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Drug Class Update with New Drug Evaluation:
Targeted Immune Modulators for Asthma and Atopic Dermatitis - Review of Non-Pulmonary Indications

Date of Review: October 2025

Date of Last Review: PA Update August 2024
Dates of Literature Search: 01/01/2022-01/30/2025

Generic Name: Nemolizumab

Brand Name (Manufacturer): NEMLUVIO (Galderma)
Dossier Received: no

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Review new evidence and expanded non-pulmonary indications for targeted immune therapies (TIMs) that are approved by the Food and Drug Administration (FDA) for management of asthma and atopic dermatitis (AD). In addition, evaluate the safety and efficacy of NEMLUVIO (nemolizumab) which was recently approved for prurigo nodularis (PN) in adults and moderate-to-severe AD in patients at least 12 years of age. A second injectable medication, EBGLYSS (lebrikizumab), which was recently FDA-approved for patients at least 12 years of age with moderate-to-severe AD, is reviewed separately.

Plain Language Summary:
- This review looks at new evidence for medicines, called targeted immune modulators, that are approved by the Food and Drug Administration (FDA) for conditions of the skin (including atopic dermatitis, prurigo nodularis and chronic spontaneous urticaria), chronic runny nose with nasal polyps (also called chronic rhinosinusitis with nasal polyps), and conditions that cause an increased number of white blood cells, or eosinophils, in the body. When compared to placebo, all these medicines improve the condition for which the FDA has approved their use. However, there is very little evidence to show that one medicine works better than another in this class of medicines.
- Chronic rhinosinusitis (CRS) is defined by having a runny nose for more than 3 months. For some people, nasal polyps (or unusual tissue growth that can block nasal passages) can worsen these symptoms. A steroid nasal spray can usually improve symptoms of CRS with nasal polyps (CRSwNP). If using a nasal spray does not improve the symptoms, then evidence shows that 3 medicines (dupilumab, mepolizumab and omalizumab) can decrease nasal congestion and improve the quality of life for people with CRSwNP.
- Chronic spontaneous urticaria (CSU) is itching that has lasted for more than 6 weeks with no known cause. Antihistamines such as cetirizine, loratadine, or fexofenadine may relieve the constant itching. If antihistamines do not work, the medicine omalizumab is approved by the FDA to treat CSU.
- Eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES) are rare disorders caused when people have an increased number of white blood cells, called eosinophils. The eosinophils can damage blood vessels, nerves, and organs. Two medicines, benralizumab and mepolizumab, are used to treat EGPA. Mepolizumab can also reduce the risk of worsening symptoms in HES.

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- Prurigo nodularis (PN) is a condition which causes itchy, firm bumps or nodules on the skin, mostly on the arms, legs and upper back. The intense itch leads to scratching, which can make the nodules worse, and even create new nodules. Steroid creams and ointments applied to the skin can help relieve the symptoms of PN. If these medicines do not work, evidence shows that 2 medicines, dupilumab and nemolizumab, may help to relieve itching and improve symptoms.
- Atopic dermatitis (AD) is a skin condition also known as eczema. People with AD have itchy, dry, and red skin. For the management of moderate-to-severe AD in adults, most clinical guidelines recommend trying medicines applied to the skin or oral immunosuppressants (like methotrexate) before starting other medicines (such as dupilumab, tralokinumab, abrocitinib, upadacitinib, or nemolizumab). When compared with placebo, all of these medicines are more effective in relieving itching and clearing skin in people with AD.
- For all of these conditions, providers must explain to the Oregon Health Authority (OHA) why someone needs the targeted immune modulator before OHA will pay for it. This process is called prior authorization.

Research Questions:

1. What is the efficacy of TIMs approved for the treatment of asthma and AD in non-pulmonary indications which are presented in **Table 3**?
2. What is the tolerability and frequency of adverse events (AEs) of TIMs approved for the treatment of asthma and AD in non-pulmonary conditions presented in **Table 3**?
3. Is there new evidence to guide the place in therapy for TIMs in AD management?
4. What is the evidence for the safety and efficacy of nemolizumab for management of PN in adults and moderate-to-severe AD in patients aged 12 years and older?
5. Are there subgroups of patients (e.g. groups defined by demographics, disease severity, comorbidities) for which TIMS used to treat asthma and AD differ in efficacy or frequency of AEs for non-pulmonary conditions?

Conclusions:

Targeted Immune Modulators in Non-Pulmonary Indications

- For the review of the safety and efficacy of TIMs in non-pulmonary conditions including CRSwNP, CSU, EGPA, HES and PN one systematic review was identified.[1] In addition, 6 clinical guidelines were identified to guide pharmacologic management of CRSwNP, CSU, EGPA and PN.[2-7]
- The October 2024 Drug Effectiveness Report (DERP) report on TIMs for non-asthma inflammatory indications updated a 2021 DERP report on this topic.[1] The evidence identified for FDA-approved TIMs includes the following outcomes from placebo-controlled studies:
    - Three randomized controlled trials (RCTs) for dupilumab, 3 RCTs for mepolizumab, and 3 RCTs for omalizumab were identified for management of CRSwNP.[1] Compared with placebo, all 3 TIMs improved nasal congestion and nasal polyp scoring assessments and improved control of CRSwNP symptoms.[1]
    - Nine RCTs demonstrated the efficacy of omalizumab for improvement in both urticaria-related symptoms and Quality of Life (QoL) measurements in participants with antihistamine-refractory CSU compared with placebo.[1]
    - One head-to-head study compared benralizumab with mepolizumab for the treatment of EGPA.[1] In this study, benralizumab was noninferior to mepolizumab, and no notable advantages were provided to select one agent over the other.[1] One placebo-controlled RCT showed mepolizumab can be used as add-on therapy to oral corticosteroids, with or without immunosuppressants, to improve rate of disease remission or delay relapse in patients with EGPA.[1]
    - In people with HES, 2 RCTs demonstrated that mepolizumab can reduce oral corticosteroid use and HES flare occurrence compared with placebo, each of which can have a significant impact on QoL.[1]

- Two RCTs showed significant improvement in PN symptoms (i.e., itching, sleep disruption, pain) with dupilumab compared with placebo.[1]

- The American Academy of Allergy, Asthma & Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI) joint task force issued guidelines for the medical management of CRSwNP in 2023.[2] Two recommendations guide treatment of CRSwNP with medication:
  - In people with CRSwNP, the guideline panel suggests inhaled nasal corticosteroid spray rather than no inhaled nasal corticosteroid spray to manage symptoms (conditional recommendation; low certainty of evidence).[2]
  - In people with CRSwNP, the guideline panel suggests biologics rather than no biologics to manage symptoms (conditional recommendation; moderate certainty of evidence).[2]
- Guidance on management of chronic urticaria (CU) was developed in 2014 by a joint task force of AAAAI and ACAAI members.[3] Three strong recommendations based on RCT evidence from meta-analyses recommend therapies for CU management:
  - Second-generation antihistamines are safe and effective therapies in patients with CU and are considered first-line agents.[3]
  - Leukotriene receptor antagonists can be considered for patients with CU with unsatisfactory responses to second-generation antihistamine monotherapy.[3]
  - Omalizumab should be considered for refractory CU if, from an individualized standpoint, a therapeutic trial of omalizumab is favorable from the standpoint of balancing the potential for benefit with the potential for harm/burden and cost and the decision to proceed is consistent with the patient's values and preferences.[3]
- The National Institute for Health and Care Excellence (NICE) issued guidance for the use of omalizumab in refractory CSU in 2015.[4] Omalizumab is recommended as an option as add-on therapy for treating severe CSU in adults and adolescents aged 12 years and over only if:
  - the severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more and
  - the person's condition has not responded to standard treatment with antihistamines and leukotriene receptor antagonists and
  - omalizumab is administered under the management of a specialist in dermatology, immunology or allergy.[4]
- In 2021, the American College of Rheumatology (ACR) and Vascular Foundation (VF) published guidance for management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis conditions including EGPA.[5] In 2021, the American College of Rheumatology (ACR) and Vascular Foundation (VF) published guidance for management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis conditions including EGPA. Specific recommendations that include mepolizumab are as follows:
  - For patients with active, nonsevere EGPA, ACR/VF conditionally recommends initiating treatment with mepolizumab and glucocorticoids over methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids (low- to very low-quality evidence).[5]
  - For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, ACR/VF conditionally recommends adding mepolizumab over switching to another agent (very low-quality evidence).[5]
  - For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving low-dose glucocorticoids and no other therapy, ACR/VF conditionally recommends adding mepolizumab over adding methotrexate, azathioprine, or mycophenolate mofetil (very low-quality evidence).[5]
- The European Alliance of Associations for Rheumatology (EULAR) updated recommendations for the management of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides including EGPA in 2022.[6] Mepolizumab is recommended for remission induction in patients with relapsing or EGPA refractory to glucocorticoid therapy and EGPA without active organ-threatening or life-threating disease (moderate recommendations; moderate-quality evidence).[6]
- A 2024 NICE guideline provides recommendations for the use of dupilumab in people with moderate-to-severe PN.[7] The clinical trial evidence shows that dupilumab improves symptoms of PN compared with best supportive care (topical treatments).[7] However care in clinical trials did not include many of the treatments (e.g., oral corticosteroids, immunosuppressants) that are usually used to manage PN.[7] These limitations in generalizability increase risk that trial

results are not representative of the true treatment effect, and therefore, dupilumab is not recommended by NICE for treating moderate-to-severe PN in adults when systemic treatment is suitable.[7]

- There is insufficient evidence to show that there are subgroups of patients based on demographics (based on age, ethnicity, comorbidities, disease duration or severity), for which one treatment for these non-pulmonary conditions is more effective or associated with fewer adverse events.

Targeted Immune Modulators in Atopic Dermatitis

- No high-quality systematic reviews have been recently published to evaluate the comparative safety and efficacy of TIMs in AD. Eight high-quality clinical guidelines were recently published to guide use of TIMs in moderate-to-severe AD.[8-15]
- NICE issued guidance for the use of abrocitinib, tralokinumab, or upadacitinib in moderate-to-severe AD in 2022.[8]
    - Abrocitinib, upadacitinib and tralokinumab are recommended as options for treating moderate-to-severe AD that is suitable for systemic treatment only if the disease has not responded to at least 1 systemic immunosuppressant.[8]
- In July 2024, NICE published recommendations for the use of lebrikizumab in treating moderate-to-severe AD in people 12 years of age and older.[15] Lebrikizumab is recommended as an option for treating moderate-to-severe AD that is suitable for systemic treatment in adults and young people aged 12 years and over, only if the disease has not responded to at least 1 systemic immunosuppressant, or these are not suitable and dupilumab or tralokinumab would otherwise be offered.[15]
- In 2023 the AAAAI/ACAAI joint task force published guidance for management of mild, moderate and severe AD.[9] Two recommendations include the use of TIMs in treating moderate-to-severe AD:
    - Dupilumab is recommended for patients 6 months of age or older or tralokinumab for patients aged 12 years and older, with moderate-to-severe AD refractory, intolerant, or unable to use mid-potency topical steroid or calcineurin-inhibitor treatment (strong recommendation; high-quality evidence).[9]
    - Oral Janus kinase (JAK) inhibitors (abrocitinib, upadacitinib) are suggested after careful consideration of risks and possible benefits in adults and adolescents 12 years of age and older with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical steroid or calcineurin-inhibitor treatment and dupilumab or tralokinumab (conditional recommendation; low-quality evidence).[9] Off-label use of baricitinib is included in this recommendation for AD management.
- The American Academy of Dermatology (AAD) published guidance in 2024 for AD management with phototherapy and systemic therapies.[10] Eleven recommendations were developed to guide treatment with phototherapy, biologics, oral JAK inhibitors and other immunomodulatory therapies.[10] The recommendations for the use of TIMs include:
    - Dupilumab and tralokinumab are recommended for adults with moderate-to-severe AD (strong recommendation; moderate-quality evidence).[10]
    - Abrocitinib, baricitinib, and upadacitinib are recommended for adults with moderate-to-severe AD (strong recommendations; moderate quality evidence).[10]
- Canada's Drug Agency issued 4 reimbursement reviews for the use of upadacitinib, abrocitinib, dupilumab, and tralokinumab for treating AD.[11-14] Based on a review of the tralokinumab evidence, Canada's Drug Agency did not recommend reimbursement for this medication and did not publish recommendations for use of tralokinumab in patients with AD.[14] Specific recommendations for TIMs include:
    - Upadacitinib or abrocitinib should only be approved to treat patients who have previously tried and are refractory to, or who are ineligible or cannot tolerate, the highest tolerated dose of topical treatments for AD combined with phototherapy (where available), and at least one 12-week trial of methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine.[11,12]
    - Dupilumab is recommended for the treatment of patients aged 6 months and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[13]

Expanded Indications

- Dupilumab received expanded FDA-approval in April 2025, for use in patients 12 years and older with CSU who remain symptomatic despite antihistamine treatment.[16] The approval was based upon 2 placebo-controlled, phase 3 RCTs in patients with symptomatic CSU despite treatment with either antihistamines or omalizumab.[17]
- In June 2020, the FDA-approved dupilumab for treatment of adults with bullous pemphigoid, a painful autoimmune blistering condition with intense itching.[16] The approval was based on data from an unpublished, placebo-controlled Phase II/III trial in 106 adults with moderate-to-severe bullous pemphigoid conducted over 52 weeks.[16] All patients enrolled in this trial were initiated on a standard regimen of oral corticosteroids, which were tapered off at 16 week as long as disease control was maintained.[16] At Week 36 18.3% of dupilumab-treated patients had achieved remission compared with 6.1% of placebo-treated patients (difference = 12.2%; 95% Confidence Interval [CI] -0.8 to 26.1; p-value not reported).[16] No other TIMs are FDA-approved for this indication.
- In May 2025, mepolizumab received expanded FDA-approval as add-on maintenance treatment of adult patients with inadequately controlled COPD and an eosinophilic phenotype.[18]

New Drug Evaluation: Nemolizumab

- Nemolizumab is an interleukin (IL)-31 receptor antagonist FDA-approved for: 1) adults with PN[19] and 2) patients 12 years of age and older with moderate-to-severe AD in combination with a topical corticosteroid (TCS) and/or a topical calcineurin inhibitor (TCI) when AD is not adequately controlled with topical therapies alone.[20]
- In adults with PN, there is moderate-quality evidence from 2 phase 3 RCTs that nemolizumab improves skin lesions and pruritus over 16 weeks compared to placebo.[21,22] Pruritus was evaluated using the patient-reported itch response (a reduction of ≥ 4 points on the Peak Pruritus Numerical Rating Scale [PP-NRS; scores range from 0 to 10, with higher scores indicating more severe itch]) and skin lesions were evaluated using an Investigator's Global Assessment (IGA) response (a score of 0 [clear] or 1 [almost clear] on the IGA [scores range from 0 to 4] and an IGA reduction from baseline to week 16 of ≥2 points).[21,22] Study results are presented in **Table 1.**

Table 1. **Results from OLYMPIA 1 and 2 Trials**

	People with Itch Response	People with IGA Response
OLYMPIA 1[21]	Nemolizumab vs Placebo: 58.4% vs. 16.7%; Difference 41.7% 95% CI, 29.4 to 50.8; P<0.001	Nemolizumab vs Placebo: 26.3% vs 7.3%; Difference 19% 95% CI, 6.7 to 22.6; P<0.025
OLYMPIA 2[22]	Nemolizumab vs Placebo: 56.3% vs. 20.9%; Difference 35.4% 95% CI, 26.3 to 48.5; P<0.001	Nemolizumab vs Placebo: 37.7% vs. 11.0%; Difference 26.7% 95% CI, 18.8 to 38.2; P<0.001

- In patients aged 12 years and older with moderate-to-severe AD, nemolizumab improved skin clearance when combined with TCS or TCI therapy in 2 RCTs (ARCADIA 1 and ARCADIA 2; moderate-quality evidence).[23] Skin clearance was measured by IGA success (a score of 0 [clear] or 1 [almost clear] on the IGA [scores range from 0 to 4] and an IGA reduction from baseline to week 16 of ≥ 2 points) and Eczema Area and Severity Index (EASI)-75 response at 16 weeks.[23] Study results are presented in **Table 2**.

Table 2. **Results from ARCADIA 1 and 2 Trials**

	People with IGA Success	People with EASI-75 Response
ARCADIA 1[23]	Nemolizumab vs Placebo 35.6% vs. 24.6%; Difference 11% 97.5% CI 4.7 to 18.3; P=0.0003	Nemolizumab vs Placebo 43.5% vs. 29%; Difference 14.5% 97.5% 7.8 to 22.0; P<0.0001

ARCADIA 2[23]	Nemolizumab vs Placebo 37.7% vs. 26%; difference 11.7% 97.5% CI, 4.6 to 19.8; P=0.0006	Nemolizumab vs Placebo 42.1% vs. 30.2%; Difference 11.9% 97.5% CI, 4.6 to 20.3; P=0.0006

- The most frequently reported adverse events (AEs) with nemolizumab in the PN trials were headache (nemolizumab 6% vs. placebo 3%) and worsening AD (nemolizumab 4% vs placebo 0.5%).[19] In clinical trials for AD, the most commonly reported AEs were headache, arthralgia, urticaria, and myalgia.[20] **Table 16** and **Table 17** summarize the most frequently reported AEs with nemolizumab compared to placebo in clinical trials for each condition.
- The effect of severe renal and severe hepatic impairments on the pharmacokinetics of nemolizumab is unknown.[19,20] Long-term safety data with nemolizumab is currently being evaluated in 2 extension studies for OLYMPIA and ARCADIA.

