DRUG DETERMINATION POLICY

Title: DDP-27 Specialty Allergic and Asthma Agents

Effective Date: 08/24/22

Physicians Health Plan
PHP Insurance Company
PHP Service Company

Important Information - Please Read Before Using This Policy

The following policy applies to health benefit plans administered by PHP and may not be covered by all PHP plans. Please refer to the member's benefit document for specific coverage information. If there is a difference between this general information and the member's benefit document, the member's benefit document will be used to determine coverage. For example, a member's benefit document may contain a specific exclusion related to a topic addressed in a coverage policy.

Benefit determinations for individual requests require consideration of:

1. The terms of the applicable benefit document in effect on the date of service.
2. Any applicable laws and regulations.
3. Any relevant collateral source materials including coverage policies.
4. The specific facts of the particular situation.

Contact PHP Customer Service to discuss plan benefits more specifically.

1.0 Policy:

This policy describes the determination process for coverage of Xolair (omalizumab), Dupixent (dupilumab), Cinqair (reslizumab), Fasenra (benralizumab), and Nucala (mepolizumab).

This policy does not guarantee or approve benefits. Coverage depends on the specific benefit plan. Drug Determination Policies are not recommendations for treatment and should not be used as treatment guidelines.

2.0 Background or Purpose:

Specialty allergic and asthma agents are specialty drugs indicated for specific diagnoses and are associated with some toxicity. These criteria were developed and implemented to ensure appropriate use of first line conventional therapy as well as use for the appropriate severity of disease.

3.0 Clinical Determination Guidelines:

Document the following with chart notes:

I. Moderate to severe persistent allergic asthma [must meet all listed below]:

   A. Age: at least six years.

   B. Diagnosis and severity [must meet all listed below]:

      1. Moderate-severe persistent asthma for over one-year duration.

      2. Allergic component [must meet both listed below]:

         a. Skin prick: positive immediate responses to at least one allergen (dust mite, cockroach, dog or cat).

         b. Total Serum IgE: at least 30 to less than or equal to 700 IU/mL.

      3. Pulmonary function test (PFT): historical PFT that confirms diagnosis of asthma.

4. Asthma status: two asthma exacerbations that required treatment with systemic corticosteroids, emergency department visits or hospitalization for asthma in the last year.

C. Other therapies: contraindicated, inadequate response or significant adverse effects to both listed below:

1. Inhaled corticosteroids (ICS) with long acting beta agonist (LABA): three months current use of high dose ICS with LABA and documentation of consistent use.

2. Systemic steroids: intermittent oral or parenteral steroids use to control asthma symptoms.

D. Dosage regimen: this agent is add-on therapy to other asthma medications.

1. Xolair subcutaneous (omalizumab SQ) (see tables in Appendix I).

E. Approval.

1. Initial: six months.

2. Re-approval: six months to one year [must meet one listed below]:

a. Decreased use of rescue meds.

b. Decreased exacerbations.

c. Increased forced expiratory volume over 1 minute (FEV1) from pre-treatment baseline.

d. Reduced symptoms: coughing, fatigue, shortness of breath, sleep disturbances, or wheezing.

II. Severe Eosinophilic Asthma.

A. Age:

1. Nucala subcutaneous (mepolizumab SQ): at least six years.

2. Fasenra subcutaneous (benralizumab SQ) and Dupixent subcutaneous (dupilumab SQ): at least 12 years.

3. Cinqair intravenous (reslizumab IV): at least 18 years.

4. Dupixent subcutaneous (dupilumab SQ): at least 12 years.

B. Diagnosis and severity.

1. Severe Eosinophilic Asthma [must meet all listed below]:

a. Blood eosinophil count: at least 150 cells/uL at start of treatment OR at least 300 cells/uL in prior 12 months. (Note: 1 microliter [uL] = 1 cubic millimeter [mm^3]).

b. Pulmonary Function Test: Forced Expiratory volume over 1 second ($FEV_{1)}$ less than 80 percent predicted and FEV_1 reversibility at least 12 percent after albuterol.
c. Asthma Status: two asthma exacerbations that required treatment with systemic corticosteroids or emergency department visits or hospitalization for asthma in the last year.

