PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Dupixent® (dupilumab subcutaneous injection – Regeneron/sanofi-aventis)

TAC APPROVAL DATE: 01/23/2019; selected revisions 3/13/2019 and 07/10/2019

OVERVIEW
Dupixent is an interleukin-4 receptor alpha (IL-4Rα) antagonist indicated:1
1) For the treatment of patients ≥ 12 years of age with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent is not indicated for the relief of acute bronchospasm or status asthmaticus.
2) As an add-on maintenance treatment in patients ≥ 12 years of age with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma.
3) As an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

Dupixent is a human monoclonal antibody that binds to the IL-4Rα subunit shared by the interleukin (IL)-4 and IL-13 receptor complexes, thereby inhibiting IL-4 and IL-13 signaling.1 This inhibition limits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and immunoglobulin (Ig)E involved in type 2 inflammation.

Clinical Efficacy

Asthma
The efficacy of Dupixent for the treatment of asthma was established in three randomized, double-blind, placebo-controlled, multicenter, pivotal studies in patients with persistent asthma.2-4 Two of these studies included patients ≥ 12 years of age who had moderate to severe asthma that was uncontrolled despite treatment with a medium- to high-dose inhaled corticosteroid (ICS) and up to two additional controller medications.2,4 In these studies, Dupixent significantly reduced the annual exacerbation rate compared with placebo. Higher baseline eosinophil levels were correlated with larger asthma exacerbation reductions and greater increases in lung function parameters than were observed in patients with lower baseline blood eosinophil levels (i.e., < 150 cells/microliter). The third Dupixent pivotal trial included patients with severe asthma who were oral corticosteroid dependent.3 Patients who received Dupixent were able to significantly reduce their oral corticosteroid doses compared with placebo. Dupixent was associated with a greater oral corticosteroid dose reduction regardless of baseline blood eosinophil count. Dupixent also reduced the rate of severe asthma exacerbations as well.

Atopic Dermatitis (AD)
The three pivotal Dupixent studies enrolled adult patients with moderate to severe chronic AD.1,5,6 Patients’ AD affected ≥ 10% of their body surface area (BSA) and had a recent history of an inadequate response to a sufficient course of topical therapy (e.g., corticosteroids and/or calcineurin inhibitors). The primary efficacy endpoint was a score of 0 (clear) or 1 (almost clear) on the Investigator’s Global Assessment (IGA) and a reduction of ≥ 2 points from baseline to Week 16. Dupixent was found to be more effective in achieving the primary endpoint at Week 16 compared with placebo. The third study also found Dupixent to be more effective in achieving the primary endpoint at Week 52 compared with
placebo. A fourth study evaluated the efficacy of Dupixent in patients 12 to 17 years of age with moderate to severe AD affecting $\geq 10\%$ of their BSA. $^1$ Dupixent was again found to be more effective in achieving an IGA score of 0 or 1 compared with placebo at Week 16 (primary endpoint).

**Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)**

Two randomized, double-blind, multicenter, placebo-controlled studies evaluated the efficacy of Dupixent in adult patients with CRSwNP.$^{1,17,18}$ Patients enrolled in these studies were also treated with intranasal corticosteroids and had failed treatment with sino-nasal surgery or systemic corticosteroids (or were ineligible or intolerant to). The co-primary efficacy endpoints were the change from baseline to Week 24 in bilateral endoscopic nasal polyp score (NPS) and the change from baseline in the nasal congestion/obstruction score (averaged over 28 days). Across both studies, Dupixent statistically significantly improved both primary endpoints when compared with placebo at Week 24. The reductions in the nasal polyp size (measure by the NPS) were sustained over a longer period of time (48 weeks in one study; 52 weeks in the other study). However, the treatment effect diminished over time. Dupixent was also found to positively impact several secondary outcomes, such as nasal congestion, loss of smell, and sino-nasal symptoms as well as reduce the need for systemic corticosteroid therapy and sino-nasal surgery.