Recommendations:

- Update prior authorization (PA) criteria for the "TIMs for Severe Asthma and Atopic Dermatitis" to include the recently approved TIM, nemolizumab and expanded indications for dupilumab and mepolizumab. Revise PA criteria to define specific medical necessity and appropriateness criteria for CSU in patients with the Early and Periodic Screening, Diagnostic and Treatment benefit. Remove requirement for co-prescribing of EpiPen for all TIMs except omalizumab.
- Based upon recent guidance, remove trial of an oral immunosuppressant (e.g., methotrexate, azathioprine) before initiating dupilumab for management of AD in adolescent and pediatric patients.
- Maintain nemolizumab as non-preferred on the Preferred Drug List (PDL).
- After executive session no changes were made to the PDL.

Summary of Prior Reviews and Current Policy

- At the August 2024 Pharmacy and Therapeutics (P & T) Committee meeting the PA criteria for the "TIMs for Severe Asthma and Atopic Dermatitis" were updated to include use of omalizumab for treatment of food allergies in patients at high risk of frequent and/or severe allergic reactions due to accidental exposure to foods.
- At the June 2022 P & T Committee meeting topical ruxolitinib was added to the clinical PA criteria for "Topical Agents for Anti-inflammatory Skin Conditions" and designated as non-preferred on the PDL. The committee members agreed to add tezepelumab injection, oral abrocitinib, and tralokinumab injection to the PA criteria for "Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis" and maintain all 3 medications as non-preferred on the PDL. An assessment of severe AD as an FDA-approved diagnosis for upadacitinib was added to the clinical PA criteria for "Targeted Immune Modulators for Autoimmune Conditions".
- The Oregon Health Plan (OHP) provides coverage with PA criteria for indications that are approved by the FDA. Common indications include asthma, atopic dermatitis, food allergies, and CRSwNP. Omalizumab is also indicated for management of CSU, a diagnosis which is not currently funded according to the Health Evidence Review Commission (HERC) 2025 prioritized list.[24] Prior authorization criteria for this class of drugs are outlined in **Appendix 4**. All TIMs in this class are nonpreferred on the PDL (see **Appendix 1**). During the first quarter of 2024 (January 1 through March 31), asthma and AD biologic agents billed through point-of-sale pharmacy claims in the fee-for-service (FFS) population included 12 claims for dupilumab. No provider administered claims were submitted for this class of drugs in the third and fourth quarters of 2024.

Background:

Five extra-pulmonary indications including CRS, CSU, EGPA, HES and PN have been approved for selected TIMs. All the TIMs that have FDA-approval for the extra-pulmonary indications were initially FDA-approved for treatment of asthma or AD (see **Table 3**). When TIMs were first in established as therapeutic alternatives for autoimmune disorders there were concerns about the risk of immune reactions, including anaphylaxis, with their administration.[25]

Hypersensitivity/allergic reactions due to TIMs are driven by the immunogenic properties of their protein component.[26] Thus, fully human monoclonal antibodies (e.g., dupilumab), which consist of 99% human components, are usually associated with a significantly lower risk of anaphylaxis compared to humanized monoclonal antibodies (e.g., omalizumab), as those can carry up to 10% of murine elements.[26] Two TIMs have a boxed warning for anaphylaxis: omalizumab (overall rate of anaphylaxis 0.2%) and reslizumab (overall rate of anaphylaxis 0.3%).[26,27] While 51% of cases of anaphylaxis occurred with the first dose of omalizumab, in about 10% this reaction was delayed to up to 24 hours.[27] It is recommended to co-prescribe an epinephrine autoinjector and to observe patients for 2 hours following the first 3 doses of omalizumab.[28] There are no observation or epinephrine pen carrying requirements for other TIMs.

Table 3. Targeted Immune Modulators FDA-Approved for Asthma, Atopic Dermatitis or Other Indications[29,30]

Generic Name/ BRAND NAME	Eosinophilic Asthma	Moderate-to-severe Allergic Asthma	Chronic Rhinosinusitis with Nasal Polyps	Eosinophilic Esophagitis	Atopic Dermatitis	IgE-Mediated Food Allergy	Other
Benralizumab FASENRA	≥6 yrs						EPGA ≥18 yrs
Dupilumab DUPIXENT	≥6 yrs		≥12 yrs	≥1 yr & weighing ≥15 kg	≥6 months	≥18 yrs	PN ≥18 yrs COPD ≥18 yrs CSU ≥ 12 yrs BP ≥18 yrs
Mepolizumab NUCALA	≥6 yrs		≥18 yrs				HES ≥ 12 yrs EPGA ≥18 yrs COPD ≥18 yrs
Nemolizumab NEMLUVIO					≥12 yrs		PN ≥ 18 yrs
Omalizumab XOLAIR		≥6 yrs	≥18 yrs			≥ 1 yo	CSU ≥ 12 yrs

Abbreviations: BP = bullous pemphigoid; COPD = chronic obstructive pulmonary disease; CSU = chronic spontaneous urticaria; EGPA = eosinophilic granulomatosis with polyangiitis; FDA = Food and Drug Administration; HES = hypereosinophilic syndrome; PN = prurigo nodularis

Chronic Rhinosinusitis with Nasal Polyps

Chronic rhinosinusitis with nasal polyps affects children and adults worldwide and involves inflammation of the nasal passages and paranasal sinuses lasting longer than 12 weeks.[31] It is diagnosed by the presence of at least 2 of 4 cardinal symptoms (nasal blockage, obstruction, or congestion; anterior or posterior nasal drainage; facial pain or pressure; and decreased sense of smell) for at least 3 consecutive months, with objective findings on imaging or nasal endoscopy.[31] There is a higher prevalence of CRSwNP in patients with severe asthma compared with patients who have mild asthma.[32] Long-term treatment with nasal irrigation, intranasal corticosteroids, or systemic corticosteroids is typically required in people with severe symptoms. Efficacy outcomes for medications used to manage CRS and CRSwNP are presented in **Table 4**. TIMs FDA-approved for add-on maintenance treatment of inadequately controlled CRSwNP include dupilumab, omalizumab, and mepolizumab (see **Table 3** for approved age ranges).

Table 4. Assessments and Questionnaires for CRS and CRSwNP[33]

Measure	Abbreviation	Meaning	Scoring
6-item Asthma Control Questionnaire	ACQ-6	Lower score indicates better asthma control	0 to 6
Asthma Quality of Life Questionnaire	AQLQ	Higher score indicates better quality of life	1 to 7 Clinically relevant change = 0.5
Lund-Mackay CT Score	-	Higher score indicated higher opacification of the sinuses	0 to 24
Nasal Congestion Score	NCS	Higher score indicates worse disease state status	0 to 3
Nasal Polyp Score	NPS	Higher score indicates worse disease state status	0 to 8
Short-Form Health Questionnaire	SF-36	Higher score indicates better QoL	0 to 100
Sino-Nasal Outcome Test (22 questions)	SNOT-22	Lower score indicates better disease control and QoL	0 to 120 MCID = 8.9
Total Nasal Symptom Score	TNSS	Higher score indicates worse disease state status	0 to 12
Total Polyp Score	TPS	Higher score indicates worse disease state status	0 to 8
Abbreviations: CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; MCID = minimal clinically important difference; QoL = quality of life			

Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (also known as chronic idiopathic urticaria) is defined as recurrent pruritic hives with or without angioedema for more than 6 weeks.[34] Chronic urticaria affects about 1% of the world population of all ages, mostly young and middle-aged women.[35] It generally lasts for several years (longer than 1 year in 25–75% of patients) and often takes more than one year before effective management is implemented.[35] Lesions result from degranulation of cutaneous mast cells, which leads to the release of histamine, the major mediator of pruritic wheals and angioedema, as well as the release of leukotrienes, prostaglandins, and platelet-activating factors.[36] Proinflammatory cytokines and vasoactive factors are also released, which results in vasodilatation and leakage of plasma from the vascular system in and below the skin.[36] Although most cases of chronic urticaria are idiopathic, this condition has been reported in association with infections (e.g., hepatitis B and C, Epstein–Barr virus, herpes simplex virus, mycoplasma, Helicobacter pylori, helminthic infestation), rheumatologic diseases (e.g., systemic lupus erythematosus, juvenile rheumatoid arthritis), thyroid disease, neoplasms (particularly lymphoreticular cancers and other lymphoproliferative disorders), ovarian tumors, and oral contraceptive use.[36]

First-line CSU treatment recommendations include oral second generation antihistamines (cetirizine, loratadine, fexofenadine) taken on a regular basis at standard doses instead of as needed (PRN) for itching.[36] Adults with CSU unresponsive to standard second generation antihistamine dosing may require dosing increased up to four times the recommended daily dose to manage symptoms (also known as up-dosing).[3,34] There is less evidence and formal guidance for up-dosing second generation antihistamines in children.[3,34] If antihistamines do not adequately control symptoms, an oral leukotriene receptor antagonist (montelukast or zafirlukast) may be added.[34] If oral therapies are ineffective or not tolerated, omalizumab may be initiated.[34] Omalizumab is FDA-approved for management of antihistamine-resistant CSU in adults and adolescents aged 12 years and older. Dupilumab received FDA-approval for use in CSU in April 2025.[16] Efficacy outcomes for medications used to manage CSU are presented in **Table 5**.

Table 5. Assessments and Questionnaires for CSU[33,34]

Measure	Abbreviation	Meaning	Scoring
Angioedema Activity Score	AAS	Higher score indicates more activity	0 to 105
Angioedema Quality of Life	AE-QoL	Lower score indicates better QoL	0 to 100
Dermatology Life Quality Index	DLQI	Lower score indicates better QoL 0-1 = no effect 2-5 = small effect on QoL 6-10 = moderate effect on QoL 11-20 = very large effect on QoL 21-30 = extremely large effect on QoL	0 to 30 MCID = 4
Skindex-29	-	Lower score indicates better QoL	0 to 100
Urticaria Activity Score	UAS	Higher score indicates more activity 0 = no wheals or itching 1-2 = mild (<20 wheals/24 hours) and mild itching 3-4 = moderate (20-50 wheals/24 hours) and moderate itching (troublesome but does not interfere with daily activities or sleep) 5-6 = intense (>50 wheals/24 hours) and intense itching which interferes with daily activities and/or sleep	0 to 6
Weekly Urticaria Activity Score	UAS7	Higher score indicates more activity	0 to 42
Weekly Itch Severity Score	ISS7	Higher score indicates more severity	0 to 21
Weekly Hive Severity Score	HSS7	High score indicates more severity	0 to 21
Abbreviations: CSU = chronic spontaneous urticaria; MCID = minimal clinically important difference; QoL = quality of life			

Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis, formerly known as Churg-Strauss syndrome, is a rare multisystem disorder that includes severe asthma, blood and tissue eosinophilia with organ involvement, and small-vessel vasculitis.[37] The incidence of EGPA ranges between 0.5 and 4.2 cases per million people per year with a prevalence between 10 and 14 cases per million people globally.[38] The frequency of the disease is comparable in men and women, and the mean age at diagnosis is 50 years.[39] Pediatric cases are extremely rare.[39]

In 1990, the American College of Rheumatology (ACR) defined classification criteria to distinguish the different vasculitic syndromes and identified 6 criteria to diagnose EGPA including: asthma; eosinophilia >10%; neuropathy; non-fixed lung infiltrates; paranasal sinus abnormalities; and histological evidence of extravascular eosinophils.[40] If 4 or more of these criteria are met, a patient with vasculitis can be classified as having EGPA with a sensitivity of 85% and a specificity of 99.7%.[40] Two main EGPA subsets can be distinguished according to anti-neutrophil cytoplasmic antibody (ANCA) status, namely an ANCA-positive subset, with predominant vasculitic lesions, and an ANCA-negative one, with prominent eosinophil-related organ involvement.[37] Eosinophilic granulomatosis with polyangiitis progresses through 3 different phases: a prodromal, an eosinophilic and a vasculitic phase.[37] The prodromal phase is dominated by asthma and CRS.[37] After a period of time (usually 8–10 years), patients may develop lung infiltrates, gastrointestinal involvement and symptoms of cardiac failure due to eosinophilic cardiomyopathy, while late stages are dominated by manifestations consistent with vasculitis (e.g. glomerulonephritis, palpable purpura and neuropathy).[37] The clinical phenotype of EGPA is extremely variable and does not necessarily follow the sequence of stages and any organ can be affected by either vasculitis- or eosinophil-related processes.[37]

Oral corticosteroids are the mainstay of EGPA treatment.[37] The recommended daily dosage at induction is 1 mg/kg of prednisone followed by gradual reduction until withdrawal or daily doses at or below 7.5 mg/day to limit adverse effects.[39] In patients with active, symptomatic disease, cyclophosphamide, methotrexate, azathioprine, or mycophenolate may be added to glucocorticoids to induce remission.[5,39] Rituximab is FDA-approved in combination with glucocorticoids in patients 2 years of age and older for treatment of EGPA.[39] Efficacy outcomes for medications used to manage EPGA are presented in **Table 6.** Benralizumab and mepolizumab are the 2 TIMs that are FDA-approved for management of EGPA in adults.

Table 6. Assessments and Questionnaires for EGPA[33]

Measure	Abbreviation	Meaning	Scoring
Asthma Control Questionnaire	ACQ	Higher score indicates less disease control	0 to 6
Birmingham Vasculitis Activity Score	BVAS	Higher score indicates more disease activity	0 to 63
Abbreviation: EGPA = eosinophilic granulomatosis with polyangiitis			

Hypereosinophilic Syndrome

Hypereosinophilic syndrome is a potentially fatal group of rare disorders characterized by persistently elevated blood eosinophils (>1.5 x 10^9/L) for more than 6 months.[41] It is marked by the sustained overproduction of eosinophils, in which eosinophilic infiltration and the release of inflammatory signaling molecules cause damage to multiple organs, including the skin, cardiopulmonary region, and the gastrointestinal tract.[41] The estimated prevalence of HES is between 0.36 to 6.3 per 100,00 people.[42] Most patients are between 20 and 50 years of age at the time of diagnosis, although HES can develop in children.[43] HES is more common in men than women at a rate of 9:1.[43] Eosinophils are derived from myeloid progenitors in the bone marrow, through the action of 3 hematopoietic cytokines: granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), and IL-5.[44] Of these three, only IL-5 is specific for eosinophil differentiation.[44]

Pharmacologic management of HES is oral corticosteroids.[44] In steroid-unresponsive patients, cyclophosphamide or rituximab have been used to reduce eosinophil counts.[44] Mepolizumab, an IL-5 antagonist, is FDA-approved for treatment of idiopathic HES in patients without an identifiable nonhematologic secondary cause. Efficacy and safety outcomes in RCTs of mepolizumab included reduction in corticosteroid dose, time to first HES flare occurrence, and AEs.[33]

Prurigo Nodularis

Prurigo nodularis is a rare skin disorder characterized by chronic pruritus for more than 6 weeks, repeated scratching, and multiple pruriginous lesions (papules and/or plaques).[45] The PN lesions are typically located on the arms, legs, and midback. Relentless itch and constant scratching lead to bleeding of skin lesions and sleep deprivation. In the United States, the estimated prevalence is 72 per 100,000 persons.[46] Prurigo nodularis can occur in all age groups but primarily affects older adults.[47] In a review of 108 cases of PN, the median age was 62 years.[47] In the United States (US), PN is more common among African Americans than other ethnic groups.[48] Systemic diseases (e.g., diabetes, chronic renal failure, cardiovascular disease, hepatitis C, gluten enteropathy, HIV infection), psychiatric disorders (e.g., anxiety, depression), sleep disorders, and emotional stress have been reported with high frequency in patients with PN.[47]

The exact pathogenesis of PN remains unknown.[49] Studies have shown that dysregulation of immune cells and neuronal circuitry plays an important role in the pathogenesis of PN.[49] Frequently prescribed agents for PN include tricyclic antidepressants with antihistamine properties (i.e., doxepin), topical calcineurin inhibitors, and first-generation antihistamines (i.e., diphenhydramine, hydroxyzine) at bedtime to control nocturnal itching. For widespread disease, narrowband ultraviolet B phototherapy is first-line therapy.[49] Other therapies that have been used to manage PN include systemic corticosteroids and immunosuppressants.[7]

Efficacy outcomes for medications used to manage PN are presented in **Table 7.** Dupilumab is FDA-approved to manage PN in adults. A recently approved IL-31 receptor antagonist, nemolizumab, is also indicated for treatment of PN in adults.