C. Other therapies: uncontrolled symptoms despite trial of both regimens below with one regimen currently in use:

1. Six months inhaled corticosteroid (ICS) plus three months LABA.

2. Three months ICS plus three months daily oral steroids plus three months LABA.

D. Dosage regimen: these agents are add-on therapy to other asthma medications.

1. Nucala subcutaneous (mepolizumab SQ): six to twelve years - 40mg every four weeks; over twelve years - 100mg every four weeks.

2. Cinqair intravenous (reslizumab IV): 3mg per Kg IV every four weeks.

3. Fasenra subcutaneous (benralizumab SQ): 30mg every week times three, then every eight weeks.

4. Dupixent subcutaneous (dupilumab SQ): 600mg initially, then 300 every two weeks.

E. Approval.

1. Initial: six months.

2. Re-approval: six months to one year [must meet one listed below]:

a. Decreased use of rescue meds.

b. Decreased exacerbations.

c. Increased forced expiratory volume over 1 minute (FEV1) from pre-treatment baseline.

d. Reduced asthma symptoms: coughing, fatigue, SOB, sleep disturbances, or wheezing.

III. Moderate to Severe Chronic Idiopathic Urticaria (CIU) [must meet all listed below]:

A. Age: at least 12 years.

B. Diagnosis and severity: moderate to severe CIU for one year [must meet one listed below]:

1. Urticaria activity score (UAS): at least 28 (see Appendix IV).

C. Other therapies (see Appendix III): contraindicated, inadequate response (continued hives with itching) or had significant adverse effects [must meet all listed below]:

1. First line: two non-sedating H1 antihistamines for two weeks each.

2. Second line: maximum dose non-sedating H1 antihistamines for one to four weeks.

3. Add to second line: cyclosporine or montelukast for four months.

D. Dosage regimen:

1. Xolair subcutaneous (omalizumab SQ): 150 to 300mg every four weeks (not dependent on serum IgE or weight).

E. Approval.

a. Initial: six months.

b. Re-approval: six months to one year; decreased hives (reduction in UAS).

IV. Atopic Dermatitis.

A. Age: at least six years.

B. Prescriber: dermatologist or allergist.

C. Diagnosis and severity: moderate to severe atopic dermatitis not controlled with topical prescription therapies or if the therapies are not advisable [must meet all listed below]:

1. Exacerbating factors that could contribute to the member's atopic dermatitis have been evaluated and addressed (e.g., non-compliance, environmental triggers, allergy patch testing etc.).

2. Body surface area (BSA): at least 10 percent.

3. Severity [must meet both below]:

a. Documentation of current pruritus and other symptoms severity (e.g. edema, erythema, erosions. excoriations, oozing/crusting and/or lichenification).

b. Interfering with routine daily activities (e.g., skin infections, sleep disturbances).

D. Other therapies: contraindicated, inadequate response after two months or significant adverseeffects to topical and systemic therapies listed below.

1. Topical: one mid-strength to super-potent corticosteroid trials or one calcineurin inhibitortrial [must meet both listed below].

a. Mid-strength to super-potent corticosteroid: unless the face, neck and/or intertriginousareas are affected.

b. Topical calcineurin Inhibitor: tacrolimus, pimecrolimus.

2. Systemic chronic disease-modifying anti-rheumatic drug (DMARD).

a. Chronic traditional DMARD's: cyclosporine, azathioprine, methotrexate or mycophenolate.

E. Dosage regimen- Dupixent subcutaneous (dupilumab SQ) [must meet all listed below]:

AGE	LOADING DOSE	MAINTENANCE DOSE
Adult	600mg	300mg every two weeks
Pediatric 15 to <30Kg 30 to <60Kg ≥60Kg	 600mg 400mg 600mg	 300mg every four weeks 300mg every two weeks 300mg every two weeks

F. Approval.

1. Initial: six months.

2. Re-approval: one year (must demonstrate reduced percentage body surface area affected, reduced pruritus/symptom severity and/or improve ability to perform routine daily ctivities).

