BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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DUPIXENT® (dupilumab) subcutaneous injection

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Dupixent (dupilumab) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Allergist, Immunologist, Pulmonologist, Otolaryngologist, or Dermatologist depending upon indication or use

2. A confirmed diagnosis of **ONE** of the following
    a. Individual is 12 years of age or older with moderate-to-severe asthma with an eosinophilic phenotype or oral corticosteroid dependent type, to be used as add-on maintenance treatment

    b. Individual 6 years of age or older with moderate-to-severe atopic dermatitis

    c. Individual 18 years of age or older with inadequately controlled bilateral chronic rhinosinusitis with nasal polyposis, to be used as add-on maintenance treatment

3. **ONE** of the following:
    a. For moderate to severe asthma
        i. Pretreatment forced expiratory volume in 1-second (FEV1) is less than or equal to 80% predicted and FEV1 reversibility is at least 12% and 200 mL after albuterol administration
        ii. There is a history of **2** or more asthma exacerbations in the past 12-months that required treatment with systemic corticosteroid bursts; an emergency department or urgent care visit; or hospitalization for the treatment of asthma
        iii. **ONE** of the following:
            1. For eosinophilic type:
                a. Blood eosinophils are greater than or equal to 150 cells/microliter within the last 6-weeks or has a history of blood eosinophils greater than or equal to 300 cells/microliter
            2. For corticosteroid type:
                a. Individual has oral corticosteroid dependent asthma requiring a minimum daily dose of prednisone 5 mg (or an equivalent dose of another corticosteroid)

    b. For moderate to severe atopic dermatitis
        i. Lesions involve at least 10% of body surface area or involve sensitive areas of the face, head, neck, hands, feet, groin, or intertriginous areas
        ii. Not adequately controlled with topical prescription therapies or when those therapies are not advisable

    c. For Bilateral chronic rhinosinusitis
        i. Evidence of nasal polyposis by direct examination, endoscopy, or sinus CT scan
        ii. Individual has anterior or posterior rhinorrhea, mucopurulent discharge, nasal obstruction and congestion, diminished sense of smell, and or facial pain or pressure that has lasted for 12 weeks or more

4. Individual has failure, intolerance, contraindication to **ONE** the following:

a. **For moderate-to-severe asthma, with uncontrolled symptoms:**
   i. At least a 3-month trial of maximally-dosed inhaled corticosteroids **AND** long-acting inhaled beta-agonists **AND** another asthma controlling medication (such as leukotriene receptor antagonist, long acting muscarinic antagonist, or theophylline) with or without daily oral corticosteroid

b. **For moderate-to-severe atopic dermatitis**:
   i. At least a 2-month trial of **each** of the following topical treatments: medium to very high potency corticosteroid **AND** a calcineurin inhibitor (Protopic (tacrolimus) or Elidel (pimecrolimus)) **AND** a phosphodiesterase 4 inhibitor (Eucrisa (crisaborole)

c. **For chronic rhinosinusitis with nasal polyposis:**
   i. At least a 2-month trial of maximally tolerated intra-nasal corticosteroid **AND** nasal saline irrigation with or without systemic corticosteroid **AND** with or without a leukotriene modifier (Singulair (montelukast), Accolate (zafirlukast), Zyflo (zileuton) or Zyflo CR (zileuton))

5. There is no concurrent use with Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab), Xolair (omalizumab), or any other biologic therapy [e.g., Rituxan (rituximab), Remicade/Inflectra (infliximab), Enbrel (etanercept)]

6. Dupixent is not being used concurrently with live vaccines

Initial approval duration: 4 months

- **Criteria for continuation of coverage (renewal request):** Dupixent (dupilumab) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Allergist, Immunologist, Pulmonologist, Otolaryngologist, or Dermatologist depending upon indication or use