Table 7. Assessments and Questionnaires for PN[21,22,33]

Measure	Abbreviation	Meaning	Scoring
Dermatology Life Quality Index	DLQI	Lower scores indicate better QoL	0 to 30 MCID = 4-point change
Investigator's Global Assessment for PN-Stage	IGA- PN-S	Higher scores indicate greater intensity of pruritus	0 to ≥100
Investigator's Global Assessment of Skin Disease	IGA	Higher scores indicate more severe disease	0 to 4
Peak Pruritus Numerical Rating Scale	PP NRS	Higher scores indicate greater intensity of pruritus	0 to 10 MCID = 4-point reduction
Sleep Disturbance Numerical Rating Scale	SD-NRS	Lower scores indicate better sleep quality	0 to 10 MCID = 4-point reduction
Worst Itch Numeric Rating Scale	WI-NRS	Higher scores indicate greater intensity	0 to 10
Abbreviation: MCID = Minimal Clinically Important Difference; PN = Prurigo Nodularis: QoL = Quality of Life			

Atopic Dermatitis

Atopic dermatitis is chronic skin disorder characterized by intense pruritus, red and swollen skin, rash, serious exudation, and recurrent lesions accompanied by inflammation with a relapsing and remitting pattern.[50] The cause is unknown, but may be due to genetics or immunologic dysfunction.[51] Many patients also have allergic asthma, allergic rhinoconjunctivitis, food allergies, and other immediate hypersensitivity (type 1) allergies.[52] Although it may affect all age groups, AD is most common in children. The disease affects 15-20% of children in developed countries.[53] Estimated prevalence of AD for adults in the U.S. is 10%.[53] Both sexes are affected, and the prevalence varies among races and ethnic groups.[54] For example, in the US, the prevalence is higher among children who identify as Black (19.3%) compared to White (16.1%).[55] Onset of AD is typically between the ages of 3 and 6 months, with approximately 60% of patients developing AD during the first year of life and 90% by the age of 5 years.[56] Atopic dermatitis can persist into adulthood in about one-third of affected individuals.[57] Itching, sleep deprivation, and social embarrassment due to visible lesions can have substantial effects on the quality of life for patients with AD.[58]

Therapy for AD is selected according to the clinical stage of disease (mild, moderate, or severe), the extent and location of body-surface area involved, age, co-existing conditions or medications being taken by the patient, the severity of pruritus, the degree to which quality of life is impaired, and the goals of the patient.[59,60] For all disease stages, recommended therapies include a topical emollient to maintain the skin's epidermal barrier, avoidance of triggers, and anti-inflammatory therapy with a TCS or TCI as needed.[51] Two additional topical agents are FDA-approved for mild-to-moderate AD. Crisaborole is a topical phosphodiesterase-4 (PDE-4) inhibitor, and ruxolitinib is a JAK inhibitor. There is inadequate evidence to assess the relative efficacy and safety of topical crisaborole or ruxolitinib compared with TCI and TCS treatments.[61]

Patients with severe AD that cannot be controlled with topical therapy can be treated with short-term, narrow band ultraviolet B phototherapy, immunosuppressants, or a systemic TIM. Older therapies such as azathioprine and cyclosporine are effective, but carry risk of significant AEs including systemic immunosuppression.[62] TIMs that have been FDA-approved for systemic treatment of moderate-to-severe AD include injectable dupilumab (an IL-4 receptor antagonist), injectable tralokinumab and lebrikizumab (IL-13 antagonists), upadacitinib and abrocitinib (oral JAK inhibitors), and injectable nemolizumab (an IL-31 receptor antagonist). The JAK inhibitors provide an oral treatment option but are not recommended for people 65 years and over, people with a history of

smoking, or people with a history or risk of cardiovascular disease or cancer because of increased risk for death, lymphoma, and cardiovascular events observed in clinical trials in people with rheumatoid arthritis.[15]

Clinical studies have utilized several scales for defining the severity of AD, including the Eczema Area and Severity Index (EASI) and Investigators Global Assessment (IGA) severity score. The EASI assesses the severity of, and body surface area affected by, AD symptoms including erythema, induration/papulation/edema, excoriations, and lichenification.[63] Each symptom is graded systematically for specific anatomical regions (the head, trunk, arms and legs) and summarized in a composite score. EASI scores range from 0 to 72, with higher scores indicating greater severity and extent of AD.[63] An EASI score of 7 or lower is considered to indicate mild disease, 8 to 21 moderate disease, 22 to 50 severe disease, and 51 to 72 very severe disease.[52] EASI outcomes are measured as a percentage improvement in EASI score from baseline as EASI 50, 75, or 90. A limitation often cited is the EASI's intermediate interobserver reliability.[64] In addition, the EASI score might underestimate the severity of AD in people with brown or black skin, which could lead to under-treatment in these populations.[15]

The IGA is a clinician-reported outcome measure that has been used to evaluate severity of AD at a given point in time using a 5-point rating scale ranging from 0 (clear) to 4 (severe) symptoms.[65] In most clinical trials, scores less than or equal to 1 were generally classified as "treatment success," whereas scores greater than 1 were considered "treatment failure."[61] The IGA does not assess disease extent as body regions are not included in the IGA scoring. One systematic review concluded that although the IGA is easy to perform, the lack of standardization precludes any meaningful comparisons between studies which impedes data synthesis to inform clinical decision making.[65] **Table 8** provide more details about the EASI and IGA assessment tools.

Table 8. Assessment of Atopic Dermatitis Severity in Clinical Trials[61]

	EASI	**IGA/ISGA**
Scoring	Range: 0 to 72 Mild AD: 7.1-21.0 Moderate AD: 21.1-50 Severe AD: 50.1-72	Range: 0 to 4 (IGA) *or* 0 to 5 (ISGA) Score of 0 or 1 indicates disease clearing
Scale	4-point scale assessing erythema, induration, infiltration/papulation, edema, excoriation, and lichenification: 0 - absent 1 - mild 2 - moderate 3 - severe	5 (IGA) or 6 (ISGA) point scale based on assessment of erythema and infiltration/papulation: 0 - clear 1 - almost clear 2 - mild disease 3 - moderate disease 4 - severe disease 5 - very severe disease (ISGA)
Body Regions	Proportionate values assigned to 4 separate body regions: • Upper limbs (20%) • Lower limbs (40%) • Trunk (30%) • Head/Neck (10%)	Not Used
Abbreviations: EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; ISGA = Investigator's Static Global Assessment		

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA) or the Canadian Agency for Drugs and Technologies in Health (CADTH), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Drug Effective Review Project Report on Targeted Immune Modulators for Non-Asthma Inflammatory Indications
The October 2024 DERP report on TIMs for non-asthma inflammatory indications updated a 2021 review on this topic.[1] At the time of the 2021 report, 3 TIMs (omalizumab, dupilumab, and mepolizumab) were FDA-approved for extra-pulmonary indications including CSU, EGPA, HES, and CRSwNP. The 2024 DERP report includes 1 additional TIM, benralizumab, and added PN as fifth non-asthma inflammatory indication. This review will summarize evidence from both reports.

For the 2024 DERP update, literature was searched through August 5, 2024.[1] Ten new RCTs were identified and 20 RCTs were carried forward from the 2021 report.[33] Of the 30 RCTs, 6 had a low risk of bias, 20 had a moderate risk of bias, and 4 RCTs had a high risk of bias.[1] Twenty-seven RCTs were conducted in adults while 3 RCTs included adolescents and adults.[1] There was one head-to-head comparison (benralizumab vs. mepolizumab in patients with EGPA) while the other 29 RCTs were placebo-controlled.[1]

Chronic Rhinosinusitis with Nasal Polyps
Thirteen RCTs met inclusion criteria for evaluation of dupilumab, mepolizumab, omalizumab, and benralizumab in management of CRSwNP.[1] Efficacy outcomes included the 4-point Nasal Congestion Score (NCS), 9-point Nasal Polyp Score (NPS), and 22 question Sino-Nasal Outcome Test (SNOT-22).[1] High scores on the NCS and NPS indicate worse disease state status, while a lower score on the SNOT-22 indicates better disease control and quality of life (QoL).[1] A minimal clinically important difference (MCID) has not been defined for the NCS and NPS.[1] The MCID for the SNOT-22 score is 8.9 points, and total score ranges from 0 to 120.[1]

Three RCTs evaluated benralizumab in patients with CRSwNP, which is not FDA-approved for this indication.[1] Compared with placebo, benralizumab did not improve SNOT-22 scores (3 RCTs; n=493; moderate certainty of evidence).[1] Efficacy outcomes with the NPS assessment were generally inconsistent among the studies, with 1 RCT (n=413) demonstrating a significant improvement with benralizumab and the 2 smaller RCTs (n=80) showing no difference with benralizumab when compared with placebo (low certainty of evidence).[1] **Table 9** summarizes evidence for safety and efficacy of the 3 FDA-approved TIMs for CRSwNP.

Table 9. DERP Evidence Summary for TIMs in CRSwNP[1]

Targeted Immune Modulator	Number of Studies and RoB (n=total population) Study Duration	Results
Dupilumab	3 Moderate RoB RCTs (n=2,686) Adults and adolescents 16 to 52 weeks	Compared to placebo, dupilumab improved: • NPS from baseline (mean difference range, −1.6 to −3.5 on 9-point scale; 2 RCTs; n=844). • NCS from baseline (mean difference range, −0.87 to −1.2 on a 4 point-scale; 1 RCT; n=784). • SNOT-22 score (mean difference -19.61, 95% CI -22.54 to -16.69; 3 RCTs; n=2,686). No differences in AEs between treatment and placebo (2 RCTs; n=844). Certainty of Evidence: Moderate for all outcomes
Mepolizumab	3 Moderate RoB RCTs 1 Low RoB RCT (n=707) Adults 25 to 52 weeks	Compared to placebo, mepolizumab improved: • NPS (treatment difference range, −0.8 to −1.3 on a 9-point scale; 4 RCTs; n=707; Low Certainty of Evidence) • SNOT-22 scores (mean change range, -10.7 to -16.5; 3 RCTs; n=684; Moderate Certainty of Evidence). No differences in AEs between treatment and placebo (4 RCTs; n=707; Moderate Certainty of Evidence) Certainty of Evidence: Low to Moderate
Omalizumab	1 High RoB RCT 1 Moderate RoB RCT 1 Low RoB RCT (n=303) Adults and adolescents 16 to 24 weeks	Compared to placebo, omalizumab improved: • NPS (mean difference range, −0.59 to −1.14; 2 RCTs; n=279; Low Certainty of Evidence). • NCS score (mean difference, −0.5 to −0.55 on a 4-point scale; 1 RCT; n=265; Moderate Certainty of Evidence). • SNOT-22 scores (mean change range, -15 to -16.1; 2 RCTs; n=279; Moderate Certainty of Evidence). Certainty of Evidence: Low to Moderate

Abbreviations: AEs = Adverse Events; CRSwNP = Chronic Rhinosinusitis with Nasal Polyps; DERP = Drug Effectiveness Review Program; FDA = Food and Drug Administration; N = number; NCS = Nasal Congestion Score; NPS = Nasal Polyp Score; QoL = Quality of Life; RCTs = Randomized Controlled Trials; RoB = Risk of Bias; SNOT-22 = 22 Question Sino-Nasal Outcome Test; TIM = Targeted Immune Modulator

Chronic Spontaneous Urticaria

Eleven RCTs met inclusion criteria for evaluation of dupilumab, omalizumab, and benralizumab in management of CRS.[1] Outcomes of interest for this condition included the Dermatology of Life Quality Index (DLQI: range 0 to 30), Weekly Itch Severity Score (ISS7; range 0 to 21), and Weekly Activity Urticaria Score (UAS7; range 0 to 42).[1] A lower score on the DLQI indicates better QoL.[1] A higher score on the ISS7 and UAS7 indicates more severity of itching and more urticaria activity over the past 7 days, respectively.[1] An MCID has not been determined for any of the 3 outcomes.

Dupilumab and benralizumab are not FDA-approved for treatment of CSU. In one RCT conducted in adults (n=155), benralizumab did not demonstrate efficacy over placebo in the weekly itch (ISS7) and urticaria scores (UAS7) over 52 weeks (moderate certainty of evidence).[1] Another RCT evaluated dupilumab in adults (n=246) over 24 weeks.[1] Results from 2 RCTs were reported one publication. Dupilumab showed improvement in UAS7 scores compared with placebo (moderate certainty of evidence).[1] However, results were mixed for improvement in ISS7 scores, as one RCT showed improvement with dupilumab while the other RCT did not have any improvement compared with placebo (low certainty of evidence).[1] **Table 10** summarizes the evidence identified for the safety and efficacy of omalizumab, the only-FDA approved TIM for treatment of CSU.

Table 10. DERP Evidence Summary for TIMs in CSU[1]

Targeted Immune Modulator	Number of Studies and RoB (n= total population) Study Duration	Results
Omalizumab	2 High RoB RCTs 7 Moderate RoB RCTs (n=1,846) Adults and Adolescents 20 to 60 weeks	Compared to placebo, omalizumab improved: • UAS7 scores from baseline (mean change range, -9.9 to -10.3; 8 RCTs; n=1,746; High Certainty of Evidence). • ISS7 scores from baseline (mean change range, -1.1 to -4.5; 5 RCTs; n=1,106; Moderate Certainty of Evidence). • DLQI scores from baseline mean change range, -23.9 to -8.4; 7 RCTs; n=1,132; Moderate Certainty of Evidence). Certainty of Evidence: Moderate to High
Abbreviations: CSU = Chronic Spontaneous Urticaria; DERP = Drug Effectiveness Review Program; DLQI = 30 Point Dermatology Life Quality Index; ISS7 = 21 Point Weekly Itch Severity Score; FDA = Food and Drug Administration; N = number; RCTs = Randomized Controlled Trials; RoB = Risk of Bias; TIM = Targeted Immune Modulator; UAS7 = 42 Point Weekly Urticaria Activity Score		

Eosinophilic Granulomatosis with Polyangiitis

Two included RCTs evaluated mepolizumab and benralizumab in management of EGPA.[1] One moderate-quality RCT assessed mepolizumab versus placebo in 136 adults over 52 weeks.[1] Efficacy outcomes included total time in remission and time to first relapse.[1] More participants in the mepolizumab group than the placebo group achieved at least 24 weeks of remission (28% [19 of 68] vs. 3% [2 of 68], respectively; (odds ratio [OR], 5.91; 95% CI 2.68 to 13.03; P <0.01).[1] Time to first relapse was delayed for participants on mepolizumab compared with placebo, with a relapse occurring during trial period for 56% (38 of 68) and 82% (56 of 68) of participants, respectively.[1] There was no significant difference between treatment groups in total AEs.[1] One death unrelated to treatment occurred in the mepolizumab group.[1] The certainty of evidence was rated as low for remission and relapse rates and moderate for risk of AEs.[1]

A moderate-quality, phase 3, noninferiority RCT compared the efficacy and safety of benralizumab with mepolizumab in 140 patients with EPGA over 52 weeks.[66] Enrolled patients were randomized 1:1 to receive benralizumab 30 mg or mepolizumab 300 mg dosed every 4 weeks.[66] Study participants included adults at least 18 years of age with an EPGA diagnosis, plus 2 additional features of EPGA and a history of relapsing or refractory disease despite corticosteroid therapy, with or without immunosuppressive therapy.[66] The primary efficacy endpoint was remission, defined as a Birmingham Vasculitis Activity Score (BVAS) score of 0 at weeks 36 and 48 with an oral glucocorticoid dose of 4 mg or less per day (prespecified noninferiority margin, -25%).[66] A higher score on the BVAS assessment indicates more disease activity, scored from 0 to 63 points.[1] Secondary end points included the duration of remission, time to first relapse, oral glucocorticoid use, eosinophil count, and safety.[66] The adjusted percentage of patients with remission at weeks 36 and 48 was 58% in the benralizumab group and 56% in the mepolizumab group (difference, 1%; 95% CI, –14 to 17; P=0.88 for superiority), showing noninferiority but not superiority of benralizumab to mepolizumab.[66] The accrued duration of remission and the time to first relapse were similar in the two groups.[66] Benralizumab was noninferior to mepolizumab for the induction of remission in patients with relapsing or refractory EGPA (moderate certainty of evidence).[1,66]

Hypereosinophilic Syndrome

Two moderate-quality RCTs evaluated mepolizumab for HES over 32 to 36 weeks.[1] Efficacy outcomes consisted of time to the first flare and reduction in prednisone dose to ≤ 10 mg per day for at least 8 weeks.[1] Participants in the mepolizumab group achieved statistically significant reductions in prednisone

dosages when compared with participants in the placebo group (84% [36 of 43] and 43% [18 of 42] respectively; hazard ratio, 2.90; 95% CI, 1.59 to 5.26; P<0.01; 1 RCT; n=85; moderate certainty of evidence).[1] More participants in the placebo group experienced their first flare over the course of the study compared to participants in the mepolizumab group (56% [30 of 54] vs. 28% [15 of 54] respectively, p<0.01; 1 RCT; n=108; moderate certainty of evidence).[1] Adverse events that occurred more frequently in the mepolizumab group included local injection-site reactions and pain in extremities (2 RCTs; n=193; low certainty of evidence).[1] One death unrelated to treatment occurred in the mepolizumab group.[1]

Prurigo Nodularis

Two identical, high-quality, phase 3 RCTs (PRIME and PRIME 2) analyzed the safety and efficacy of dupilumab in the treatment of adults with PN (n=153).[1] Eligible participants included adults with a confirmed PN diagnosis inadequately controlled with topical treatments, an average Worst Itch Numeric Rating Scale (WI-NRS) score of at least 7 in the week prior to screening, and at least 20 PN lesions.[1] The primary endpoint was the proportion of study subjects with a reduction in WI-NRS score of at least 4 points at week 24 or week 12.[1] Higher scores in the WI-NRS indicate greater itch intensity with a score ranging from 0 to 10.[1] At week 24, more patients treated with dupilumab achieved the primary endpoint of WI-NRS score reduction compared to placebo in PRIME (60% vs. 18.4%; difference, 41.6%; 95% CI 27.8 to 57.5; P<0.001) and PRIME 2 (37.2% vs. 22%; difference, 15.2%; 95% CI 2.3 to 31.2; P=0.002).[1]

A secondary endpoint in both trials was a reduction in skin lesion number as assessed by the Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA PN-S) score of 0 to 1 at week 24.[1] Compared to placebo, more participants in the dupilumab group achieved an IGA PN-S score of 0 to 1 in both trials at week 24 (PRIME, 48.0% vs. 18.4%; 95% CI 13.4 to 43.2; P<0.001; PRIME 2, 44.9% vs. 15.9%; 95% CI 16.4 to 45.2; P<0.01).[1] Dupilumab also improved this endpoint at week 12 in PRIME (32.0% vs. 11.8%; 95% CI 7.8 to 34.0; P=0.003) and PRIME 2 (25.6% vs. 12.2%; 95% CI 2.6 to 27.0; P=0.019).[1] There were serious adverse events in 5 (6.7%) and 6 (8.0%) participants in the dupilumab and placebo groups in PRIME, and 2 (2.6%) in dupilumab group and 2 (2.4%) in placebo group participants in PRIME 2.[1] The certainty of evidence for all outcomes was rated as moderate.[1]

In summary, the DERP report provided evidence to support the following TIMs in non-asthma indications:

- Compared with placebo, dupilumab, mepolizumab and omalizumab improved nasal congestion and symptoms related to CRSwNP (3 RCTs for each drug).[1]
- When compared to placebo, omalizumab improved urticaria-related symptoms and QoL measurements in participants with antihistamine-refractory CSU (9 RCTs).[1]
- Mepolizumab can be used as add-on therapy to oral corticosteroids, with or without immunosuppressants, to cause disease remission or to delay relapse in patients with EGPA (1 RCT).[1] Benralizumab was noninferior to mepolizumab, and no notable advantages were provided to select one agent over the other (1 RCT).[1]
- Mepolizumab can reduce oral corticosteroid use and HES flare occurrence, each of which can have a significant impact on QoL (2 RCTs).[1]
- Dupilumab can improve some symptoms of PN such itching, sleep disruption, and pain compared to placebo (2 RCTs).[1]

No high-quality systematic reviews were identified for the use of TIMs in AD. After review, 27 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

A. High-Quality Guidelines for Targeted Immune Modulators in Indications Besides Asthma or Atopic Dermatitis

The American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma, and Immunology: Management of Chronic Rhinosinusitis with Nasal Polyposis

An AAAAI and ACAAI Joint Task Force developed guidance for management of CRSwNP in 2023.[2] Two specific pharmacologic recommendations are included in the guideline:

- In people with CRSwNP, the guideline panel suggests inhaled nasal corticosteroid spray rather than no inhaled nasal corticosteroid spray (conditional recommendation based on low certainty of evidence).[2]
- In people with CRSwNP, the guideline panel suggests biologics rather than no biologics (conditional recommendation based on moderate certainty of evidence).[2]

For the mean difference in disease-specific quality of life using the SNOT-22 scale where a difference of ≥ 8.9 is the MCID, dupilumab (MD: -19.91; 95% CI -22.50 to -17.32) and omalizumab (MD: -16.09; 95% CI -19.88 to -12.30) were more clinically significant compared to placebo.[2] For nasal symptoms scores, where 1 point is the MCID on a 0- to 10-point symptom, dupilumab (MD: -3.25; 95% CI -4.31 to -2.18), omalizumab (MD: -2.09; 95% CI -3.15 to -1.03), and mepolizumab (MD: -1.82; 95% CI -3.13 to -0.50) were the most beneficial compared to placebo.[2] For all biologics adverse event rate was similar compared to placebo; however, the certainty of evidence was low or very low.[2] Data from use of biologics for other conditions suggest some infrequent risks, such as anaphylaxis with omalizumab (0.09% for people with asthma) and conjunctivitis with dupilumab (2% for patients with CRSwNP).[2]

The American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma, and Immunology: Management of Chronic Urticaria

Guidance on management of CU was developed in 2014 by a joint task force of AAAAI and ACAAI members.[3] Chronic urticaria is defined in this guideline as urticaria that has been continuously or intermittently present for at least 6 weeks.[3] The panel determined strength of recommendations based upon quality of evidence as presented in **Table 11**.

Table 11. Classification of AAAAI/ACAAI Evidence and Recommendations[3]

Strength of Recommendation	Category of Evidence
A: Directly based on Category I evidence B: Directly based on Category II evidence or extrapolated recommendation from Category I evidence C: Directly based on Category III evidence or extrapolated recommendation from Category I or II evidence D: Directly based on Category IV evidence or extrapolated recommendation from Category I, II, or III evidence E: Based on consensus of the Joint Task Force	Ia: Evidence from a meta-analysis of RCTs Ib: Evidence from at least one RCT IIa: Evidence from at least one controlled study without randomization IIb: Evidence from at least 1 other type of quasiexperimental study III: Evidence from nonexperimental descriptive studies IV: Evidence from expert committee reports or opinions or clinical experience of respected authorities or both
Abbreviations: AAAAI = American Academy of Allergy, Asthma & Immunology; ACAAI = American College of Allergy, Asthma, and Immunology; RCT = randomized controlled trial	

Recommendations for pharmacologic management and strength of recommendations are:

- Second-generation antihistamines are safe and effective therapies in patients with CU and are considered first-line agents. (A)[3]
- Higher doses of second-generation antihistamines might provide more efficacy, but data are limited and conflicting for certain agents. (B)[3]

- First-generation antihistamines can be considered in patients who do not achieve control of their condition with higher-dose second-generation antihistamines. (D)[3]
- Leukotriene receptor antagonists can be considered for patients with CU with unsatisfactory responses to second-generation antihistamine monotherapy. (A)[3]
- Treatment with hydroxyzine or doxepin can be considered in patients whose symptoms remain poorly controlled with dose advancement of second-generation antihistamines and the addition of H2-antihistamines, first-generation H1-antihistamines at bedtime, and/or antileukotrienes. (D)[3]
- Because of the risk of adverse effects with systemic corticosteroids, long-term use for treatment of patients with CU should be avoided as much as possible. (D)[3]
- Omalizumab should be considered for refractory CU if, from an individualized standpoint, a therapeutic trial of omalizumab is favorable from the standpoint of balancing the potential for benefit with the potential for harm/burden and cost and the decision to proceed is consistent with the patient's values and preferences. (A)[3]

National Institute for Health and Care Excellence: Omalizumab for Previously Treated Chronic Spontaneous Urticaria
In 2015, NICE issued guidance for the use of omalizumab in refractory CSU.[4] Omalizumab is a recommended option for add-on therapy in adults and young people aged 12 years and over with severe CSU only if:

- the severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more and
- the person's condition has not responded to standard treatment with antihistamines and leukotriene receptor antagonists and
- omalizumab is stopped at or before the fourth dose if the condition has not responded and
- omalizumab is stopped at the end of a course of treatment (6 doses) if the condition has responded, to establish whether the condition has gone into spontaneous remission, and is restarted only if the condition relapses and
- omalizumab is administered under the management of a specialist in dermatology, immunology or allergy.[4]

American College of Rheumatology/Vasculitis Foundation: Guideline on Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis
In 2021, ACR/VF issued guidance for management of ANCA-associated vasculitis conditions including EGPA.[5] At the time of publication, mepolizumab was FDA-approved for treatment of EGPA, but benralizumab had not yet received FDA-approval for this indication. Of note, patients with active, severe EGPA were excluded from the 2017 placebo-controlled RCT for mepolizumab.[67]

Recommendations for treatment based upon disease severity and activity are presented in **Table 12**. Active disease is defined as new, persistent, or worsening clinical signs and/or symptoms attributed to EGPA and not related to prior damage.[5] Severe disease is defined as vasculitis with life- or organ-threatening manifestations (e.g., alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, limb/digit ischemia).[5] Nonsevere disease is characterized as vasculitis without life- or organ-threatening manifestations (e.g., rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis).[5]

Table 12. ACR/VF Recommendations for Pharmacologic Management of EGPA[5]

Recommendation	Strength	Level of Evidence
Remission Induction for Active, Severe Disease		
For patients with active, severe EGPA, either IV pulse GCs or high-dose oral GCs may be prescribed as initial therapy.	Not graded	Very Low

For patients with active, severe EGPA, either cyclophosphamide or rituximab may be prescribed for remission induction.	Not graded	Very Low
For patients with active, severe EGPA, we conditionally recommend treatment with cyclophosphamide or rituximab over mepolizumab for remission induction.	Conditional	Low
Remission Induction for Active, Nonsevere Disease		
For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with mepolizumab with GCs over methotrexate, azathioprine, or mycophenolate mofetil and GCs.	Conditional	Very Low to Low
For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and GCs over GCs alone.	Conditional	Low
For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and GCs over cyclophosphamide or rituximab and GCs.	Conditional	Very Low to Low
Remission Maintenance		
For patients with severe EGPA whose disease has entered remission with cyclophosphamide therapy, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over rituximab for remission maintenance.	Conditional	Very Low
For patients with severe EGPA whose disease has entered remission, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over mepolizumab for remission maintenance.	Conditional	Very Low
Treatment of Relapse		
For patients with EGPA who have experienced relapse with severe disease manifestations after prior successful remission induction with cyclophosphamide, we conditionally recommend treatment with rituximab over cyclophosphamide for remission re-induction.	Conditional	Very Low
For patients with EGPA who have experienced relapse with severe disease manifestations after prior successful remission induction with rituximab, we conditionally recommend treatment with rituximab over switching to cyclophosphamide for remission re-induction.	Conditional	Very Low
For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, we conditionally recommend adding mepolizumab over switching to another agent.	Conditional	Very Low
For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving low-dose GCs and no other therapy, we conditionally recommend adding mepolizumab over adding methotrexate, azathioprine, or mycophenolate mofetil.	Conditional	Very Low
For patients with EGPA and high serum IgE levels who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, we conditionally recommend adding mepolizumab over adding omalizumab.	Conditional	Very Low
Abbreviations: ACR = American College of Rheumatology: EGPA = Eosinophilic Granulomatosis with Polyangiitis; GCs = glucocorticoids; IgE = Immunoglobulin E; IV = Intravenous; VF = Vasculitis Foundation		

2022 European Alliance of Associations for Rheumatology: Management of Vasculitides

In 2022, the EULAR updated recommendations for the management of ANCA-associated vasculitides including EGPA due to publication of several RCTs that had the potential to change clinical care and supported the need for an update.[6] The recommendations were drafted using the EULAR standardized operating procedures described in **Table 13**.[68]

Table 13. EULAR Category of Evidence and Strength of Recommendations[68]

Level of Evidence	
Category	Evidence
1A	From meta-analysis of randomized controlled trials
1B	From at least one randomized controlled trial
2A	From at least one controlled study without randomization
2B	From at least one type of quasi-experimental study
3	From descriptive studies, such as comparative studies, correlation studies or case–control studies
4	From expert committee reports or opinions and/or clinical experience of respected authorities
Strength of Recommendation	
A	Category I evidence
B	Category II evidence or extrapolated recommendations from category I evidence
C	Category III evidence or extrapolated recommendation from category I or II evidence
D	Category IV evidence or extrapolated recommendation from category II or III evidence
Abbreviations: EULAR: European Alliance of Associations for Rheumatology	

Level of evidence (LoE) and strength of recommendations (SoR) for the use of mepolizumab in EGPA include:

- For the induction of remission in new-onset or relapsing EGPA with organ-threatening or life-threatening manifestations, EULAR recommends treatment with a combination of high-dose glucocorticoids and cyclophosphamide. A combination of high-dose glucocorticoids and rituximab may be considered as an alternative (LoE: 2B; SoR: B).[6]
- For induction of remission in new-onset or relapsing EGPA without organ-threatening or life-threatening manifestations, EULAR recommends treatment with glucocorticoids (LoE; 2B; SoR: B).[6]
- For induction of remission in patients with relapsing or refractory EGPA without active organ-threatening or life-threatening disease, EULAR recommends the use of mepolizumab (LoE: 1B; SoR: B).[6]
- For maintenance of remission of EGPA after induction of remission for organ-threatening or life-threatening disease, treatment with either methotrexate (LoE: 2B; SoR: B) or azathioprine, mepolizumab, or rituximab should be considered (LoE: 4, SoR: C).[6]
- For maintenance of remission of relapsing EGPA after induction of remission for non-organ-threatening or life-threatening manifestations at the time of relapse, EULAR recommends treatment with mepolizumab (LoE: 1b; SoR: B).[6]

National Institute for Health and Care Excellence: Dupilumab for Treating Moderate-to-Severe Prurigo Nodularis

A 2024 NICE guideline does not recommend dupilumab for treating moderate-to-severe PN in adults when systemic treatment is suitable.[7] There is no standard care for PN, but in the United Kingdom's National Health Service (NHS), care usually starts with topical treatments to relieve symptoms.[7] Other treatments including antihistamines, oral corticosteroids, and immunosuppressants are added if symptoms are more severe.[7] Dupilumab would be used as an alternative for some of these later treatments.[7] The clinical trial evidence shows that dupilumab improves symptoms of prurigo nodularis compared with best supportive care (topical treatments).[7] But in the trials, this care did not include many of the treatments (e.g., oral corticosteroids, immunosuppressants) that are usually used in the NHS.[7] So, the trial results are uncertain and may not be generalizable to the NHS.[7]

B. High-Quality Guidelines for Targeted Immunomodulators in Atopic Dermatitis

National Institute for Health and Care Excellence: Abrocitinib, Tralokinumab, or Upadacitinib for Treating Moderate-to-Severe Atopic Dermatitis

NICE issued guidance for the use of abrocitinib, tralokinumab, or upadacitinib in management of moderate-to-severe AD in 2022.[8] Recommendations are as follows:

- Abrocitinib and upadacitinib are recommended as options for treating moderate-to-severe AD that is suitable for systemic treatment in adults and young people aged 12 years and over, only if the disease has not responded to at least one systemic immunosuppressant or immunosuppressants are not suitable.[8]
- Tralokinumab is recommended as an option for treating moderate-to-severe AD that is suitable for systemic treatment in adults only if the disease has not responded to at least one systemic immunosuppressant, or these are not suitable.[8]
- Stop abrocitinib, upadacitinib, or tralokinumab at 16 weeks if the AD has not responded adequately. An adequate response is defined as at least a 50% improvement in the EASI score (EASI-50) and at least a 4-point reduction on the DLQI from when treatment started.[8]

National Institute for Health and Care Excellence: Lebrikizumab for Treating Moderate-to-Severe Atopic Dermatitis

In July 2024, NICE published recommendations for the use of lebrikizumab in treating moderate-to-severe AD in people 12 years of age and older.[15] Standard treatment for moderate-to-severe AD includes topical emollients, TCAs, and/or TCIs.[15] If these treatments are not effective, systemic immunosuppressant treatments such as cyclosporin and methotrexate can be added.[15] If there is an inadequate response after at least one of these systemic treatments, or if these are unsuitable, a JAK inhibitor (abrocitinib, baricitinib or upadacitinib) or a biological medicine (dupilumab or tralokinumab) can be used.[15] (Note: baricitinib is approved in the United Kingdom for adults, but is not FDA-approved in the U.S. for AD for any age group). The pivotal RCTs that led to FDA-approval for lebrikizumab were placebo-controlled trials over 16 weeks. To date, there is no comparative evidence to evaluate the efficacy of lebrikizumab with other TIMs. Recommendations include:

- Lebrikizumab is recommended as an option for treating moderate-to-severe AD that is suitable for systemic treatment in adults and young people aged 12 years and over, only if the disease has not responded to at least one systemic immunosuppressant, or these are not suitable and dupilumab or tralokinumab would otherwise be offered.[15]
- Stop lebrikizumab at 16 weeks if the AD has not responded adequately. An adequate response is defined as at least a 50% improvement in the EASI score (EASI-50) and at least a 4-point reduction on the DLQI from when treatment started.[15]

American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force: Atopic Dermatitis Guidelines

In 2023, the AAAAI/ACAAI joint task force published guidance for AD management.[9] Twenty-five recommendations were issued to guide treatment in patients with mild, moderate and severe AD.[9] Combination therapy with azathioprine, methotrexate, mycophenolate, oral corticosteroids in addition to biologics or JAK inhibitors is not recommended for management of AD (conditional recommendations; low-quality evidence).[9] Cyclosporine may be used to treat moderate-to-severe AD in adults and adolescents who have refractory disease, are intolerant to therapy, or are unable to use to high-potency topical treatments or biologics (conditional recommendation; low-quality evidence).[9]

Two recommendations specifically address the use of biologics or JAK inhibitors in AD:

- Dupilumab (for patients 6 months of age or older) or tralokinumab (for patients aged 12 years and older) are recommended for people with moderate-to-severe AD who have refractory disease, intolerance to therapy, or inability to use mid-potency TCA or TCI treatment (strong recommendation; high-quality evidence).[9]
- Oral JAK inhibitors (abrocitinib, upadacitinib) are suggested after careful consideration of risks and possible benefits in adults and adolescents with moderate-severe AD who have refractory disease, intolerance to therapy, or inability to use mid- to high-potency TCA or TCI treatment, dupilumab, or

tralokinumab (conditional recommendation; low-quality evidence). Baricitinib is included in this recommendation but is not FDA-approved for management of AD in the United States.

American Academy of Dermatology: Management of Atopic Dermatitis in Adults with Phototherapy and Systemic Therapies

In 2024, AAD updated guidance for AD management with phototherapy and systemic therapies.[10] Eleven recommendations were developed to guide treatment with phototherapy, biologics, oral JAK inhibitors and other immunomodulatory therapies.[10] Therapy with strong recommendations included dupilumab, tralokinumab, abrocitinib, baricitinib and upadacitinib.[10] Phototherapy, azathioprine, cyclosporine, methotrexate, and mycophenolate had conditional recommendations for use in AD, and systemic corticosteroids were not recommended (conditional recommendation).[10] The workgroup noted that most RCTs of phototherapy and systemic therapies for AD are of short duration with subsequent extension studies, limiting comparative long-term efficacy and safety conclusions.[10] Recommendations for use of systemic therapy in treating AD are summarized in **Table 14**.

Table 14. American Academy of Dermatology: Recommendations for Management of Atopic Dermatitis with Systemic Therapies[10]

Intervention	FDA-Approved	Recommendation	Strength	Certainty of Evidence
Monoclonal Antibodies				
Dupilumab Tralokinumab	Yes	For adults with moderate-to-severe AD, we recommend dupilumab or tralokinumab	Strong	Moderate
JAK Inhibitors				
Abrocitinib Upadacitinib Baricitinib	Yes Yes No	For adults with moderate-to-severe AD, we recommend upadacitinib, abrocitinib, or baricitinib. *Remarks: Upadacitinib and abrocitinib are approved by the FDA in patients with AD who have failed other systemic therapies (pills or injections, including biologics) or when use of those therapies is inadvisable. Baricitinib is not approved by the FDA for use in AD but is approved for AD in Europe.*	Strong	Moderate
Antimetabolites				
Methotrexate	No	For adults with moderate-to-severe AD, we conditionally recommend methotrexate with proper monitoring. *Remarks: Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients. The FDA has not approved methotrexate for use in AD.*	Conditional	Low
Immunosuppressants				
Systemic Corticosteroids	Yes	For adults with AD, we conditionally recommend against systemic corticosteroids. *Remarks: Their use should be reserved exclusively for acute, severe exacerbations and as a short-term bridge therapy to other systemic, corticosteroid-sparing therapy.*	Conditional	Low
Mycophenolate Mofetil	No	For adults with refractory moderate-to-severe AD, we conditionally recommend mycophenolate mofetil with proper monitoring. *Remarks: Mycophenolate mofetil is not approved by the FDA for use in AD. Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.*	Conditional	Very Low
Azathioprine	No	For adults with refractory moderate-to-severe AD, we conditionally recommend TPMT-dosed azathioprine with proper monitoring.	Conditional	Low

		Remarks: Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.		
Cyclosporine	No	For adults with refractory moderate-to-severe AD, we conditionally recommend limited-term use of cyclosporine with proper monitoring. *Remarks: Evidence suggests an initial dose of 3 mg/kg/day to 5 mg/kg/day is effective. The FDA has not approved cyclosporine for use in AD. The FDA has approved limited-term use (up to 1 year) in psoriasis. Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.*	Conditional	Low
Abbreviations: AD = Atopic Dermatitis; FDA = Food and Drug Administration; JAK = Janus Kinase; kg = kilogram; mg = milligram; TPMT = thiopurine methyltransferase enzyme or genotype				

Canada's Drug Agency: Management of Atopic Dermatitis with Dupilumab, Tralokinumab, Abrocitinib, or Upadacitinib

Since early 2022, CADTH or Canada's Drug Agency have issued 4 reimbursement reviews for the use of upadacitinib, abrocitinib, dupilumab, and tralokinumab for treating AD.

- *Upadacitinib*

CADTH published guidance for the use of upadacitinib in June 2022.[11] Four clinical studies evaluated the use of upadacitinib in patients with moderate to severe chronic AD and inadequate response to topical or systemic treatments.[11] Three double-blind, placebo-controlled RCTs in adults and adolescents (≥ 40 kg) demonstrated that upadacitinib 15 mg and 30 mg improved disease severity based on the EASI 75 score and IGA scores when compared to placebo.[11] Disease severity was improved whether upadacitinib was used as monotherapy or in addition to topical corticosteroids.[11] One comparative study demonstrated superior efficacy of upadacitinib 30 mg in reducing disease severity and symptoms (based on the EASI 75 and pruritus NRS) when compared to dupilumab 300 mg at week 16; however, after 24 weeks this difference was no longer observed.[11] Recommendations for the use of upadacitinib in AD include:

- Upadacitinib should only be approved for patients who have inadequate response to, are ineligible for, or cannot tolerate, the highest dose of topical treatments for AD combined with phototherapy (where available), and at least one 12-week trial of methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine.[12]
- The physician must provide the EASI score and IGA score at the time of initial request for coverage.[12]
- The maximum duration of initial authorization is 20 weeks. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a 75% or greater improvement from baseline in the EASI score (EASI-75) 20 weeks after treatment initiation.[12]
- For subsequent renewal, the physician must provide proof of maintenance of EASI 75 response from baseline every 6 months for subsequent authorizations.[12]
- The patient must be under the care of a dermatologist, allergist, clinical immunologist, or pediatrician who has expertise in the management of moderate to severe AD.[12]
- Upadacitinib should not be used in combination with phototherapy or immunomodulatory agents (including biologics or other JAK inhibitors) for moderate to severe AD.[12]

- *Abrocitinib*

Guidance for the use of abrocitinib was issued by CADTH in September 2022.[12] The development committee evaluated 4 double-blind RCTs which demonstrated that, compared with placebo, 12 or 16 weeks of treatment with abrocitinib was associated with statistically significant and clinically meaningful improvements in a range of outcomes that are important in the management of AD, including overall severity of AD (EASI and IGA response), severity of itching (severity of PP-NRS response), QoL, and fatigue.[12] All trials enrolled patients with moderate-to-severe AD and an inadequate response to topical AD therapies. These trials included the use of abrocitinib as monotherapy and as combination therapy with topical products in adults and adolescents. One active-controlled trial demonstrated that abrocitinib 200 mg once daily was superior to dupilumab for improving symptoms in the initial weeks after starting treatment, but that there were no significant differences between the 2 drugs at 26 weeks.[12] Recommendations for the use of abrocitinib in AD are similar to upadacitinib.

- *Dupilumab*

In October 2023, CADTH updated dupilumab recommendations, based upon the expanded approval for pediatric patients aged 6 months and older with AD.[13] Based on expert opinion, dupilumab is recommended as a second-line therapy after failure of an adequate trial with topical therapies (e.g., TCSs, TCIs), but before systemic immunosuppressants.[13] However, experts recommended against step therapy with either phototherapy or systemic immunosuppressants in patients younger than 12 years of age before being eligible for dupilumab.[13] Recommendations for the use of dupilumab in AD include:

  - Dupilumab is recommended for the treatment of patients aged 6 months and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[13]
  - The maximum duration of initial authorization is 6 months.[13]
  - Similar to abrocitinib and upadacitinib, recommendations of use include baseline assessment of symptom severity, proof of beneficial clinical effects for continuation, involvement of a specialist with expertise in AD, and recommendations against combination use with other immunomodulatory drugs or phototherapy.

- *Tralokinumab*

Canada's Drug Agency guidance for the use of tralokinumab in AD was published in May 2024.[14] To make its recommendations, the committee evaluated 5 double blind, placebo-controlled RCTs, 1 long-term extension study, 3 indirect treatment recommendations, and 2 observational studies.[14] Based on a review of the tralokinumab evidence, Canada's Drug Agency did not recommend reimbursement for this medication and did not publish recommendations for use of tralokinumab in patients with AD.[14] Their evaluation considered the following points:

- The observed treatment effects with respect to the coprimary end points of the IGA 0 or 1 and EASI 75 in pivotal tralokinumab RCTs were modest.[14]
- For the key secondary outcomes with an identified MCID estimate (i.e., change from baseline in DLQI, Children's Dermatology Life Quality Index [CDLQI], and SCORAD scores), the difference between tralokinumab and placebo at week 16 did not consistently meet the MCID estimate across the trials increasing uncertainty related to the magnitude of benefit with tralokinumab.[14]
- Studies evaluated outcomes at 16 weeks, but the optimal response to tralokinumab is usually expected 6 months after treatment initiation based on clinical expert input. The short duration of follow-up in clinical trials hinders interpretation of the magnitude of benefit in the trials.[14]
- There is a lack of comparative evidence for tralokinumab with currently available treatments.[14] Two observational studies assessing the efficacy and safety of tralokinumab in patients who previously received dupilumab and/or JAK inhibitors. However, results were limited by small sample size and open-label, non-comparative study designs.[14] Therefore, the committee was unable to conclude if tralokinumab treatment could fill the unmet need for an effective treatment in patients who had prior treatment with dupilumab or determine appropriate place in therapy of tralokinumab as a first-line, second-line, or subsequent-line therapy.[14]

New Indications:

- 4/25: Dupilumab received expanded FDA-approval for use in patients 12 years and older with CSU who remain symptomatic despite antihistamine treatment.[16] The approval was based upon 2 placebo-controlled, phase 3 RCTs in patent who remained symptomatic despite treatment with antihistamines or omalizumab.[17] In LIBERTY-CSU CUPID Study A, patients were omalizumab-naive (n = 138, aged ≥6 years).[17] In Study B, patients were omalizumab-intolerant/incomplete responders (n = 108, aged ≥12 years).[17] The primary end point was either change from baseline over 7 days in the Urticaria Activity Score (UAS7) (range 0-42) or Itch Severity Score (ISS7) (range 0-21) at week 24, with the other as a key secondary end point, depending on regional regulatory requirements.[17] In Study A, UAS7 and ISS7 improved with dupilumab versus placebo (difference −8.5; 95% CI, −13.2 to −3.9; P=0.0003] and −4.2; 95% CI, −6.6 to −1.8; P=0.0005) after 24 weeks of treatment.[17] In Study B, after 24 weeks of treatment, UAS7 improved (difference −5.8; 95% CI, −11.4 to −0.3; P=0.0390) but not in ISS7 (difference −2.9; 95% CI, −5.7 to −0.07; P=0.0449).[17] Pooled safety data were consistent between dupilumab and placebo and with the known dupilumab safety profile.[17] Proportions of patients with any treatment-emergent adverse event (TEAE) were similar with dupilumab versus placebo: 57.3% versus 56.6%, respectively.[17] TEAEs that occurred with frequency (≥5%) in any treatment group were nasopharyngitis (2 [1.6%] in dupilumab and 7 [5.7%] in placebo), CSU (10 [8.1%] in dupilumab and 9 [7.4%] in placebo), and injection-site erythema (3 [2.4%] in dupilumab and 7 [5.7%] in placebo).[17]
- 6/25: In June 2020, the FDA-approved dupilumab for treatment of adults with bullous pemphigoid, a painful autoimmune blistering condition with intense itching.[16] The approval was based on data from an unpublished, placebo-controlled Phase II/III trial in 106 adults with moderate-to-severe bullous pemphigoid conducted over 52 weeks.[16] All patients enrolled in this trial were initiated on a standard regimen of oral corticosteroids, which were tapered off at 16 week as long as disease control was maintained.[16] The primary endpoint was the proportion of patients who achieved sustained remission at Week 36, which was defined as no longer taking corticosteroids by week 16, no disease relapse after steroid taper, and no use of rescue therapy during the 36 week double-blind treatment period.[16] At Week 36 18.3% of dupilumab-treated patients had achieved remission compared with 6.1% of placebo-treated patients (difference = 12.2%; 95% CI -0.8 to 26.1; p-value not reported).[16] No other TIMs are FDA-approved for this indication.
- 5/25: Mepolizumab received expanded FDA-approval as add-on maintenance treatment of adult patients with inadequately controlled COPD and an eosinophilic phenotype.[18] The data that led to this approval was compiled in 2 double-blind, placebo-controlled RCTs (n=1,640).[18] Mepolizumab was administered as 100 mg SC every 4 weeks over 52 to 104 weeks. Enrolled patients had a diagnosis of moderate-to-severe COPD and at least 1 or 2 COPD exacerbations within the previous year despite receiving triple inhaled therapy.[18] The primary endpoint was the annualized rate of COPD exacerbations per year. Compared to placebo, mepolizumab reduced the rate of annualized exacerbations (study 1: 1.01 vs. 0.80; rate ratio, 0.79; 95% CI 0.66 to 0.94 and study 2: 1.71 vs. 1.40; rate ratio, 0.82; 95% CI 0.68 to 0.98).[18]

New FDA Safety Alerts:

Table 15. Description of New FDA Safety Alerts[69]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Dupilumab	Dupixent	9/22	Warnings and Precautions	In subjects with prurigo nodularis, the frequency of conjunctivitis was 4% in the dupilumab group compared to 1% in the placebo group; these subjects recovered or were recovering during the treatment period. There were no cases of keratitis reported in the PN development program

Dupilumab	Dupixent	9/24	Warnings and Precautions	Among subjects with chronic obstructive pulmonary disease (COPD), the frequency of conjunctivitis and keratitis was 1.4% and 0.1% in the dupilumab group and 1% and 0% in the placebo group, respectively.

Randomized Controlled Trials:
A total of 132 citations were manually reviewed from the initial literature search. After further review, 132 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: NEMLUVIO (Nemolizumab)
See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Nemolizumab is an IL-31 receptor antagonist.[19] Interleukin-31 is a cytokine involved in pruritus, inflammation, epidermal dysregulation, and fibrosis.[19] Nemolizumab is FDA-approved for 2 conditions: 1) patients at least 12 years of age with moderate-to-severe AD in combination with a TCS and/or TCI when AD is not adequately controlled with topical prescription therapies alone,[20] and 2) adults with PN.[19] To manage AD, nemolizumab is administered via subcutaneous (SC) injection with a loading dose of 60 mg at baseline, followed by 30 mg given every 4 weeks.[20] After 16 weeks of treatment, if patients have achieved clear or almost clear skin, the dose can be reduced to 30 mg every 8 weeks.[20] The nemolizumab dosing in PN is weight based. For adults weighing less than 90 kg, the recommended dose is a loading dose of 60 mg at baseline followed by 30 mg every 4 weeks.[19] In adults weighing 90 kg or more the recommended dose is a loading dose of 60 mg followed by 60 mg every 4 weeks.[19] Four clinical trials (OLYMPIA 1, OLYMPIA 2, ARCADIA 1, and ARCADIA 2) contribute to the efficacy data of nemolizumab to manage PN or AD and are described and evaluated below in **Table 19**.

Nemolizumab Efficacy in Prurigo Nodularis
Two randomized, double-blind, multi-center, placebo-controlled, phase 3 trials (OLYMPIA 1 [n=276] and OLYMPIA 2 [n=274]) assessed the effect of nemolizumab for PN, targeting improvement in skin lesions and pruritus over 16 weeks.[21,22] Patients were randomized 2:1 to receive nemolizumab or placebo. After completion of either RCT, patients were eligible to enter an ongoing long-term extension trial (OLYMPIA LTE).

The study protocols specified that if deemed to be medically necessary by the investigator (e.g., to control intolerable PN signs/symptoms), rescue therapies can be prescribed to the enrolled patients. Rescue therapy could not be prescribed during the screening period and could not be prescribed within the first 4 weeks after baseline to allow a minimum time for study drug exposure. The following rescue therapies were permitted: TCS, TCIs, oral antihistamines, systemic or intralesional corticosteroids, biologics (including their biosimilars), systemic nonsteroidal immunosuppressants, and phototherapy. For the purpose of efficacy analysis, subjects receiving any rescue therapies were considered treatment failures.[21] In OLYMPIA 1, 6% (n=12) of nemolizumab-treated patients required rescue therapy versus 20% (n=19) of placebo-treated patients.[21] In OLYMPIA 2, 5% (n=9) of nemolizumab-treated patients required rescue therapy compared with 15% (n=14) of placebo-treated patients.[22] Oral antihistamines and TCAs were the most frequently utilized rescue treatments.[22]

The primary end points in OLYMPIA 1 and OLYMPIA 2 were a patient-reported itch response (a reduction of ≥4 points on the PP-NRS; scores range from 0 to 10, with higher scores indicating more severe itch) and IGA response (a score of 0 [clear] or 1 [almost clear] on the IGA [scores range from 0 to 4] and an IGA

reduction from baseline to week 16 of ≥2 points).[21,22] At each visit, the investigator completed the IGA score and the Prurigo Activity Score (PAS) to evaluate disease progression. The PAS includes a count of the number of lesions in a representative area and a calculated staging (stage 0 to stage 4) based on the percentage of lesions with excoriations/crusts and healed lesions compared to all lesions.[22] Patients recorded their PP-NRS score daily in an electronic diary. In OLYMPIA 1, a more patients assigned to nemolizumab achieved itch response (58.4% vs. 16.7%; difference 41.7%; 95% CI, 29.4 to 50.8; P<0 .001) and IGA success with nemolizumab compared to placebo (26.3% vs. 7.3%; difference 19%; 95% CI, 6.7 to 22.6; P=0.0025) at week 16.[21] Similarly in OLYMPIA 2, more patients in the nemolizumab group had an itch response (56.3% vs. 20.9%; difference, 35.4%; 95% CI, 26.3 to 48.5; P<0.001), and an IGA response compared with placebo (37.7% vs. 11.0%; difference, 26.7%; 95% CI, 18.8 to 38.2; P<0.001).[22]

Five key secondary end points were evaluated based on a hierarchical plan. They included a reduction from baseline of 4 points or more on the PP-NRS score at week 4, a weekly average PP-NRS score of less than 2 at weeks 4 and 16, and a reduction from baseline of 4 or more points on the sleep disturbance numerical rating scale (SD-NRS; range, 0 [no sleep loss] to 10 [unable to sleep at all]) at weeks 4 and 16.[22] A reduction from baseline of 4 points or more on the PP-NRS and on the SD-NRS represents a clinically meaningful improvement.[21,22] In both trials, people treated with nemolizumab had significantly greater improvements in all key secondary end points compared with placebo with numbers-needed-to-treat (NNT) ranging from 3 to 5 depending on the outcome (**Table 18**).[21]

Trial Limitations:
In the U.S., PN may disproportionally affect more Black than White patients (3:1 ratio) and may be less common in other race/ethnic groups.[22] However, people identifying as Black were underrepresented in both RCTs (9.8% in Olympia 1 and 4.4% in Olympia 2).[21,22] As PN is a chronic disease, studies of longer duration are needed to support long-term use.[21] An open-label extension study of 184-week duration is ongoing.

Nemolizumab Efficacy in Atopic Dermatitis
In two identical, multicenter, phase 3 RCTs (ARCADIA 1 and ARCADIA 2), 1728 patients at least 12 years of age with moderate-to-severe AD were randomized 2:1 to receive nemolizumab 30 mg SC every 4 weeks (after a loading dose of 60 mg at week 0) plus a TCA or TCI, or matching placebo plus a TCA or TCI over 16 weeks.[23] At week 16, patients who had a clinical response (defined as a ≥75% improvement in EASI score from baseline or an IGA score of 0 or 1, representing a ≥2-point improvement from baseline) were randomly reassigned (1:1:1) to receive either nemolizumab 30 mg once every 4 weeks, nemolizumab 30 mg once every 8 weeks (with matching placebo injections for every other dose to maintain blinding), or placebo once every 4 weeks in a maintenance period (weeks 16 to 48).[23] All placebo-treated participants who had a clinical response to placebo during the first 16 weeks continued to receive placebo once every 4 weeks in the maintenance period.[23] Patients who were non-responders at week 16 or patients who received rescue medications during the first 16 weeks (defined as treatment failure) were eligible for enrollment into the ARCADIA long-term extension study.[23] Concomitant low and/or medium potency TCS and/or 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.[23] At baseline, 70% of patients had an IGA score of 3 (moderate AD), and 30% of patients had a baseline IGA score of 4 (severe AD).[23] Overall, 63% of people had received other previous systemic treatments for AD.[20]

If medically necessary to control intolerable signs or symptoms of atopic dermatitis, rescue therapies could be prescribed to participants at any time during the study except during the run-in period (14 days before baseline) and within the first 2 weeks after baseline to allow a minimum time for study drug exposure.[23] Topical treatments were recommended before escalating to systemic rescue therapy, which could include biologics (and biosimilars), systemic non-steroidal immunosuppressants or immunomodulators, and phototherapy. Antihistamines, sleep aids, topical and systemic antibiotics, and anti-itch creams were not considered rescue therapy because they do not directly treat atopic dermatitis.[23] The proportion of participants who received rescue therapy was similar between the nemolizumab and placebo groups in ARCADIA 1 (5% vs. 7%) and ARCADIA 2 (3% vs. 5%).[23]

Coprimary endpoints at week 16 were IGA success (score of 0 or 1 with a ≥2-point improvement from baseline) and at least 75% improvement in Eczema Area and Severity Index score from baseline (EASI-75 response).[23] 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.[20] The coprimary endpoints, IGA and EASI assessments, were completed by investigators every 4 weeks. Both trials met the coprimary endpoints. At week 16, a greater proportion of participants receiving nemolizumab plus TCS–TCI versus placebo plus TCS–TCI had IGA success (ARCADIA 1: 36% vs. 25%; difference 11%; 97.5% CI, 4.7 to 18.3; P=0.0003; ARCADIA 2: 38% vs. 26%; difference 12%; 97.5% CI, 4.6 to 19.8; P=0.0006) and an EASI-75 response (ARCADIA 1: 44% vs. 29%; difference 15%; 97.5%, CI 7.8 to 22.0; P<0.0001; ARCADIA 2: 42% vs. 30%; difference 12%; 97.5% CI, 4.6 to 20.3; P=0.0006).[23]
The key secondary endpoints were the proportion of participants with Peak Pruritus Numerical Rating Scale (PP-NRS) score improvement of at least 4 points at weeks 1, 2, 4, and 16; PP-NRS score below 2 at weeks 4 and 16; Sleep Disturbance Numerical Rating Scale score improvement of at least 4 points at week 16; EASI-75 response plus PP-NRS score improvement of at least 4 points at week 16; and IGA success plus PP-NRS score improvement of at least 4 points at week 16. The PP-NRS and Sleep Disturbance Numerical Rating Scale (SD-NRS) were recorded daily by patients.[23] The weekly mean scores on the PP-NRS and SD-NRS were calculated as the average of the 7 previous days, requiring at least four values.[23] Significant benefits were observed with nemolizumab plus TCS–TCI for all key secondary endpoints, with consistent improvement in pruritus and sleep disturbance outcomes between studies (see **Table 19** for week 16 outcomes).[23]

Trial Limitations:
Limitations of the results include the absence of long-term safety data.[23] A long-term extension study is ongoing. People enrolled in trials were predominantly White and other races and ethnicities were under-represented.[23] Patients with uncontrolled asthma were excluded from enrollment for safety reasons, presumably due to the risk of hypersensitivity reactions with administration of a monoclonal antibody. In addition, people who received 16-week treatment with dupilumab and experienced worsening of AD or failed to achieve improvement were excluded from trial enrollment. Investigators did not justify the reasons for excluding this patient population. Comparative trials with other TIMs approved for AD with nemolizumab would provide additional insights as to the place in therapy for nemolizumab.

Clinical Safety:
In clinical trials of nemolizumab to assess efficacy in PN, the proportion of subjects who discontinued treatment because of adverse reactions was 4% in the nemolizumab group versus 3% in the placebo group.[19] The most frequently reported AEs with nemolizumab in the PN trials were headache and AD.[21] **Table 15** summarizes the AEs reported in PN trials. In clinical trials for AD efficacy, the most commonly reported events reported with nemolizumab were headache, arthralgia, urticaria, and myalgia. Injection site reactions were rare (<1%).[23] **Table 16** summarizes AEs reported in the AD population who received nemolizumab and placebo through week 16.

Table 16. Adverse Effects the Occurred in Adult Subject with Prurigo Nodularis[19]

Adverse Effects	Nemolizumab (n=370)	Placebo (n=186)
Headache	23 (6%)	6 (3.0%)
Atopic Dermatitis	16 (4%)	1 (0.5%)
Eczema	14 (4%)	3 (2%)
Eczema nummular	11 (3%)	0 (0%)

Table 17. Adverse Effects that Occurred in Adult and Pediatric Subjects 12 Years of Age and Older with Atopic Dermatitis [20]

Adverse Effects	Nemolizumab (n=1,135)	Placebo (n=584)
Headache	52 (5%)	22 (4.0%)
Arthralgia	12 (1%)	1 (0.2%)
Urticaria	12 (1%)	2 (0.3%)
Myalgia	11 (1%)	1 (0.2%)

Administration of live vaccines should be avoided during treatment with nemolizumab.[19] Treatment with nemolizumab may modulate serum levels of some cytokines and influence the formation of CYP450 enzymes.[19] Therefore, upon initiation or discontinuation of nemolizumab in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate.[19]

Look-alike / Sound-alike Error Risk Potential: Nemolizumab and Mepolizumab

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduced number of PN skin lesions (PN RCTs) or improved skin clearing (AD RCTs)
2) Improvement in itching
3) Improved sleep
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoints:

1) For the PN studies, the co-primary endpoints were: a) reduction on the PP-NRS score $\geq$ 4 points and b) IGA score of 0 or 1 plus a reduction of IGA score > 2 points from baseline score
2) For the AD studies, coprimary endpoints were: a) IGA score of 0 or 1 plus a reduction of IGA score > 2 points from baseline score and b) achievement of EASI-75.

Table 18. Pharmacology and Pharmacokinetic Properties[20]

Parameter	
Mechanism of Action	IL-31 inhibition
Oral Bioavailability	N/A; administered via subcutaneous injection
Distribution and Protein Binding	Vd = 7.67 L; protein binding N/A as this is a monoclonal antibody
Elimination	Clearance: 0.263 L/day
Half-Life	18.9 days
Metabolism	Degraded into small peptides by catabolic pathways

Abbreviations: IL = interleukin; L = Liters; N/A = not applicable; Vd = Volume of distribution

Table 19. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Stander, et al[21] Olympia 1 Phase 3, DB, MC, PC, RCT	1. Nemolizumab 60 mg SC loading dose followed by 30 or 60 mg (depending on baseline weight) every 4 weeks x 16 weeks 2. Matching placebo at some dosing interval	Demographics: -Female: 58% -Mean Age: 57.5 yo -Mean Weight: 85 kg -Race Asian: 4.2% Black: 9.8% White: 84.3% Other: 1.3% -Time since PN diagnosis: 7.6 years -Average baseline PP-NRS score: 8.5 -Moderate PN: 59.1% -Severe PN: 40.9% -PN lesions ranging from 20 to 100: 65% -PN lesions > 100: 35% Key Inclusion Criteria: -Age ≥ 18 yo -PN > 6 mos -PP-NRS score ≥ 7 -PN nodules ≥ 20 with bilateral distribution on arms, legs, & trunk -IGA score ≥ 3 (moderate PN) Key Exclusion Criteria: -Body weight < 30 kg -Chronic itching due to other conditions -Unilateral PN lesions -Active atopic dermatitis -Uncontrolled asthma -History of COPD or bronchitis	ITT: 1. 190 2. 96 PP: 1. 166 2. 83 Attrition: 1. 24 (13%) 2. 13 (14%)	Co-Primary Endpoints (ITT population): A. PP-NRS ≥ 4-point reduction at week 16 1. 111 (58.4%) 2. 16 (16.7%) Difference: 41.7% 95% CI 29.4 to 50.8; P<0.0001 B. IGA Response* at week 16 1. 50 (26.3%) 2. 7 (7.3%) Difference: 19% 95% CI 6.7 to 22.6; P<0.0025 Secondary Endpoints (ITT population): A. PP-NRS improvement ≥ 4 points at 4 weeks 1. 78 (41.1%) 2. 6 (6.3%) Difference: 34.8% 95% CI 23.0 to 40.4; P<0.001 B. PP-NRS score < 2 at week 4 1. 41 (21.6%) 2. 1 (1.0%) Difference: 20.6% 95% CI 12.3 to 25.0; P<0.001 C. PP-NRS score < 2 at week 16 1. 65 (34.2%) 2. 4 (4.2%) Difference: 39% 95% CI 22.3 to 38.7; P<0.001 D. Improvement of ≥ 4 points on sleep disturbance NRS at week 4 1. 59 (31.1%) 2. 5 (5.2%) Difference: 25.9% 95% CI 14.7 to 30.7; P<0.001	41.7%/ 2 19%/5 34.8%/ 3 20.6%/ 5 39%/3 25.9%/ 4	Any TEAE 1. 134 (71.7%) 2. 62 (65.3%) Serious TEAE 1. 16 (8.6%) 2. 10 (10.5%) TEAE leading to discontinuation 1. 9 (4.8%) 2. 4 (4.2%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients assigned using IRT 2:1 to nemolizumab or matching placebo for 16 weeks. Stratified according to body weight (≥ 90 kg or < 90 kg). Groups were well balanced at baseline. However, baseline mean body weight (87 kg vs. 81 kg) and percentage of patients with severe IGA (44% vs 35%) were higher in the nemolizumab group than the placebo group. Performance Bias: Low. Kits were blinded and coded to mask assigned regimen. Staff and patients blinded to treatment assignment. Detection Bias: Unclear. Two efficacy assessments (IGA and PAS) were assessed at each visit by the same evaluator, who was blinded to treatment, to reduce intra-subject variability. Attrition Bias: High. Attrition rates were high (>10%) for a short-term study. Patients with missing data were considered non-responders. Reporting Bias: Low. Protocol published online and all outcomes reported as planned. Other Bias: High. Study designed and funded by the manufacturer. Several authors were employed by the manufacturer, served as consultants for the manufacturer, or received grant funding from the manufacturer. **Applicability**: Patient: Majority of study patients were White, which may limit the ability to generalize results to the overall PN population PN is more prevalent in Black populations compared with White populations (3:1 ratio). All patients had moderate-to-severe PN. Intervention: Dosing determined in a Phase 2 RCT along with pharmacokinetic modeling and simulation analyses. Comparator: Placebo is an appropriate comparator for a first in class medication. Dupilumab was not yet approved for PN at the time of this study. Further studies with nemolizumab and dupilumab

				E. Improvement ≥ 4 points on sleep disturbance NRS at week 16 1. 95 (50.0%) 2. 11 (11.5 %) Difference: 38.5% 95% CI 27.8 to 48.2; P<0.001	38.5%/3			would provide comparative evidence amongst biologic medications. Outcomes: Relief of itching (PP-NRS) and skin clearing (IGA) are clinically relevant outcomes. Setting: 77 centers in 10 countries located in Europe and North America: Austria, Canada, Denmark, Germany, Hungary, Italy, Poland, Sweden, United Kingdom, United States
2. Kwatra, et al[22] Olympia 2 Phase 3, DB, MC, PC, RCT	1. Nemolizumab 60 mg SC loading dose followed by 30 or 60 mg (depending on baseline weight) every 4 weeks x 16 weeks 2. Matching placebo at some dosing interval	Demographics: -Female: 61.3% -Mean Age: 52.7 yo -Mean Weight: 80 kg -Race Asian: 13.5% Black: 4.4% White: 78.5% Other: 3.6% -Time since PN diagnosis: 8.75 years -Average baseline PP-NRS score: 8.4 -Moderate PN: 56.9% -Severe PN: 43.1% -PN lesions ranging from 20 to 100: 62.8% -PN lesions > 100: 37.2% Key Inclusion Criteria: see Olympia 1 Key Exclusion Criteria: see Olympia 1 -	ITT: 1.183 2.91 PP: 1. 174 2. 88 Attrition: 1. 9 (5%) 2. 3 (3%)	Co-Primary Endpoints (ITT population): A. PP-NRS≥ 4-point reduction at week 16 1. 103 (56.3%) 2. 19 (20.9%) Difference: 35.4% 95% CI 26.3 to 48.5; P<0.001 B. IGA Response* at week 16 1. 69 (37.7%) 2. 10 (11.0%) Difference: 26.7% 95% CI 18.8 to 38.2; P<0.001 Secondary Endpoints (ITT population): A. PP-NRS improvement ≥ 4 points at 4 weeks 1. 75 (41.0%) 2. 7 (7.7%) Difference: 33.4% 95% CI 24.3 to 42.4; P<0.001 B. PP-NRS score < 2 at week 4 1. 36 (19.7%) 2. 2 (2.2%) Difference: 18.8% 95% CI 12.0 to 25.7; P<0.001 C. PP-NRS score < 2 at week 16 1. 64 (35.0%) 2. 7 (7.7%) Difference: 30.0% 95% CI 21.3 to 38.6; P<0.001 D. Improvement of ≥ 4 points on sleep disturbance NRS at week 4	35.4%/3 26.7%/4 33.4%/3 18.8%/5 30%/3	Any TEAE 1. 112 (61.2%) 2. 48 (52.7%) Serious TEAE 1. 4 (2.2%) 2. 5 (5.5%) TEAE leading to discontinuation 1. 4 (2.2%) 2. 2 (2.2%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients assigned using IRT 2:1 to nemolizumab or matching placebo for 16 weeks. Stratified according to body weight (≥ 90 kg or < 90 kg). Groups were well balanced at baseline. Performance Bias: see Olympia 1 Detection Bias: see Olympia 1 Attrition Bias: Low. Low rates of attrition. Reporting Bias: see Olympia 1 Other Bias: see Olympia 1 **Applicability**: Patient: see Olympia 1 Intervention: see Olympia 1 Comparator: see Olympia 1 Outcomes: see Olympia 1 Setting: 55 sites across 9 countries: Belgium, France, Canada, South Korea, The Netherlands, Poland, Spain, Switzerland, and the United States 67% of sites were located in Europe, 25% in North America, and 8% in the Asian-Pacific region.

				1. 68 (37.2%) 2. 9 (9.9%) Difference: 27.9% 95% CI 18.4 to 37.5; P<0.001 E. Improvement ≥ 4 points on sleep disturbance NRS at week 16 1. 59 (31.1%) 2. 5 (5.2%) Difference: 22.7% 95% CI 20.7 to 43.2; P<0.001	27.9%/4 22.7%/4			
3. Silverberg et al[23] ARCADIA 1 and ARCADIA 2 Phase 3, DB, MC, PC, RCT	1. Nemolizumab 60 mg SC at Week 0 followed by 30 mg SC every 4 weeks x 16 weeks plus TCA or TCI 2. Matched placebo at same dosing interval plus TCA or TCI	Demographics: **ARCADIA 1** -Male: 53.1% -Mean age: 33.3 yo -Race White: 73.9% Black: 5.7% Asian: 17.9% Other: 1% -Baseline ESAI: 10 -IGA score 3: 73.5% -IGA score 4: 27.5% PP-NRS score: 6 **ARCADIA 2** -Male: 51.6% -Mean age: 34 yo -Race White: 87.0% Black: 5.7% Asian: 6.7% Other: 1% -Baseline ESAI: 10.8 -IGA score 3: 68.5% -IGA score 4: 31.5% -PP-NRS score: 6 **Both Trials** Key Inclusion Criteria: - Age ≥ 12 yo -Moderate-to- severe AD (IGA score of 3 or 4) for at least 2 yrs	**ARCADIA 1** ITT: 1. 620 2. 321 PP: 1.560 2.296 Attrition: 1. 60 (9.6%) 2. 25 (7.8%) **ARCADIA 2** ITT: 1. 522 2. 265 PP: 1. 470 2. 241 Attrition: 1. 52 (8.4%) 2. 24 (9.1%)	**ARCADIA 1 Co-Primary Endpoints (ITT population):** A. IGA Response* at week 16 1. 221 (35.6%) 2. 79 (24.6%) Difference: 11% 97.5% CI 4.7 to 18.3; P=0.0003 B. EASI-75 at week 16 1. 270 (43.5%) 2. 93 (29%) Difference: 14.5% 97.5% CI 7.8 to 22.0; P<0.0001 Secondary Endpoints (ITT population): A. PP-NRS improvement ≥ 4 points at 16 weeks 1. 265 (42.7%) 2. 57 (17.8%) Difference: 24.9% 97.5% CI 18.4 to 31.5; P<0.0001 B. PP-NRS score < 2 at week 16 1. 190 (30.6%) 2. 36 (11.2%) Difference: 19.4% 97.5% CI 13.7 to 25.2; P<0.0001 C. Improvement of ≥ 4 points on sleep disturbance NRS at week 16 1. 235 (37.9%)	11%/9 14.5%/7 24.9%/4 19.4%/5 18%/6	**ARCADIA 1** Any TEAE 1. 306 (50%) 2. 146 (45%) Serious TEAE 1. 6 (1%) 2. 4 (1%) TEAE leading to drug discontinuation 1. 11 (2%) 2. 13 (4%) **ARCADIA 2** Any TEAE 1. 215 (41%) 2. 117 (44%) Serious TEAE 1. 13 (3%) 2. 3 (1%) TEAE leading to drug discontinuation 1. 18 (3%) 2. 3 (1%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized 2:1 to nemolizumab or placebo via IRT. Stratified by baseline disease severity (IGA score 3 or 4) and pruritis severity (PP-NRS score < 7 or ≥ 7). Groups were well balanced at baseline. Performance Bias: Low. Study staff and patients blinded to treatment assignment. Detection Bias: Low. Outcome assessors for co-primary endpoints blinded to treatment assignment. Attrition Bias: Low. Attrition rates were low based on the number of enrolled patients. Reporting Bias: Low. Protocol available online and all outcomes reported as planned. Other Bias: High. Manufacturer had a role in study design, data collection, data analysis, data interpretation, writing of report, and funding. Several investigators were consultants or advisory board members for the manufacturer. **Applicability**: Patient: Most participants in the trial were White, and other races were under-represented. Results may not be generalizable to those populations. Patients with uncontrolled asthma were excluded from enrollment for safety reasons, presumably due to the risk of hypersensitivity reactions with administration of a monoclonal antibody. Intervention: Dosing was determined in Phase 2 RCTs. Comparator: Placebo was appropriate to determine efficacy. Several biologics are approved for AD

		-EASI score ≥ 16 -BSA involvement ≥ 10% -PP-NRS ≥ 4 -Inadequate response to TCS with or without TCI treatment (within 6 mos of screening) <u>Key Exclusion Criteria</u>: -Body weight < 30 kg -Asthma exacerbation within the previous 12 mos -Uncontrolled asthma within the previous 3 mos -History of COPD and/or chronic bronchitis -Patients who had an AD relapse after 16 weeks of dupilumab therapy		2. 64 (19.9%) Difference: 18% 97.5% CI 11.3 to 24.5; P<0.0001 **<u>ARCADIA 2 Co-Primary Endpoints (ITT population):</u>** A. IGA Response* at week 16 1. 197 (37.7%) 2. 69 (26%) Difference: 11.7% 97.5% CI 4.6 to 19.8; P=0.0006 B. EASI-75 at week 16 1. 220 (42.1%) 2. 80 (30.2%) Difference: 11.9% 97.5% CI 4.6 to 20.3; P=0.0006 <u>Secondary Endpoints (ITT population)</u>: A. PP-NRS improvement ≥ 4 points at 16 weeks 1. 214 (41%) 2. 39 (18.1%) Difference: 22.9% 97.5% CI 16.1 to 30.3; P<0.0001 B. PP-NRS score < 2 at week 16 1. 148 (28.4%) 2. 16 (8%) Difference: 20.4% 97.5% CI 10.9 to 23.3; P<0.0001 C. Improvement of ≥ 4 points on sleep disturbance NRS at week 16 1. 175 (33.5%) 2. 47 (16.2%) Difference: 27.3% 97.5% CI 10.8 to 24.3; P<0.0001	11.7%/ 9 11.9%/ 9 22.9%/ 5 20.4%/ 5 27.3%/ 4	95% CI and p-values NR		treatment, and comparative analysis would be beneficial to determine the place in AD therapy for nemolizumab. People who received 16-week treatment with dupilumab and experienced worsening of AD or failed to achieve improvement were excluded from enrollment. Investigators did not justify the reasons for excluding this patient population. <u>Outcomes</u>: IGA response and EASI-75 are appropriate outcomes for assessment of AD clearing. <u>Setting</u>: **ARCADIA 1**: 161 centers in 14 countries: Australia, Austria, Canada, Czech Republic, Germany, Latvia, Lithuania, The Netherlands, New Zealand, Poland, South Korea, Spain, United Kingdom, United States 51% of sites were in Europe 33% of sites were in North America 16% of sites were in Asia-Pacific **ARCADIA 2**: 120 centers in 11 countries: Belgium, Bulgaria, Estonia, Georgia, Germany, Hungary, Italy, Poland, Singapore, United States 73.5% of sites were in Europe 24.5% of sites were in North America 2% of sites were in Asia-Pacific

<u>Abbreviations</u>: AD = atopic dermatitis; ARR = absolute risk reduction; BSA = body surface area; COPD = chronic obstructive pulmonary disease; DB = double blind; CI = confidence interval; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; IRT = interactive response technology; ITT = intention to treat; kg = kilograms; MC = multi-center; mITT = modified intention to treat; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NRS = numerical rating scale; PAS = Prurigo Activity Score; PC = placebo-controlled; PN = prurigo nodularis; PP = per protocol; PP-NRS = Peak Pruritus Numerical Rating Scale; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid; TEAE = treatment emergent adverse events; yo = years old

*IGA Response = Score of 0 or 1 with ≥ 2-point reduction from baseline

References:

1. Lindsey W, Chung A, Hartsell F, Loosier C, Grabowsky A. Biologic drugs for nonasthma indications: clinical update. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2024.
2. Rank MA, Chu DK, Bognanni A, et al. The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis. *J Allergy Clin Immunol*. Feb 2023;151(2):386-398. doi:10.1016/j.jaci.2022.10.026
3. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. May 2014;133(5):1270-7. doi:10.1016/j.jaci.2014.02.036
4. National Institute for Health and Care Excellence (NICE). Omalizumab For Previously Treated Chronic Spontaneous Urticaria. June 2015. https://www.nice.org.uk/guidance/ta339/chapter/1-Guidance.
5. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Arthritis & Rheumatology*. 73(8):1366-1383. doi:https://dx.doi.org/10.1002/art.41773
6. Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Systematic Review. *Ann Rheum Dis*. 83(1):30-47. doi:https://dx.doi.org/10.1136/ard-2022-223764
7. National Institute for Health and Care Excellence (NICE). Dupilumab for treating moderate to severe prurigo noduularis. March 2024. https://www.nice.org.uk/guidance/ta955.
8. National Institute for Health and Care Excellence (NICE). Abrocitinib, tralokinumab, or upadcitinib for treating moderate to severe atopic dermatitis. August 2022. https://www.nice.org.uk/guidance/ta814.
9. Chu DK, Schneider L, Asiniwasis RN, et al. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE- and Institute of Medicine-based recommendations. *Ann Allergy Asthma Immunol*. 132(3):274-312. doi:https://dx.doi.org/10.1016/j.anai.2023.11.009
10. Davis DMR, Drucker AM, Alikhan A, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. *Journal of the American Academy of Dermatology*. 90(2):e43-e56. doi:https://dx.doi.org/10.1016/j.jaad.2023.08.102
11. Canadian Agency for Drugs and Technologies. Upadacitinib Reimbursement Recommendation. June 2022. https://www.cda-amc.ca/upadacitinib-1.
12. Canadian Agency for Drugs and Technologies. Abrocitinib Reimbursement Review. September 2022. https://www.cda-amc.ca/abrocitinib.
13. Canadian Agency for Drugs and Technologies. Dupilumab Reimbursement Review. October 2023. https://www.cda-amc.ca/dupilumab-5.
14. Canada's Drug Agency. Tralokinumab Reimbursement Review. May 2024. https://www.cda-amc.ca/tralokinumab-0.
15. National Institute for Health and Care Excellence (NICE). Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and older. July 2024. https://www.nice.org.uk/guidance/ta986/chapter/1-Recommendations.
16. DUPIXENT (dupilumab) Injection. Prescribing Information. Tarrytown, NY; Regeneron Pharmaceuticals. June 2025.
17. Maurer M, Casale TB, Saini SS, et al. Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): Two randomized, double-blind, placebo-controlled, phase 3 trials. *J Allergy Clin Immunol*. Jul 2024;154(1):184-194. doi:10.1016/j.jaci.2024.01.028
18. NUCALA (mepolizumab) Subcutaneous Injection. Prescribing Information. Philadelphia, PA; GlaxoSmithKline. May 2025.
19. NEMLUVIO (nemolizumab-ilto) subcutaneous injection. Prurigo Nodularis Prescribing Information. Dallas, TX; Galderma Laboratories 08/2024.
20. NEMLUVIO (nemolizumab-ilto) subcutaneous injection. Atopic Dermatitis Prescribing Information. Dallas, TX; Galderma Laboratories 12/2024.
21. Ständer S, Yosipovitch G, Legat FJ, et al. Efficacy and Safety of Nemolizumab in Patients With Moderate to Severe Prurigo Nodularis: The OLYMPIA 1 Randomized Clinical Phase 3 Trial. *JAMA Dermatol*. 2024;doi:10.1001/jamadermatol.2024.4796
22. Kwatra SG, Yosipovitch G, Legat FJ, et al. Phase 3 Trial of Nemolizumab in Patients with Prurigo Nodularis. *The New England journal of medicine*. Oct 26 2023;389(17):1579-1589. doi:10.1056/NEJMoa2301333

23. 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, randomised controlled phase 3 trials. *Lancet*. 404(10451):445-460. doi:https://dx.doi.org/10.1016/S0140-6736(24)01203-0
24. Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx. Accessed February 17, 2025.
25. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. *Nat Rev Drug Discov*. Apr 2010;9(4):325-38. doi:10.1038/nrd3003
26. Baddini-Martinez J, Leitão Filho FS, Caetano LSB. Anaphylactic risks associated with immunobiological agents in asthma therapy. *Rev Assoc Med Bras (1992)*. 2023;69(3):367-369. doi:10.1590/1806-9282.20221358
27. Sitek A, Chiarella SE, Pongdee T. Adverse effects of biologics used to treat asthma. *Ther Adv Respir Dis*. Jan-Dec 2025;19:17534666251319175. doi:10.1177/17534666251319175
28. XOLAIR (omalizuamb) injection for subcutaneous use. Prescribing Information. South San Francisco, CA; Genentech, Inc. 2/2024.
29. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed August, 4, 2025.
30. Lexicomp Online. Wolters Kluwer Health, Hudson, Ohio, USA. Available at http://online.lexi.com. Accessed July 10, 2025.
31. Keating MK, Phillips JC, Phillips J. Chronic Rhinosinusitis. *Am Fam Physician*. Oct 2023;108(4):370-377.
32. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol*. Feb 2007;119(2):405-13. doi:10.1016/j.jaci.2006.11.639
33. Gamston CE, Blaine E, Lindsey W, Grabowsky A. Biologic drugs for nonasthma indications: clinical evidence. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2021.
34. Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. Mar 2022;77(3):734-766. doi:10.1111/all.15090
35. Gonçalo M, Gimenéz-Arnau A, Al-Ahmad M, et al. The global burden of chronic urticaria for the patient and society. *Br J Dermatol*. Feb 2021;184(2):226-236. doi:10.1111/bjd.19561
36. Lang DM. Chronic Urticaria. *The New England journal of medicine*. Sep 1 2022;387(9):824-831. doi:10.1056/NEJMra2120166
37. Trivioli G, Terrier B, Vaglio A. Eosinophilic granulomatosis with polyangiitis: understanding the disease and its management. *Rheumatology (Oxford)*. May 1 2020;59(Suppl 3):iii84-iii94. doi:10.1093/rheumatology/kez570
38. Mohammad AJ, Jacobsson LT, Westman KW, Sturfelt G, Segelmark M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. *Rheumatology (Oxford)*. Dec 2009;48(12):1560-5. doi:10.1093/rheumatology/kep304
39. Emmi G, Bettiol A, Gelain E, et al. Evidence-Based Guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. *Nat Rev Rheumatol*. Jun 2023;19(6):378-393. doi:10.1038/s41584-023-00958-w
40. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum*. Aug 1990;33(8):1094-100. doi:10.1002/art.1780330806
41. Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol*. Sep 2012;130(3):607-612.e9. doi:10.1016/j.jaci.2012.02.019
42. Crane MM, Chang CM, Kobayashi MG, Weller PF. Incidence of myeloproliferative hypereosinophilic syndrome in the United States and an estimate of all hypereosinophilic syndrome incidence. *J Allergy Clin Immunol*. Jul 2010;126(1):179-81. doi:10.1016/j.jaci.2010.03.035
43. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. *Blood*. May 15 1994;83(10):2759-79.

44. Constantine GM, Klion AD. Recent advances in understanding the role of eosinophils. *Fac Rev*. 2022;11:26. doi:10.12703/r/11-26
45. Zeidler C, Yosipovitch G, Ständer S. Prurigo Nodularis and Its Management. *Dermatol Clin*. Jul 2018;36(3):189-197. doi:10.1016/j.det.2018.02.003
46. Huang AH, Canner JK, Khanna R, Kang S, Kwatra SG. Real-World Prevalence of Prurigo Nodularis and Burden of Associated Diseases. *J Invest Dermatol*. Feb 2020;140(2):480-483.e4. doi:10.1016/j.jid.2019.07.697
47. Iking A, Grundmann S, Chatzigeorgakidis E, Phan NQ, Klein D, Ständer S. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. *J Eur Acad Dermatol Venereol*. May 2013;27(5):550-7. doi:10.1111/j.1468-3083.2012.04481.x
48. Boozalis E, Tang O, Patel S, et al. Ethnic differences and comorbidities of 909 prurigo nodularis patients. *J Am Acad Dermatol*. Oct 2018;79(4):714-719.e3. doi:10.1016/j.jaad.2018.04.047
49. Williams KA, Huang AH, Belzberg M, Kwatra SG. Prurigo nodularis: Pathogenesis and management. *J Am Acad Dermatol*. Dec 2020;83(6):1567-1575. doi:10.1016/j.jaad.2020.04.182
50. Nomura T, Kabashima K. Advances in atopic dermatitis in 2015. *Journal of Allergy and Clinical Immunology*. 2016/12/01/ 2016;138(6):1548-1555. doi:https://doi.org/10.1016/j.jaci.2016.10.004
51. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. Mar 12 2016;387(10023):1109-1122. doi:10.1016/s0140-6736(15)00149-x
52. Stander S. Atopic Dermatitis. *The New England journal of medicine*. Mar 25 2021;384(12):1136-1143. doi:10.1056/NEJMra2023911
53. Laughter MR, Maymone MBC, Mashayekhi S, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990-2017. *Br J Dermatol*. Feb 2021;184(2):304-309. doi:10.1111/bjd.19580
54. McKenzie C, Silverberg JI. The prevalence and persistence of atopic dermatitis in urban United States children. *Ann Allergy Asthma Immunol*. Aug 2019;123(2):173-178 e1. doi:10.1016/j.anai.2019.05.014
55. Brunner PM, Guttman-Yassky E. Racial differences in atopic dermatitis. *Ann Allergy Asthma Immunol*. May 2019;122(5):449-455. doi:10.1016/j.anai.2018.11.015
56. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. Feb 2014;70(2):338-51. doi:10.1016/j.jaad.2013.10.010
57. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol*. Nov 2013;132(5):1132-8. doi:10.1016/j.jaci.2013.08.031
58. Beattie* PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol*. 2006;155(1):145-151. doi:10.1111/j.1365-2133.2006.07185.x
59. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. Aug 2014;71(2):327-49. doi:10.1016/j.jaad.2014.03.030
60. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol*. May 2018;32(5):657-682. doi:10.1111/jdv.14891
61. McDonagh M, Crabtree E, Blazina I, Liebow S. Drugs to Treat Atopic Dermatitis. Final Report prepared by the Pacific Northwest Evidence-Based Practice Center for the Drug Effectiveness Review Project. Oregon Health and Science University, Portland, Oregon. December 2017.
62. Lindsey W, Fahim S, Chung A, Smithgall S, Zao C, Grabowsky A. Pharmaceutical Treatments for Atopic Dermatitis: An Update. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; February 2022.
63. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol*. Feb 2001;10(1):11-8.
64. Yang YB, Lynde CW, Fleming P. Common Atopic Dermatitis Rating Scales: A Practical Approach and Brief Review. *Journal of Cutaneous Medicine and Surgery*. 2020;24(4):399-404. doi:10.1177/1203475420923644

65. Futamura M, Leshem YA, Thomas KS, Nankervis H, Williams HC, Simpson EL. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards. *J Am Acad Dermatol*. Feb 2016;74(2):288-94. doi:10.1016/j.jaad.2015.09.062
66. Wechsler ME, Nair P, Terrier B, et al. Benralizumab versus Mepolizumab for Eosinophilic Granulomatosis with Polyangiitis. *The New England journal of medicine*. Mar 7 2024;390(10):911-921. doi:10.1056/NEJMoa2311155
67. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *The New England journal of medicine*. May 18 2017;376(20):1921-1932. doi:10.1056/NEJMoa1702079
68. van der Heijde D, Aletaha D, Carmona L, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis*. Jan 2015;74(1):8-13. doi:10.1136/annrheumdis-2014-206350
69. Food and Drug Administration (FDA) Drug Safety Labeling Changes. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm Accessed July 16, 2025.

Appendix 1: Current Preferred Drug List

Targeted Immune Modulators for Asthma and Atopic Dermatitis Biologics

Generic	Brand	Route	Form	PDL
abrocitinib	CIBINQO	ORAL	TABLET	N
benralizumab	FASENRA PEN	SUBCUT	AUTO INJCT	N
benralizumab	FASENRA	SUBCUT	SYRINGE	N
dupilumab	DUPIXENT PEN	SUBCUT	PEN INJCTR	N
dupilumab	DUPIXENT SYRINGE	SUBCUT	SYRINGE	N
lebrikizumab-lbkz	EBGLYSS PEN	SUBCUT	PEN INJCTR	N
lebrikizumab-lbkz	EBGLYSS SYRINGE	SUBCUT	SYRINGE	N
mepolizumab	NUCALA	SUBCUT	AUTO INJCT	N
mepolizumab	NUCALA	SUBCUT	SYRINGE	N
mepolizumab	NUCALA	SUBCUT	VIAL	N
omalizumab	XOLAIR	SUBCUT	AUTO INJCT	N
omalizumab	XOLAIR	SUBCUT	SYRINGE	N
omalizumab	XOLAIR	SUBCUT	VIAL	N
reslizumab	CINQAIR	INTRAVEN	VIAL	N
tezepelumab-ekko	TEZSPIRE	SUBCUT	PEN INJCTR	N
tezepelumab-ekko	TEZSPIRE	SUBCUT	SYRINGE	N
tralokinumab-ldrm	ADBRY AUTOINJECTOR	SUBCUT	AUTO INJCT	N
tralokinumab-ldrm	ADBRY	SUBCUT	SYRINGE	N

Atopic Dermatitis PDL Class (Topical Products)

Generic	Brand	Route	Form	PDL
pimecrolimus	ELIDEL	TOPICAL	CREAM (G)	Y
pimecrolimus	PIMECROLIMUS	TOPICAL	CREAM (G)	Y
tacrolimus	PROTOPIC	TOPICAL	OINT. (G)	Y
tacrolimus	TACROLIMUS	TOPICAL	OINT. (G)	Y
crisaborole	EUCRISA	TOPICAL	OINT. (G)	N
ruxolitinib phosphate	OPZELURA	TOPICAL	CREAM (G)	N

Targeted Immune Modulators (Select Systemic Products)

Generic	Brand	Route	Form	PDL
upadacitinib	RINVOQ	ORAL	TAB ER 24H	N
upadacitinib	RINVOQ	ORAL	TAB ER 24H	N

Appendix 2: Medline Search Strategy

TIMS in non-asthma or non-AD indications

Ovid MEDLINE(R) ALL 1946 to January 30, 2025

1	benralizumab.mp.	1007
2	mepolizumab.mp.	1791
3	exp Omalizumab/	2640
4	reslizumab.mp.	475
5	dupilumab.mp.	3792
6	tezepelumab.mp.	283
7	Janus Kinase Inhibitors/ or abrocitinib.mp.	2508
8	reslizumab.mp. or Interleukin-5/	6989
9	Interleukin-13/ or tralokinumab.mp.	6590
10	nemolizumab.mp.	155
11	Rhinitis/ or Sinusitis/ or chronic rhinosinusitis.mp. or Nasal Polyps/	35819
12	Chronic Urticaria/	995
13	Granulomatosis with Polyangiitis/ or eosinophilic granulomatosis.mp. or Churg-Strauss Syndrome/	10624
14	Eosinophilia/ or Hypereosinophilic Syndrome/	18848
15	Prurigo/ or prurigo nodularis.mp. or Pruritus/	16278
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	22221
17	11 or 12 or 13 or 14 or 15	80903
18	16 and 17	3268
19	limit 18 to (english language and humans and yr="2022 -Current" and (clinical trial, phase iii or guideline or meta-analysis or practice guideline or randomized controlled trial or "systematic review"))	132

TIMS in Atopic Dermatitis

Ovid MEDLINE(R) ALL <1946 to February 18, 2025>

1	dupilumab.mp.	3848
2	Janus Kinase Inhibitors/ or abrocitinib.mp.	2560
3	Interleukin-13/ or tralokinumab.mp.	6615
4	nemolizumab.mp.	157
5	Janus Kinase Inhibitors/ or upadacitinib.mp.	3183
6	1 or 2 or 3 or 4 or 5	9976
7	Dermatitis, Atopic/	26972
8	6 and 7	941
9	limit 8 to (english language and humans and yr="2022 -Current")	492
10	limit 9 to (comparative study or meta-analysis or practice guideline or "systematic review")	61

Author: Moretz

Date: October 2025

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEMLUVIO safely and effectively. See full prescribing information for NEMLUVIO.

NEMLUVIO® (nemolizumab-ilto) for injection, for subcutaneous use
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------

NEMLUVIO is an interleukin-31 receptor antagonist 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. (1)

----------DOSAGE AND ADMINISTRATION----------

- Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to treatment with NEMLUVIO. (2.1)
- The recommended dosage is an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks. (2.2)
- After 16 weeks of treatment, for patients who achieve clear or almost clear skin, a dosage of 30 mg every 8 weeks is recommended. (2.2)
- Use NEMLUVIO with topical corticosteroids and/or topical calcineurin inhibitors. When the disease has sufficiently improved, discontinue use of topical therapies. (2.2)
- Administer NEMLUVIO by subcutaneous injection. (2.4)
- NEMLUVIO must be reconstituted prior to administration. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: single-dose pre-filled dual-chamber pen containing 30 mg of nemolizumab-ilto lyophilized powder and diluent, water for injection. (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to nemolizumab-ilto or to any of the excipients in NEMLUVIO. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity: Hypersensitivity reactions have been reported with NEMLUVIO use. If a clinically significant hypersensitivity reaction occurs, immediately institute appropriate therapy and discontinue NEMLUVIO. (5.1)
- Vaccinations: Avoid use of live vaccines during treatment with NEMLUVIO. (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reaction (incidence ≥1%) headache (including migraine), arthralgia, urticaria, and myalgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P at 1-866-735-4137 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2024

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEMLUVIO safely and effectively. See full prescribing information for NEMLUVIO.

NEMLUVIO® (nemolizumab-ilto) for injection, for subcutaneous use

Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------

NEMLUVIO is an interleukin-31 receptor antagonist indicated for the treatment of adults with prurigo nodularis. (1)

----------DOSAGE AND ADMINISTRATION----------

- Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to treatment with NEMLUVIO, (2.1)
- Adult Patients Weighing Less Than 90kg: The recommended dosage is an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (Q4W). (2.2)
- Adult Patients Weighing 90kg or More: The recommended dosage is an initial dose of 60 mg (two 30 mg injections), followed by 60 mg given every 4 weeks (Q4W). (2.2)
- Administer NEMLUVIO by subcutaneous injection. (2.4)
- NEMLUVIO must be reconstituted prior to administration. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: single-dose prefilled dual chamber pen containing 30 mg of nemolizumab-ilto lyophilized powder and diluent, water for injection. (3).

----------CONTRAINDICATIONS----------

Known hypersensitivity to nemolizumab-ilto or to any of the excipients in NEMLUVIO. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity: Hypersensitivity reactions have been reported with NEMLUVIO use. If a clinically significant hypersensitivity reaction occurs, immediately institute appropriate therapy and discontinue NEMLUVIO. (5.1)
- Vaccinations: Avoid use of live vaccines during treatment with NEMLUVIO. (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥1%) are headache, dermatitis atopic, eczema, and eczema nummular. (6.1)

----------DRUG INTERACTIONS----------

Cytochrome P450 (CYP450) Substrates: Upon initiation or discontinuation of NEMLUVIO, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate.

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P at 1-866-735-4137 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2024

Immune Modulators for Severe Asthma and Atopic Dermatitis

Goal(s):

- Promote use is consistent with national clinical practice guidelines, medical evidence, and OHP-funded conditions. Allow case-by-case review for members covered under the EPSDT program.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All targeted immune modulators with indications for severe asthma, atopic dermatitis, or other indications (see **Table 1** below) for both pharmacy and provider-administered claims.
- This PA does not apply to topical agents for inflammatory skin conditions which are subject to separate clinical PA criteria.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-Approved Indications and Ages

Generic Name/ BRAND NAME	Eosinophilic Asthma	Moderate-to-severe Allergic Asthma	Difficult To Treat, Severe Asthma*	Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)	Eosinophilic Esophagitis	Atopic Dermatitis (AD)	IgE-Mediated Food Allergy	Other
Abrocitinib CIBINQO						≥12 yrs		
Benralizumab FASENRA	≥6 yrs							EGPA ≥18 yrs
Dupilumab DUPIXENT	≥6 yrs (or with oral corticosteroid dependent asthma)			≥12 yrs	≥1 yr & weighing ≥15 kg	≥6 months	≥18 yrs	PN ≥18 yrs COPD ≥18 yrs CSU ≥ 12 yrs BP ≥18 yrs
Lebrikizumab EBGLYSS						≥12 yrs		
Mepolizumab NUCALA	≥6 yrs			≥18 yrs				HES ≥ 12 yrs EGPA ≥18 yrs

								COPD ≥ 18 yrs
Nemolizumab NEMLUVIO						≥12 yrs		PN ≥ 18 yrs
Omalizumab XOLAIR		≥6 yrs		≥18 yrs			≥ 1 yo	CSU ≥ 12 yrs
Remibrutinib RHAPSIDO								CSU > 18 yrs
Reslizumab CINQAIR	≥18 yrs							
Tezepelumab TEZSPIRE			≥ 12 yrs	≥ 12 yrs				
Tralokinumab ADBRY						≥12 yrs		

Abbreviations: BP = bullous pemphigoid; COPD = chronic obstructive pulmonary disease; CSU = chronic spontaneous urticaria; EGPA = eosinophilic granulomatosis with polyangiitis; HES = hypereosinophilic syndrome; PN = prurigo nodularis
* Difficult to treat, severe asthma is defined as asthma with poor symptom control on high-dose inhaled corticosteroid-long-acting beta agonist (ICS-LABA) or maintenance oral corticosteroids (OCS).

Table 2. Recommended First-Line Conventional Treatments

Indication	Conventional treatment
Asthma	Maximally dosed inhaled corticosteroid (**Table 3**) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)
Atopic Dermatitis (AD)	4-week trial of either one the following treatments in pediatrics and adults: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) OR a topical calcineurin inhibitor (e.g., tacrolimus) AND for adults only: • Oral immunomodulator therapy (e.g., cyclosporine, methotrexate, mycophenolate mofetil or azathioprine) for at least 12 weeks
Chronic Obstructive Pulmonary Disease (COPD)	Triple inhaler therapy (inhaled corticosteroid (ICS) with long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA) inhalers) for at least 3 months
Chronic Rhinosinusitis with Nasal polyps (CRSwNP)	Intranasal corticosteroids (2 or more courses administered for at least 12 weeks each)

Chronic Spontaneous Urticaria (CSU)	• 4-week trial of second-generation antihistamines (cetirizine, loratadine, fexofenadine) taken once daily (may try four-fold dosing increases in adults) AND • 4-week trial of a leukotriene receptor antagonist (montelukast, zafirlukast) added to second-generation antihistamine therapy.
Eosinophilic Granulomatosis with Polyangiitis (EGPA)	4-week trial of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)
Eosinophilic Esophagitis	• Proton pump therapy for at least 8 weeks OR • Corticosteroid therapy with local administration of fluticasone multi-use inhaler for at least 8 weeks (use nasal inhaler and swallow contents of the spray).
Other	Documentation for conventional treatment(s) are not required

Table 3. Maximum Adult Doses for Inhaled Corticosteroids

High Dose Corticosteroids:	**Maximum Dose**
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID
Alvesco (ciclesonide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Armonair (fluticasone propionate)	232 mcg BID
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	**Maximum Dose**
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Wixela Inhub (fluticasone/salmeterol)	500/50 mcg BID
AirDuo Digihaler (fluticasone/salmeterol)	232/14 mcg BID
Airduo RespiClick (fluticasone/salmeterol)	232/14 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Table 4. Required Baseline Documentation of Disease Severity

Indication	Disease severity definitions
Atopic dermatitis or prurigo nodularis	Functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on another validated tool) AND one or more of the following: • At least 10% of body surface area involved, or • Hand, foot, face, or mucous membrane involvement
Asthma	• At least 4 asthma exacerbations requiring systemic corticosteroids in the previous 12 months OR • Taking continuous oral corticosteroids at least the equivalent of prednisolone 5 mg per day for the previous 6 months OR • At least 1 hospitalization or ≥ 2 emergency department (ED) visits in the past 12 months while on conventional treatment outlined in **Table 2 and 3**
Chronic Rhinosinusitis with Polyps (CRSwNP)	• Presence of at least 2 of 4 cardinal symptoms (nasal blockage, obstruction, or congestion; anterior or posterior nasal drainage; facial pain or pressure; and decreased sense of smell) for at least 3 consecutive months, with objective findings on imaging or nasal endoscopy AND • Documentation of severity of CRSwNP with one of the following scores: o Nasal Polyp Score (NPS) ≥ 5 OR o Sinonasal Outcome Test (SNOT-22) ≥ 50
Chronic Spontaneous Urticaria (CSU)_	• Recurrent pruritic hives with or without angioedema for more than 6 weeks AND • Documentation of severity of CSU with one of the following scores: o Weekly Urticaria Score (UAS7) ≥ 28 OR o Urticaria Activity Score (UAS) ≥ 3 OR o Dermatology Life Quality Index (DLQI) ≥ 10
Chronic Obstructive Pulmonary Disease (COPD)	• Blood eosinophil counts 300 cells/μL AND • At least 1 hospitalization or ≥ 2 emergency department (ED) visits in the past 12 months while on conventional treatment outlined in **Table 2 and 3**

IgE-mediated food allergy	• Number of epinephrine administrations and hospital/emergency department visits (if any) in past 12 months which were caused by presumed exposure to food that triggered an allergic response
Hypereosinophilic Syndrome (HES)	• Duration of disease of at least 6 months without an identifiable non-hematologic secondary cause

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the diagnosis funded by OHP? Note: chronic idiopathic urticaria and mild-to-moderate atopic dermatitis are not OHP-funded conditions	**Yes**: Go to #5	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP. If eligible for EPSDT review: Go to #4
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.
5. Is the request for an FDA-approved age and indication (**Table 1**)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for omalizumab?	**Yes:** Go to # 7	**No:** Go to #8
7. Does the patient have a concurrent prescription for EpiPen® or equivalent, so they are prepared to manage delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
8. Is the medication being prescribed by, or in consultation with, an appropriate specialist? Examples include allergist for any condition, dermatologist for atopic dermatitis, otolaryngologist for nasal polyps, or pulmonologist for asthma	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the patient currently receiving another monoclonal antibody (e.g., dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, tezepelumab etc.) without documentation indicating the patient is switching between treatments?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #10
10. Is there documentation of failure to have benefit with, or contraindication to, recommended conventional first-line treatments options (**Table 2 and 3**)?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. Is there documentation of disease severity prior to initiation of a targeted immune modulator (**Table 4**)?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the request for asthma?	**Yes:** Go to #13	**No:** Go to #14
13. Is the request for add-on therapy for a patient who has been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the request for eosinophilic asthma, allergic asthma, or food allergies?	**Yes:** Go to #15	**No:** Go to #16

Approval Criteria		
15. Is there diagnostic documentation for the requested indication? • Eosinophilic asthma: blood eosinophil count ≥150 cells/μL OR fractional exhaled nitric oxide (FeNO) ≥25 ppb in the past 12 months • Allergic IgE-mediated asthma: positive skin test OR in vitro reactivity to perennial allergen • Food allergy: IgE-mediated food allergy with skin testing to confirm allergy OR in vitro reactivity to perennial allergen	**Yes:** Approve for up to 12 months. Document test and result: _____	**No:** Pass to RPh. Deny; medical appropriateness.
16. Is the request for a JAK inhibitor (e.g., abrocitinib)?	**Yes:** Go to #17	**No:** Go to #18
17. Has the patient failed to have benefit with or have intolerance or contraindication to alternative targeted immumodulatory therapy?	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness.
18. Duration of approval based on indication:	Asthma, COPD, hypereosinophilic syndrome, and eosinophilic granulomatosis with polyangiitis: 12 months. Chronic spontaneous urticaria* and all other conditions: requested duration or 6 months, whichever is less.	

Renewal Criteria		
1. Is the request to renew therapy for inflammatory skin disease?	**Yes:** Go to #2	**No:** Go to #5

Renewal Criteria		
2. Have the patient's symptoms improved after 16 weeks of treatment with targeted immune modulator therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI from when treatment started OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for lebrikizumab, tralokinumab, or nemolizumab in a patient with atopic dermatitis?	Yes: Go to #4	No: Approve for 12 months
4. Is the request for a maintenance dose as outlined in the FDA-label: • For lebrikizumab and tralokinumab every 4 weeks OR • For nemolizumab every 8 weeks?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request to renew therapy for asthma or COPD?	**Yes:** Go to #6	**No:** Go to #8
6. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium) for asthma or triple inhaler therapy (ICS/LABA/LAMA) for COPD or is there documentation of failure to have benefit with, or contraindication to continued use of conventional first-line treatment options?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
7. Has the number of emergency department (ED) visits or hospitalizations in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline or has the number of COPD exacerbations decreased?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the request to renew therapy for CSU with omalizumab (Xolair)?	**Yes:** Go to #9	**No:** Go to #10
9. Has the patient stopped therapy after the 6th dose and is now having a relapse?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness. *2015 NICE guidance recommends omalizumab be stopped at or before the 4th dose if symptoms of chronic spontaneous urticaria have not responded to therapy. Omalizumab should be stopped after 6 doses to assess if the condition has responded or gone into spontaneous remission and should be restarted only if the condition relapses.[5]
10. Is the request to renew therapy for another FDA approved indication?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
11. Have the patient's symptoms improved with therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

1. *Oregon Health Evidence Review Commission. Coverage Guidance and Reports.* *http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed 2/17/2025.*
2. National Institute for Health and Care Excellence (NICE) Guidance. Mepolizumab for Treating Severe Eosinophilic Asthma. https://www.nice.org.uk/guidance/ta671 February 2021.
3. National Institute for Health and Care Excellence (NICE) Guidance. Dupilumab for Treating Severe Asthma with Type 2 Inflammation. https://www.nice.org.uk/guidance/ta751 December 2021
4. Global Initiative for Asthma. Global strategy for asthma management and prevention (2021 update). 2021. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf
5. National Institute for Health and Care Excellence (NICE). Omalizumab For Previously Treated Chronic Spontaneous Urticaria. June 2015. https://www.nice.org.uk/guidance/ta339/chapter/1-Guidance

P&T Review: *10/25 (DM); 12/24 (DM), 8/24; 6/23; 10/22; 6/22; 8/2; 10/20,7/19; 7/18; 7/16*
Implementation: *1/1/26; 1/1/25; 9/1/24; 7/1/23; 1/1/23; 7/1/22; 1/1/22*