G. Exclusions: use in conjunction with other biologicals (e.g., Xolair, infliximab, Enbrel, Nucala, etc.).

V. Chronic rhinosinusitis with nasal polyps [must meet all listed below]:

A. Age: at least 18 years.

B. Diagnosis and severity [must meet all listed below]:

1. Mucosal inflammation: moderate to severe.

2. Symptoms for at least 12 weeks [must meet two listed below]:

a. Decreased or loss of smell.

b. Nasal obstruction.

c. Mucopurulent rhinorrhea.

d. Facial pressure, pain, fullness.

3. Polyps: confirmed by direct examination, endoscopy or sinus CT scan.

C. Other therapies: contraindicated, inadequate response or had significant side effects to initial and maintenance medications; and surgery.
:

1. Initial [must meet both listed below]:

a. Oral corticosteroids for 10 to 15 days within the last two years.

b. Current infection: treated with antibiotics.

2. Maintenance [must meet both listed below]:

a. Intranasal corticosteroids for six months.

b. Anti-leukotrienes plus intranasal corticosteroids for three months.

3. Surgery: primary or revision endoscopic sinus surgery.

D. Dosage regimen:

1. Dupixent Subcutaneous (dupilumab SQ): 300mg every two weeks.

2. Nucala subcutaneous (mepolizumab SQ): 100mg every four weeks.

E. Approval:

1. Initial: six months.

2. Re-approval: six months to one year (reduction of symptoms and polyps number and/or size).

VI. Eosinophilic granulomatosis with polyangiitis [must meet all listed below]:

A. Diagnosis and severity [must meet all listed below]:

1. Diagnostic criteria [must meet four of the six listed below]:

a. Asthma.

b. Eosinophilia: above ten percent on differential shite blood cell count.

c. Mononeuropathy or polyneuropathy.

d. Migratory or transient pulmonary opacities detected by radiographically.

e. Paranasal sinus abnormality.

f. Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas.

2. Labs: eosinophilia (above 500/uL) or hypereosinophllia (above 1,500/uL).

3. Severity.

a. Five-factor score: 1 (see Appendix II).

B. Other therapies: contraindication, inadequate response or significant adverse effects to one each systemic steroids, cyclophosphamide and disease modifying agents.

1. Systemic corticosteroids: treat until manifestation of disease are controlled and taper over approximately 12 to 18 months [must meet one listed below]:

a. Systemic vasculitis: prednisone 0.5-1mg per Kg.

b. Acute multi-organ disease: methylprednisolone 1g daily for three days followed by oral therapy.

2. Cyclophosphamide [must meet both listed below]:

a. Five factor score: 2 or 1 with cardiac or central nervous system involvement.

b. Use corticosteroids concomitantly.

3. Maintenance therapy.

a. Disease modifying agents: azathioprine, methotrexate, leflunomide.

C. Dosage regimen: [must meet both listed below]:

1. Nucala subcutaneous (meplizumab SQ): 300mg every four weeks.

2. Concomitant drugs: corticosteroids.

D. Approval.

1. Initial: six months.

2. Reapproval: one year (reduced eosinophil count and steroid dose).

VII. Hypereosinophilic syndrome.

A. Age: at or above twelve years.

B. Diagnosis and severity [must meet all listed below]:

1. Diagnosis [must meet both listed below]:

a. Non-myeloid disease with T cell lymphocytic variant or idiopathic.

b. IgE level: at or above 1,500 eosinophils per mm^3

2. Severity.

a. Symptomatic patients or those with evidence of end-organ damage.

C. Other therapies: contraindicated, inadequate response or significant adverse effects to corticosteroids and hydroxyurea.

1. Corticosteroids: prednisone 20 to 60mg daily depending on the severity of disease manifestations and eosinophilia presence; titrate to response.

2. Hydroxyurea: 500 to 1000mg per day, titrate to 2000mg per day as tolerated [must meet one below]:

a. Add to corticosteroids if steroid toxicity has become dose limiting.

b. Monotherapy for corticosteroid resistant patients.