2. Individual's condition responded or has worsened while on therapy [this can be modified or changed depending on drug or condition]
   a. Response is defined as:
      i. **For asthma**, achieved and maintains **TWO** of the following:
         1. Decreased incidence of asthma exacerbation
         2. Decreased need for use of rescue medications
         3. Decrease need for systemic corticosteroids
         4. Decrease in hospitalizations/emergency room visits
         5. Improvement in FEV1 from baseline
         6. Reduced severity or frequency of asthma related symptoms

      ii. **For atopic dermatitis**, achieved and maintains **BOTH** of the following:
         1. 20% reduction in percent BSA involved over baseline
         2. Reduction in severity of pruritus, cracking, and if initially present, oozing/bleeding of affected skin

iii. **For chronic rhinosinusitis with nasal polyposis**, achieved and maintains **THREE** of the following:
   1. Reduction in sinus opacification
   2. Reduction in nasal congestion
   3. Reduction in rhinorrhea
   4. Reduction in facial pain or pressure
   5. Improved sense of smell
   6. Reduced need for systemic corticosteroid

iv. No evidence of disease progression

3. Individual has been adherent with the medication and other medications for the condition being treated (moderate to severe atopic dermatitis, moderate to severe asthma, or chronic rhinosinusitis)

4. Dupixent is not being used concurrently with live vaccines

5. There is no concurrent use with Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab), Xolair (omalizumab), or any other biologic therapy for atopic dermatitis [e.g., Rituxan (rituximab), Remicade/Inflectra (infliximab), Enbrel (etanercept)]

6. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
   a. Significant adverse effect such as:
      i. Hypersensitivity reaction to Dupixent or other ingredients of the product
      ii. Severe/serious systemic eosinophilia, eosinophilic pneumonia, or eosinophilic granulomatosis with polyangiitis

Renewal duration: 12 months

- Dupixent (dupilumab) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any one or more of the following criteria are met:
  1. Lack of final approval from the Food and Drug Administration;
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes;
  3. Insufficient evidence to support improvement of the net health outcome;
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; **or**
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, but are not limited to:
  - Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration.

Description:

Dupixent (dupilumab) is a monoclonal antibody used for the treatment of adults with moderate-to-severe atopic dermatitis not adequately controlled with topical prescription therapies or when those therapies are not advisable.

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It can be used with or without topical corticosteroids. Dupixent (dupilumab) is also indicated for add-on maintenance treatment of moderate-to-severe asthma with an eosinophilic phenotype or with corticosteroid dependent asthma in patients 12 years of age and older. Dupixent is not indicated for the relief of acute bronchospasm or status asthmaticus. Dupixent (dupilumab) is also indicated as add-on maintenance treatment in adults with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

Treatment of atopic dermatitis initially involves use of topical prescription therapies such as corticosteroids, calcineurin inhibitors (tacrolimus ointment, pimecrolimus cream) and topical phosphodiesterase 4 (PDE-4) inhibitors (crisaborole ointment). Topical corticosteroids are considered the standard of care; strength and formulation of the preparation is selected based on severity, duration of treatment, location of exacerbation, and age of individual. Topical calcineurin and topical PDE-4 inhibitors should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

Asthma is a complex disorder characterized by variable and recurring clinical symptoms, airflow obstruction, bronchial hyper-responsiveness, and underlying inflammation.

Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) are involved in inflammation.

Asthma can be divided into subtypes, which are associated with airway inflammation with eosinophils. It is estimated that about half of individuals with severe asthma exhibit the eosinophilic phenotype with elevated eosinophil levels (a marker of inflammation) in both the blood and airways. Activated eosinophils can increase airway smooth muscle contraction and mucous secretion. Interleukin-5 (IL-5) is an important cellular signal in eosinophilic inflammation.

About 10% of asthma patients have severe asthma that may be uncontrolled despite high doses of standard-of-care asthma controller medicines and can require the use of chronic oral corticosteroids (OCS). Severe, uncontrolled asthma is debilitating and potentially fatal with patients experiencing frequent exacerbations and significant limitations on lung function and quality of life.