**Guidelines**

**Asthma Guidelines**

The 2019 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention proposes a step-wise approach to asthma treatment.$^7$ Patients with persistent symptoms or exacerbations despite a medium-dose ICS/long-acting beta$_2$-agonist (LABA) combination with or without an additional controller, GINA recommends referral of the patient to a specialist with expertise in the management of severe asthma for phenotypic assessment and add-on treatment. Dupixent is listed as an option for add-on therapy in patients $\geq 12$ years of age with severe Type 2 asthma or oral corticosteroid-dependent asthma. Evidence of Type 2 inflammation can include elevated sputum or blood eosinophils, elevated fractional concentration of exhaled nitric oxide (FeNO), the need for maintenance oral corticosteroid therapy, or clinically allergen-driven asthma.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.$^8$ Uncontrolled asthma is defined as asthma that meets one of the following four criteria: poor symptom control, frequent severe exacerbations, serious exacerbations, or airflow limitation. Additionally, patients may also have severe asthma if their asthma worsens upon tapering of corticosteroids.

**Atopic Dermatitis (AD) Guidelines**

The American Academy Dermatology (AAD) guidelines of care for the management of AD (2014) and the Joint Task Force AD practice parameter (from the American Academy of Allergy, Asthma, and Immunology [AAAAI], the American College of Allergy, Asthma, and Immunology [ACAAI], and the Joint Council of Allergy, Asthma, and Immunology [JCAAI]) [2012] make similar recommendations for AD therapy.$^9$ Dupixent is not addressed. It is noted that the majority of patients with AD can achieve disease control with non-pharmacologic interventions (e.g., emollients), standard topical anti-inflammatory therapies (e.g., topical corticosteroids, topical calcineurin inhibitors), and elimination of exacerbating factors (e.g., allergens, irritants, and emotional stress). A patient who does not respond to first-line therapy should be referred to a provider who specializes in the treatment of AD. If topical
Regimens and/or phototherapy continue to inadequately control the signs and symptoms of AD, systemic immunomodulatory therapies are indicated, particularly if the patient’s disease has significant negative physical, psychological, or social effects.

European consensus guidelines for the treatment of AD (2018) from multiple European dermatology associations, including the European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), and the European Academy of Allergy and Clinical Immunology (EAACI), recommend Dupixent as a disease-modifying drug for patients with moderate to severe AD, in whom topical treatment does not produce a sufficient response and other systemic treatment is not advisable. These guidelines note that daily emollients should be used with Dupixent and it may be combined with other topical anti-inflammatory medications as needed.

**Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) Guidelines**

Dupixent is not addressed in current guidelines. A 2014 Joint Practice Parameter on the Diagnosis and Management of Rhinosinusitis and a 2008 (evidence update in 2017) Joint Practice Parameter for the Management of Rhinitis recommend nasal corticosteroids be used in patients with CRSwNP. Data demonstrate that nasal corticosteroids decrease nasal polyp size and prevent regrowth of nasal polyps following removal. Additionally, these agents improve nasal patency, reduce nasal symptoms, and improve quality of life. Short courses of oral corticosteroids are also recommended in CRSwNP, because they can decrease polyp size and alleviate symptoms. Endoscopic surgical intervention may be considered as an adjunct to medical therapy in patients with CRS that is not responsive or is poorly responsive to medical therapy. A 2015 Clinical Practice Guideline update on Adult Sinusitis from the American Academy of Otolaryngology makes similar recommendations, stating that clinicians should recommend saline nasal irrigation, topical intranasal corticosteroids, or both for symptom relief in patients with CRS (with or without nasal polyps).

**POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of Dupixent. Because of the specialized skills required for evaluation and diagnosis of patients treated with Dupixent as well as the monitoring required for adverse events and long-term efficacy, approval requires Dupixent to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

**Automation:** None.

**RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Dupixent is recommended in those who meet the following criteria:

