Comments
	Naltrexone	Mu-opioid receptor antagonist. Has been dosed at 50 mg/d.[25] Long-term treatment has been associated with tachyphylaxis and worsening of PN-related pruritus.[26]
	Nalbuphine	Kappa-opioid receptor agonist and mu-opioid receptor antagonist. Showed promising antipruritic effects at 162 mg or 81 mg BID in a 10-week phase 2 placebo-controlled RCT.[27]
	Butorphanol	Kappa- and sigma-opioid receptor agonist and mu-opioid receptor antagonist. E.g., intranasal butorphanol 1 mg
	Thalidomide	Neurotoxic and teratogenic. Generally reserved for patients who fail conventional agents. Use is supported by case series.[28,29]
	Immunomodulators	
	Dupilumab	The only systemic agent with confirmed efficacy and safety and FDA approval in PN. Notable adverse effects: Conjunctivitis, keratitis, arthralgia.
	Corticosteroids	Can be considered for refractory PN or refractory, severe acute flares. Notable adverse effects: diabetes mellitus, hypertension, osteoporosis, muscle atrophy, etc.
	Methotrexate	Retrospective studies. Notable adverse effects: mucositis, GI, myelosuppression, liver toxicity, acute kidney injury, pulmonary fibrosis, malignancy, skin cancer. Dosage per expert consensus: 7.5–15 mg PO weekly.
	Cyclosporine	Retrospective studies. Can be considered for short-term treatment of severe, chronic, refractory PN for 3–6 months. Notable adverse effects: nephrotoxicity, HTN, liver toxicity, myelosuppressive, neurotoxicity, lipid elevation, hypertrichosis. Dosage per expert consensus: 3 mg/kg/d for 2–4 weeks, then increase by 0.5–1 mg/kg/d every 2–4 weeks as tolerated.
	Mycophenolate mofetil	No published studies in PN.
	Azathioprine	Retrospective studies. Notable adverse effects: transaminitis, GI, myelosuppression, infection, lymphoproliferative malignancy, nonmelanoma skin cancer. Pretreatment testing for thiopurine methyl transferase (TPMT) deficiency may help identify patients at increased risk of severe drug toxicity. Dosage per expert consensus: 50–200 mg PO daily.
	Abrocitinib	Investigational in PN
	Tofacitinib	Investigational in PN

Sources: 4,30

Projected Place in Therapy

- **Epidemiology and Prevalence of Prurigo Nodularis**. PN is a rare, chronic, inflammatory dermatosis manifested by severely pruritic nodules or papules that develop in areas within reach of scratching on both sides of the body usually after the onset of itching. The upper-mid region of the back is often spared. The itching tends to be uncontrollable. Prolonged, repetitive scratching and rubbing results in erosive, hyperkeratotic, lichenified skin lesions. PN causes more intense itching and quality of life impairment than chronic pruritus. The disease is associated with immune and neural dysregulation although the etiopathogenesis of PN is not definitely known. While PN may be associated with other conditions, such as atopic dermatitis, malignancy, and chronic kidney disease, it should be considered a distinct disease entity. Itching does not necessarily improve with treatment of any associated diseases. The prevalence of chronic prurigo in the US has been estimated to be 13 per 100,000,[31] 36.7–43.9 per 100,000,[32] and 72 per

100,000.[33] African Americans may be more likely to develop PN than white patients.[34,35] The elderly are most frequently affected.[4]

- **Potential Place in Therapy Based on the Evidence**. Although no head-to-head trials were available, moderate-quality evidence from a placebo-controlled trial supports the use of dupilumab in patients with PN who have had an inadequate response to medium to super-high potency topical corticosteroids or for whom such therapy is medically inadvisable. The majority of patients had received prior systemic medications for PN, mainly antihistamines, corticosteroids, and nonsteroidal immunomodulators. Overall, the combined antiprurigenic and complete / near complete lesion clearance benefits are small to medium and clinically meaningful.
- **Potential Place in Therapy in VHA**. Dupilumab may be used in patients with a documented diagnosis of PN and ≥ 20 nodules who have an inadequate response (after ≥ 2 weeks per therapy) or intolerance to either of the following: (1) two topical therapies (e.g., medium, high, or super-high corticosteroids [where different strengths count as different therapies], calcipotriene, or calcineurin inhibitor), or (2) one topical therapy and an intralesional corticosteroid, unless these therapies are medically inadvisable.

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