Inhaled corticosteroids are the most effective long-term therapy for control and management of asthma. Asthma is said to be well controlled when asthma symptoms are twice a week or less; rescue bronchodilator medication use is twice a week or less; there is no nocturnal or early morning awaking due to asthma symptoms; there are no limitations of work, school, or exercise; and the Forced Expiratory Volume (FEV1) is normal or the patient's personal best. On the other hand, indicators of asthma that is not adequately controlled include limitation of normal activities, poor lung function with FEV1 of < 80% predicted, at least 2 episodes per year of asthma exacerbations requiring oral systemic corticosteroids. More frequent and intense exacerbations requiring urgent, unscheduled care, hospitalization, or ICU admission point toward worse disease control.

Chronic rhinosinusitis (CRS) is an inflammatory condition of the nose and paranasal sinuses characterized by the presence of two or more of the following symptoms for greater than 12-weeks duration: 1) nasal blockage/obstruction/congestion; 2) nasal discharge that is mucopurulent; 3) facial pain/pressure; 4) reduction or loss of smell. Confirmation of the diagnosis is made by sinus CT scan or nasal endoscopy to determine if there is nasal polyposis in both nasal passages. In general, individuals with nasal polyposis (CRSwNP) have more extensive disease than CRS without nasal polyposis (CRSsNP). The underlying mechanisms that contribute to

the chronic sinonasal inflammation observed in CRSwNP are not completely defined. Individuals with CRSwNP may also have concurrent diagnoses of asthma, chronic rhinitis, and allergic rhinitis.

Topical corticosteroids and nasal saline irrigations are recommended as initial therapy. Intranasal corticosteroids decrease nasal polyp size, lessen nasal symptoms, and improve patient quality of life. Oral corticosteroids can also reduce polyp size and improve symptoms but are associated with serious systemic side effects. Patients with significant sinonasal disease and/or those who fail medical management should be evaluated for sinus surgery. However, nasal polyps can reoccur despite sinus surgery.

Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the interleukin-4 receptor alpha (IL-4Rα) subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor.

Inflammation is an important component in the pathogenesis of asthma, atopic dermatitis and chronic rhinosinusitis with nasal polyposis. Multiple cell types that express IL-4Rα (mast cells, eosinophils, macrophages, lymphocytes, epithelial cells, goblet cells) and inflammatory mediators (histamine, eicosanoids, leukotrienes, cytokines, chemokines) are involved in inflammation. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of pro-inflammatory cytokines, chemokines, nitric oxide, and IgE; however, the mechanism of dupilumab action in asthma has not been definitively established.

Definitions:

Adult: Age 18 years and older

Atopic Dermatitis Therapies:

Topical corticosteroids (TCS):
- Low-potency corticosteroids are recommended for maintenance therapy
- Intermediate and high-potency corticosteroids should be used for the treatment of clinical exacerbation over short periods of time
- Ultra-high-potency corticosteroids should be used only for very short periods (1-2 weeks) and in non-facial non-skinfold areas.
- Do not use potent fluorinated corticosteroids on the face, eyelids, genitalia, and intertriginous areas or in young infants.

Topical calcineurin inhibitors (TCI):
- Tacrolimus ointment (Protopic and generics) is indicated as second-line therapy for moderate to severe atopic dermatitis
- Elidel (pimecrolimus) cream is indicated as second line therapy for mild to moderate atopic dermatitis

Topical phosphodiesterase 4 (PDE-4) inhibitor:
- Eucrisa (crisaborole) ointment is indicated for treatment of mild to moderate atopic dermatitis

Relative Potency of Selected Topical Corticosteroid Products:

Product	Dosage form	Strength
Category I – Very high potency		

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Augmented betamethasone dipropionate	Gel, ointment	0.05
Clobetasol propionate	Ointment, gel, cream	0.05
Fluocinonide	Cream	0.1
Diflorasone diacetate	Ointment	0.05
Halobetasol propionate	Ointment, cream	0.05
Category II – High potency		
Amcinonide	Ointment, cream, lotion	0.1
Augmented betamethasone dipropionate	Cream, lotion	0.05
Betamethasone dipropionate	Ointment, cream	0.05
Betamethasone valerate	Ointment	0.1
Desoximetasone	Ointment, cream	0.25
Desoximetasone	Gel	0.05
Diflorasone diacetate	Ointment (emollient base), cream	0.05
Fluocinonide	Ointment, gel, cream	0.05
Halcinonide	Ointment, cream	0.1

Asthma Control Classification:

	Classification of Asthma Control (12 years of age and older)		
	Well Controlled	Not Well Controlled	Very Poorly Controlled
Symptoms	≤ 2 days/week	≥ 2 days/week	Throughout the day
Nighttime awakenings	≤ 2 days/month	1-3x/week	≥ 4x/week
Interference with normal activities	None	Some limitation	Extremely limited
SABA use to control symptoms (not for EIB prevention	≤ 2 days/week	> 2 days/week	Several times/day
FEV1 or peak flow	> 80% predicted or personal best	60-80% predicted or personal best	< 60% predicted or personal best
Asthma Control Test	≥ 20	16-19	≤ 15

Asthma control test: a validated set of questions
The Asthma Control Test provides a numerical score to help determine if your asthma symptoms are well controlled.
Step 1: Circle the number of each answer in the score box provided [ ].
Step 2: Add up each score in each box [ ] for the total.
Step 3: Take the completed test to your healthcare provider to talk about your score.

Asthma Control Test				
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?				
All of the time [1]	Most of the time [2]	Some of the time [3]	A little of the time [4]	None of the time [5]
2. During the past 4 weeks, how often have you had shortness of breath?				
More than once a day [1]	Once a day [2]	3 to 6 times a week [3]	Once or twice a week [4]	Not at all [5]
3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?				
4 or more nights a week [1]	2 to 3 nights a week [2]	Once a week [3]	Once or twice [4]	Not at all [5]
4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?				

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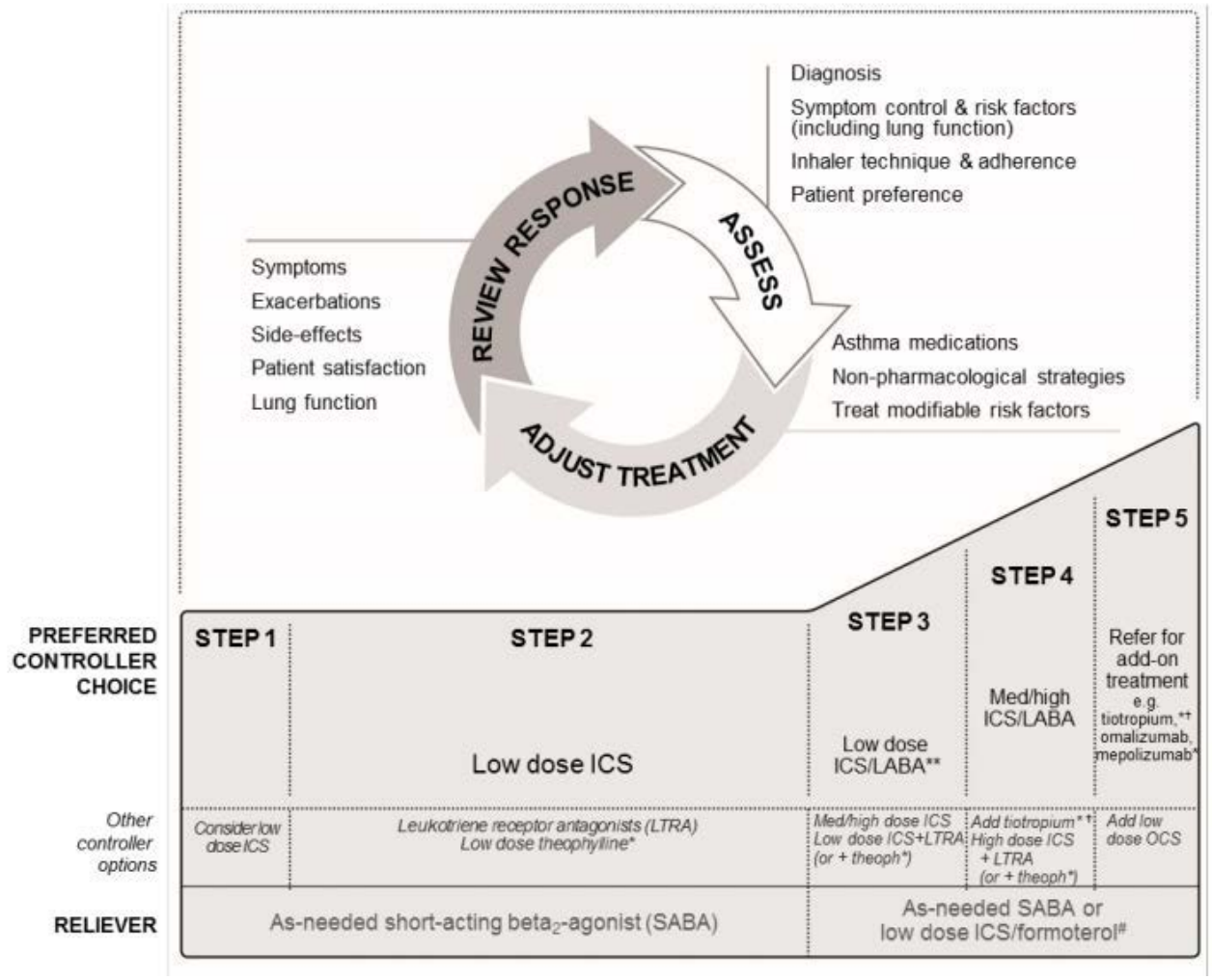
3 or more times per day [1]	1 to 2 times per day [2]	2 or 3 times per week [3]	Once a week or less [4]	Not at all [5]
5. How would you rate your asthma control during the past 4 weeks?				
Not Controlled at all [1]	Poorly controlled [2]	Somewhat controlled [3]	Well controlled [4]	Completely controlled [5]
Total Score: _____				
Interpretation of Total Score: Well controlled: ≥ 20 Not well controlled: 16-19 Very poorly controlled: ≤ 15				

2016 GINA Guidelines on Stepwise Approach to Treatment of Asthma



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Chronic rhinosinusitis with nasal polyposis:

- Inflammation of the nose and paranasal sinuses characterized by the presence of two or more of the following symptoms for greater than 12-weeks duration:
  1) Nasal blockage/obstruction/congestion
  2) Nasal discharge
  3) Facial pain/pressure;
  4) Reduction or loss of smell (hyposmia or anosmia)
- Confirmation of the diagnosis is made by sinus CT scan or nasal endoscopy to determine if there is nasal polyposis in both nasal passages

Types of Chronic Rhinosinusitis:

Features	CRSwNP	CRSsNP	AFRS
Bilateral nasal polyps	Presence required for diagnosis*	Exclusion required for diagnosis	Yes in most cases
Allergic mucin	May be present	May be present	Required for diagnosis
Aspirin associated respiratory disease	Asthma present in 40% Aspirin intolerance & asthma present I 15%	Rare	May be present
IgE-mediated allergy to fungus	May be present	May be present	Required for diagnosis
* Unless medical record documents removal of bilateral nasal polyps during surgery CRSwNP: Chronic rhinosinusitis with nasal polyps CRSsNP Chronic rhinosinusitis without nasal polyps AFRS: Allergic fungal rhinosinusitis			

Resources:

Dupixent (dupilumab) product information, revised by Sanofi-Aventis U.S. LLC. 06-2020, at DailyMed http://dailymed.nlm.nih.gov accessed January 28, 2021.

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