**FDA-Approved Indications**

1. **Asthma.** Approve Dupixent for the duration noted if the patient meets one of the following conditions (A or B):
   A) **Initial Therapy.** Approve Dupixent for 6 months if the patient meets the following criteria (i, ii, iii, iv and v):
   i. Patient is ≥ 12 years of age; AND
   ii. Dupixent is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND
iii. Patient meets ONE of the following criteria (a or b):
   a) Patient has a blood eosinophil level of ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any anti-interleukin therapy or Xolair; OR
      Note: Examples of anti-interleukin therapies include Dupixent, Nucala, Cinqair, and Fasenra.
   b) Patient has oral (systemic) corticosteroid-dependent asthma per the prescriber (e.g., the patient has received ≥ 5 mg oral prednisone or equivalent per day for ≥ 6 months); AND

iv. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
   a) An inhaled corticosteroid; AND
   b) At least one additional asthma controller/maintenance medication; AND
      Note: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-interleukin-5 therapy (e.g., Cinqair, Fasenra, Nucala) or Xolair used concomitantly with an inhaled corticosteroid for at least 3 consecutive months. Use of a combination inhaler containing both an inhaled corticosteroid and a long-acting beta₂-agonist would fulfill the requirement for both criteria a and b. Examples of inhaled corticosteroids include Aerospan, Alvesco, ArmonAir RespiClick, Arnuppy Ellipta, Asmanex Twisthaler/HFA, Flovent Diskus/HFA, Pulmicort Flexhaler, Qvar/Qvar RediHaler, and budesonide suspension for inhalation (Pulmicort Respules, generics). Examples of additional asthma controller/maintenance medications include long-acting beta₂-agonists (e.g., Serevent Diskus); inhaled long-acting muscarinic antagonists (e.g., Spiriva Respimat); leukotriene receptor antagonists (e.g., montelukast tablets/granules [Singulair, generics], zafirlukast tablets [Accolate, generics]); theophylline (e.g., Theo 24, TheoChron ER, generics). Examples of a combination inhaled corticosteroid/long-acting beta₂-agonist inhaler include Advair Diskus/HFA, AirDuo RespiClick, Breo Ellipta, Dulera, Symbicort.

v. Patient’s asthma is uncontrolled or was uncontrolled prior to starting any anti-interleukin therapy or Xolair as defined by ONE of the following (a, b, c, d or e):
   a) The patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
   b) The patient experienced one or more asthma exacerbation requiring hospitalization or an Emergency Department (ED) visit in the previous year; OR
   c) Patient has a forced expiratory volume in 1 second (FEV₁) < 80% predicted; OR
   d) Patient has an FEV₁/forced vital capacity (FVC) < 0.80; OR
   e) The patient’s asthma worsens upon tapering of oral corticosteroid therapy.
      Note: Examples of anti-interleukin therapies include Dupixent, Nucala, Cinqair, and Fasenra.

B) Patients Continuing Dupixent Therapy. Approve Dupixent for 1 year if the patient meets the following criteria (i, ii, and iii):
   i. The patient has already received at least 6 months of therapy with Dupixent; AND
      Note: Patients who have received < 6 months of therapy or those who are restarting therapy with Dupixent should be considered under criterion 1A (Asthma, Initial Therapy).
   ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND
      Note: Examples of an inhaled corticosteroid or an inhaled corticosteroid-containing combination inhaler include Flovent Diskus/HFA, ArmonAir RespiClick, Arnuppy Ellipta, Asmanex Twisthaler/HFA, Aerospan, Alvesco, Pulmicort Flexhaler, budesonide suspension
for inhalation (Pulmicort Respules, generics), Qvar/Qvar RediHaler, Advair Diskus/HFA, AirDuo RespClick, Symbicort, Breo Ellipta, and Dulera.

iii. The patient has responded to Dupixent therapy as determined by the prescriber.
Note: Examples of a response to Dupixent therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department (ED)/urgent care, or medical clinic visits due to asthma; decreased requirement for oral corticosteroid therapy.