D. Dosage regimen:

1. Nucala subcutaneous (mepolizumab SQ): 300mg every four weeks.

2. Concomitant administration with corticosteroids.

VIII. Appropriate medication use [must meet one listed below]:

A. FDA approval status [must meet one listed below]:

1. FDA approved: product, indication, and/or dosage regimen.

2. Non-FDA approved: Compendium support (Lexicomp™) for use of a drug for a non-FDA approved indication or dosage regimen.

B. Place in therapy: sequence of therapy supported by national or international accepted guidelines and/or studies (e.g., oncologic, infectious conditions).

4.0 Coding:

AFFECTED CODES				
Code	**Brand Name**	**Generic Name**	**Billing (1 unit)**	**Prior Approval**
J2357	Xolair	omalizumab	5mg	Y
J2182	Nucala	mepolizumab	1mg	Y
J2786	Cinqair	reslizumab	1mg	Y
J0517	Fasenra	benralizumab	1mg	Y
J3490	Dupixent	dupilumab	NA	Y

Medication	**Process through pharmacy benefit**	**Process through medical benefit**
Dupixent	Pre-filled syringe Pen injector	*(none)*
Xolair	*(none)*	Pre-filled syringe Vial
Cinqair	*(none)*	Vial
Fasenra	Pen auto-injector Pre-filled syringe (HCP administration only)	Pre-filled syringe (HCP administration only)
Nucala	Auto-injector Syringe	Vial

**HCP = health care professional*

5.0 References, Citations & Resources:

1. Update on optimal use of omalizumab in management of asthma. Journal of Allergy and Clinical Immunology.2001:108(2):184-90.
2. Omalizumab for the treatment of chronic idiopathic or spontaneous Urticaria. N Engl J Med 2013:368(10); 924-35.
3. A randomized, placebo-controlled, dose-ranging study of a single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticarial. J Allergy Clin Immunol 2011:128(3):567-73.
4. EAACI/GA^{2}LEN/EDF/WAO guidelines: Management of urticarial. Allergy 2009:64(10):1417-43.
5. EAACI/GA^{2}LEN/EDF/WAO guidelines for the definition, classification, diagnosis and management of urticarial: the 2013 revision and update. Allergy 2014:69(7):868-887.
6. Lexicomp Online® Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Xolair, Nucala, Cinqair, Fasenra, Dupixent, accessed October 2020.
7. The Urticaria Activity Score (UAS), http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20150614174531231819, accessed August 2017.
8. Xolair package insert: Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936-1080 https://www.gene.com/download/pdf/xolair_prescribing.pdf accessed October 2020
9. UpToDate Treatment and prognosis of eosinophilic granulomatosis with polyangiitis; https://www.uptodate.com/contents/treatment-and-prognosis-of-eosinophilic-granulomatosis-with-polyangiitis-churg-strauss?search=Eosinophilic%20granulomatosis%20with%20polyangiitis&source=search_result&selectedTitle=2~145&usage_type=default&display_rank=2#H25 accessed March 2021.

10. UpTo Date Hypereosinophilic Syndrome: Treatment tps://www.uptodate.com/contents/hypereosinophilic-syndromes-treatment?search=Hypereosinophilic%20syndrome&source=search_result&selectedTitle=2~73&usage_type=default&display_rank=2 accessed March 2021
11. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf. Updated 2021. Accessed October 7, 2021.

6.0 Appendices:

See pages 9-12.

7.0 Revision History:

Original Effective Date: 05/03/2004

Next Review Date: 11/10/2022

Revision Date	Reason for Revision
7/19	Moved to new format
9/19	Replaced abbreviations, added Dupixent, added diagnosis of chronic rhinosinusitis with polys, clarified dosage, reformatted approval sections
10/20	Annual review; clarify criteria instructions, revised Xolair/Nucala/Dupixent age, indicated add-on treatment for asthma, revised other therapies language, updated Xolair dosage table, changed Fasenta J code; replaced abbreviations, added exclusion of use in non-FDA approved indications, clarified Dupixent dosing, formatting, approved by P&T Committee 12/9/20
2/21	Off cycle review, added diagnoses eosinophilic granulomatosis with polyangiitis and hyperesosinophilic syndrome; replaced abbreviation, clarified criteria instructions
10/21	Annual review; added Nucala for rhinosinusitis with nasal polyps, added diagnosis Atopic dermatitis, removed NCCN reference under appropriate use
6/22	Ad Hoc review; addition of Atopic Dermatitis indication, addition of GINA guidelines in references

Appendix I: Adult and Pediatric Xolair Dosing

Adult and adolescent patients 12 years of age and older: Initiate dosing according to Table 1.

Table 1. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Patients 12 Years of Age and Older with Asthma

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight			
		30–60 kg	>60–70 kg	>70–90 kg	>90–150 kg
		Dose (mg)			
≥30–100	Every 4 weeks	150	150	150	300
>100–200		300	300	300	225
>200–300		300	225	225	300
>300–400	Every 2 weeks	225	225	300	
>400–500		300	300	375	
>500–600		300	375	Insufficient Data to Recommend a Dose	
>600–700		375			

*Dosing frequency:

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

Table 2. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Pediatric Patients with Asthma Who Begin XOLAIR Between the Ages of 6 to <12 Years

Pre-treatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight									
		20-25 kg	>25-30 kg	>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	>125-150 kg
		Dose (mg)									
30-100	Every 4 weeks	75	75	75	150	150	150	150	150	300	300
>100-200		150	150	150	300	300	300	300	300	225	300
>200-300		150	150	225	300	300	225	225	225	300	375
>300-400		225	225	300	225	225	225	300	300		
>400-500		225	300	225	225	300	300	375	375		
>500-600		300	300	225	300	300	375				
>600-700		300	225	225	300	375					
>700-800	Every 2 weeks	225	225	300	375						
>800-900		225	225	300	375						
>900-1000		225	300	375	Insufficient Data to Recommend a Dose						
>1000-1100		225	300	375							
>1100-1200		300	300								
>1200-1300		300	375								

*Dosing frequency:

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

Appendix II Five-factor score in eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

- Age above 65
- Cardiac insufficiency
- Renal insufficiency (stabilized peak creatinine 1.7mg/dL
- Gastrointestinal involvement
- Absence of ear, nose and throat manifestations (presence is associated with a better prognosis)

Scoring: The presence of each factor is given one point. The five factor score ranges from 0 to 2; a score of 0 is given when none of the factors are present. A score of 1 for one factor, and a score of 2 for two or more factors.

Appendix III: Monitoring & Patient Safety

Drug	Adverse Reactions	Monitoring	REMS
Xolair omalizumab SQ	• Dermatology: injection site reactions (45%; severe – 12%) pregnancy: IgG monoclonal antibodies expected to cross placenta in 3rd trimester	• Asthma Severity: forced expiatory volume ($FEV_{1)}$, peak flow and/or pulmonary function tests (PFT) • Injection Site Reaction: monitor post infusion (most occur ≤1 hour) • Infections: signs and symptoms	Med Guide: Dispensed w drug
Nucala mepolizumab SQ	• Central Nervous System: headache (19%) • Pregnancy: IgG monoclonal antibodies expected to cross placenta in 3rd trimester	• Asthma Severity: FEV_1, peak flow and/or PFT, use of beta agonist	Not needed
Cinqair reslizumab IV	• Musculoskeletal (MSK): increased creatinine, phosphokinase (20% transient) • Pregnancy: IgG monoclonal antibodies expected to cross placenta in third trimester	• Anaphylaxis: during and post infusion • Asthma Severity: FEV_1, peak flow and/or PFT • Infection: signs and symptoms	Not needed
Fasenra benralizumab SQ	• Immunological: antibody development (12-13%) • Pregnancy: IgG monoclonal antibodies expected to cross placenta in third trimester	• Anaphylaxis: during and post infusion • Asthma Severity: FEV_1, peak flow and/or PFT • Infection: signs and symptoms	Not needed
Dupixent dupilumab SQ	• Local: injection site reaction (10%) • Ophthalmology: conjunctivitis (10%)	• Asthma Severity: PFT • Hypersensitivity • Ophthalmology: ocular effects	None needed

Appendix III: Recommended Treatment Algorithm for Chronic Urticaria

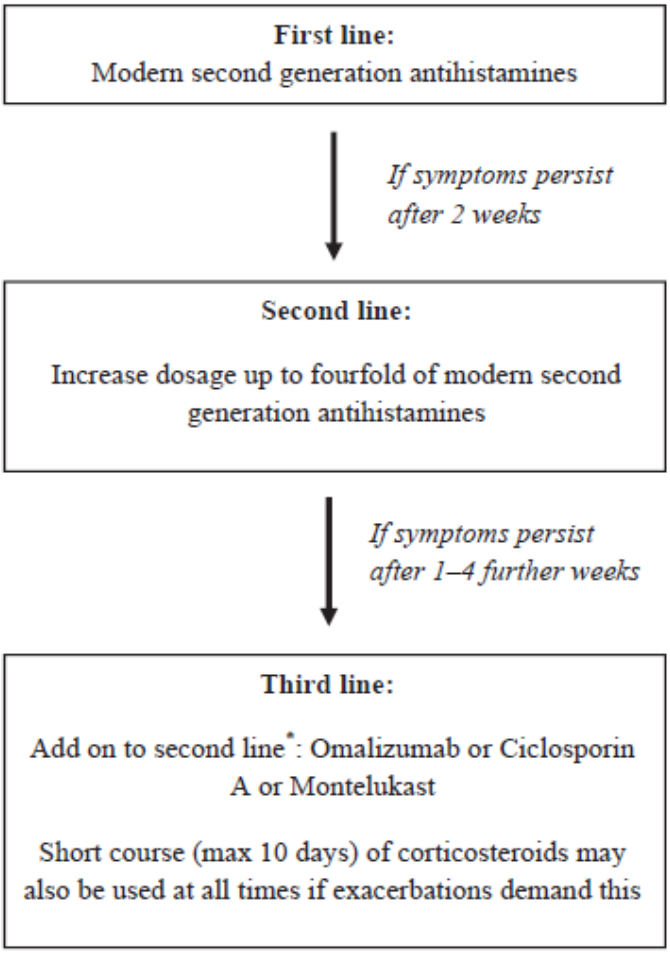

Figure 2 Recommended treatment algorithm for urticaria. *The order of third-line treatments does not reflect preference. *First line = High-quality evidence:* Low cost and worldwide availability (e.g., modern second-generation antihistamines exist also in developing countries mostly cheaper than old sedating Antihistamines), per daily dose as the half-life time is much longer, very good safety profile, good efficacy. *Second line = high-quality evidence:* Low cost, good safety profile, good efficacy. *Third line as add-on to AH. Ciclosporin A = High-quality evidence:* Medium to high cost, moderate safety profile, good efficacy. *Omalizumab = High-quality evidence:* High cost, very good safety profile, very good efficacy. *Montelukast = Low quality evidence:* Low cost, good safety, low efficacy. *Short course of corticosteroids = Low quality evidence:* Low cost, worldwide availability, good safety profile (for short course only), good efficacy during intake, but very low for lasting efficacy.

EAACI/GA²LEN/EDF/WAO guidelines for the definition, classification, diagnosis and management of urticarial: the 2013 revision and update. Allergy 2014:69(7):868-887

Appendix IV: The Urticaria Activity Score (UAS)

The Urticaria Activity Score (UAS) is a composite score of itch severity and hive count

To assess disease severity in patients with chronic idiopathic urticaria (CIU), patients record the severity of their itch and the number of hives 2 times per day (AM AND PM)

Each component of the UAS is scored on a scale of 0 to 3; the 2 scores are added together for a daily total of 0 to 6

Daily scoring the urticaria activity score (UAS)

Score	Itch Severity	Number of Hives
0	None	None
1	Mild	1-6
2	Moderate	7-12
3	Severe	>12

The UAS7 is the sum of the average daily UAS over 7 days

After 7 days, average daily scores from the morning and evening assessments are added together

Values can range between 0 to 21 for weekly itch severity, and 0 to 21 for weekly hive count

The UAS7 ranges from 0 to 42