2. Atopic Dermatitis. Approve Dupixent for the duration noted if the patient meets one of the following conditions (A or B):
   A) Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, and iii):
   i. Patient is ≥ 12 years of age; AND
   ii. Dupixent is prescribed by or in consultation with an allergist, immunologist, or dermatologist; AND
   iii. Patient meets ONE of the following (a or b):
      a) Patient has atopic dermatitis involvement estimated to be ≥ 10% of the body surface area (BSA) according to the prescriber and meets ALL of the following criteria ([1], [2], and [3]):
         (1) Patient has tried at least one medium-, medium-high, high-, and/or super-high-potency prescription topical corticosteroid; AND
         (2) This topical corticosteroid was applied daily for at least 28 consecutive days; AND
         (3) Inadequate efficacy was demonstrated with this topical corticosteroid therapy, according to the prescriber; OR
      b) Patient has atopic dermatitis involvement estimated to be < 10% of the BSA according to the prescriber and meets ALL of the following criteria ([1], [2], [3], and [4]):
         (1) Patient has atopic dermatitis affecting ONLY the following areas: face, eyes/eyelids, skin folds, and/or genitalia; AND
         (2) Patient has tried tacrolimus ointment (Protopic®, generics); AND
         (3) Tacrolimus ointment (Protopic, generics) was applied daily for at least 28 consecutive days; AND
         (4) Inadequate efficacy was demonstrated with tacrolimus ointment (Protopic, generics), according to the prescriber.
   B) Patients Continuing Dupixent Therapy. Approve for 1 year if the patient meets the following criteria (i and ii):
   i. The patient has already received at least 4 months of therapy with Dupixent; AND
   Note: Patients who have received < 4 months of therapy or those who are restarting therapy with Dupixent should be considered under criterion 2A (Atopic Dermatitis, Initial Therapy).
   ii. The patient has responded to Dupixent therapy as determined by the prescriber.
   Note: Examples of a response to Dupixent therapy are marked improvements in erythema, induration/papulation/edema, excoriations, and lichenification; reduced pruritus; decreased requirement for other topical or systemic therapies; reduced body surface area (BSA) affected with atopic dermatitis; or other responses observed.

3. Chronic Rhinosinusitis with Nasal Polyps. Approve Dupixent for the duration noted if the patient meets one of the following conditions (A or B):
   A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv and v):
   i. Patient is ≥ 18 years of age; AND
ii. Dupixent is prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT] physician specialist); AND

iii. Patient is currently receiving therapy with an intranasal corticosteroid; AND

iv. Patient is experiencing significant rhinosinusitis symptoms such as nasal obstruction, rhinorrhea, or reduction/loss of smell according to the prescriber; AND

v. Patient meets ONE of the following (a or b):
   a) Patient has received treatment with a systemic corticosteroid within the previous 2 years or has a contraindication to systemic corticosteroid therapy; OR
   b) Patient has had prior surgery for nasal polyps.

B) Patients Continuing Dupixent Therapy. Approve for 1 year if the patient meets the following criteria (i, ii and iii):

i. The patient has already received at least 6 months of therapy with Dupixent; AND
   Note: Patients who have received < 6 months of therapy or those who are restarting therapy with Dupixent should be considered under criterion 3A [Chronic Rhinosinusitis with Nasal Polyposis, Initial Therapy]).

ii. Patient continues to receive therapy with an intranasal corticosteroid; AND

iii. The patient has responded to Dupixent therapy as determined by the prescriber.
   Note: Examples of a response to Dupixent therapy are reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sino-nasal symptoms, improved sense of smell.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Dupixent has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. Concurrent use of Dupixent with another Anti-Interleukin (IL) Monoclonal Antibody. The efficacy and safety of Dupixent in combination with any other anti-IL monoclonal antibody (e.g., Cinqair, Nucala, Fasenra) have not been established.

2. Concurrent use of Dupixent with Xolair® (omalizumab injection for subcutaneous use). Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody indicated for use in patients ≥ 6 years of age with moderate to severe persistent asthma and who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs.14 The efficacy and safety of Dupixent used in combination with Xolair have not been established.

3. Eosinophilic Esophagitis. A Phase II study has been conducted evaluating Dupixent for the treatment of eosinophilic esophagitis.13 Results are not yet available. There is an additional Phase III study that is currently underway in patients with eosinophilic esophagitis. Results are anticipated in 2022. The efficacy and safety of Dupixent for the treatment of eosinophilic esophagitis have not been established.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.
REFERENCES

20. Joint Task Force on Practice Parameters: American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: An updated practice parameter. J Allergy Clin Immunol. 2008;122(2):S1-S84.

OTHER REFERENCES USED
<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes’</th>
<th>TAC Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Policy</td>
<td>Removed requirement that patient have chronic atopic dermatitis for a minimum of 3 years. Changed topical corticosteroid requirement from 60 days to 28 days. Added exception for patients with atopic dermatitis involvement of &lt; 10% of their body surface area (only on the face, eyes/eyelids, skin folds, and/or genitalia) to allow for approval if they have tried tacrolimus ointment daily for at least 28 consecutive days with an inadequate response according to the prescribing physician. Removed requirement for previous systemic therapy. In “Continuation Therapy” removed requirement for continued adjunctive therapy.</td>
<td>03/29/2017</td>
</tr>
<tr>
<td>Selected Revision</td>
<td>Updated the criteria for “Patients Continuing on Dupixent Therapy” to include only patients who have received ≥ 16 weeks of Dupixent. Patients who have received &lt; 16 weeks of Dupixent would be referred to Initial Therapy criteria. Also, removed the age requirement and specialist involvement from Continuation Criteria.</td>
<td>04/11/2018</td>
</tr>
<tr>
<td>Selected Revision</td>
<td>Removed Asthma from “Conditions Not Recommended for Approval”.</td>
<td>07/25/2018</td>
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<tr>
<td>Selected Revision</td>
<td>Added approval criteria for “Asthma in Patients with Moderate to Severe Disease” which includes an age requirement, involvement of a specialist, minimum eosinophil count or oral corticosteroid-dependent asthma, prior inhaler therapy, and criteria to determine asthma is currently uncontrolled.</td>
<td>10/31/2018</td>
</tr>
<tr>
<td>Early Annual Revision</td>
<td>Updated initial therapy criteria for “Asthma in Patients with Moderate to Severe Disease” to state that the blood eosinophil level requirement of ≥ 150 cells per microliter should be from a level prior to treatment with Xolair, as well as prior to treatment with any anti-interleukin (IL) agent. Previously criteria only noted the level should be prior to any anti-IL therapy.</td>
<td>01/23/2019</td>
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<tr>
<td>Early Annual Revision</td>
<td>Updated initial therapy criteria for “Asthma in Patients with Moderate to Severe Disease” to more concisely state the previous therapies required. Added the following note: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-IL-5 therapy (e.g., Cinqair, Fasenra, Nucala) or Xolair used concomitantly with an ICS for at least 3 consecutive months.</td>
<td>01/23/2019</td>
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<tr>
<td>Early Annual Revision</td>
<td>Updated initial therapy criteria for “Asthma in Patients with Moderate to Severe Disease” to state that the patient’s asthma is uncontrolled or was uncontrolled prior to starting any anti-IL therapy (e.g., Cinqair, Fasenra, Nucala, Dupixent) or Xolair. Previously criteria only stated it should be uncontrolled prior to anti-IL therapy.</td>
<td>01/23/2019</td>
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<tr>
<td>Selected Revision</td>
<td>Changed the age requirement for “Atopic Dermatitis, Moderate to Severe” from ≥ 18 years of age to ≥ 12 years of age.</td>
<td>03/12/2019</td>
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<tr>
<td>Selected Revision</td>
<td>Asthma: Approval indication was changed from “Asthma in Patients with Moderate to Severe Disease” to “Asthma”. Wording in reference to “according to the prescribing physician” was changed to “according to the prescriber”.</td>
<td>07/10/2019</td>
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<tr>
<td>Selected Revision</td>
<td>Atopic Dermatitis: Approval indication was changed from “Atopic Dermatitis, Moderate to Severe” to “Atopic Dermatitis”. Duration of initial approval was clarified to 4 months (previously 16 weeks). Wording in reference to “according to the prescribing physician” was changed to “according to the prescriber”.</td>
<td>07/10/2019</td>
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<tr>
<td>Selected Revision</td>
<td>Chronic Rhinosinusitis with Nasal Polyposis: Added new approval criteria for this indication which include an age requirement, involvement of a specialist, current intranasal corticosteroid therapy, the presence of significant rhinosinusitis symptoms, and previous systemic therapy (or contraindication) or surgery for nasal polyps.</td>
<td>07/10/2019</td>
</tr>
<tr>
<td>Selected Revision</td>
<td>Conditions Not Recommended for Approval: Removed “Nasal Polyps”.</td>
<td>07/10/2019</td>
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TAC – Therapeutic Assessment Committee; IL – Interleukin; * For a further summary of criteria changes, refer to respective TAC minutes available at: [http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx](http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx)