dupilumab (Dupixent®)

Policy # 00567
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Atopic Dermatitis

Based on review of available data, the Company may consider dupilumab (Dupixent®)‡ for the treatment of atopic dermatitis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for dupilumab (Dupixent) for the treatment of atopic dermatitis will be considered when ALL of the following criteria are met:

Initial

I. Patient has a diagnosis of moderate to severe atopic dermatitis; AND
II. Patient is 6 years of age or older; AND
III. Patient has had chronic atopic dermatitis for at least 3 years; AND
*(Note: This criterion is an additional Company requirement, based on clinical trials, for coverage eligibility and will be denied as not medically necessary** if not met.)*
IV. Patient has atopic dermatitis involvement estimated to be ≥ 10% of the body surface area (BSA) according to the prescribing physician; AND
*(Note: This criterion is an additional Company requirement, based on clinical trials, for coverage eligibility and will be denied as not medically necessary** if not met.)*
V. Patient has tried and failed (e.g., intolerance or inadequate response) at least ONE prescription generic topical corticosteroid, unless there is clinical evidence or patient history that suggests the use of ONE prescription generic topical corticosteroid will be ineffective or cause an adverse reaction to the patient; AND

VI. Patient has tried and failed (e.g., intolerance or inadequate response) generic tacrolimus ointment, unless there is clinical evidence or patient history that suggests the use of generic tacrolimus ointment will be ineffective or cause an adverse reaction to the patient; AND

VII. Patient has tried and failed (e.g., intolerance or inadequate response) one of the following generic systemic agents for the treatment of atopic dermatitis: oral cyclosporine, oral azathioprine, oral methotrexate, or oral mycophenolate mofetil, unless there is clinical evidence or patient history that suggests the use of the generic systemic agents listed above will be ineffective or cause an adverse reaction to the patient.
*(Note: This criterion is an additional Company requirement, based on national guidelines, for coverage eligibility and will be denied as not medically necessary** if not met.)*

Continuation

I. Patient has received an initial authorization; AND

II. Patient has had an improvement in atopic dermatitis symptoms per the prescribing physician.
*(Note: This criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

Asthma

Based on review of available data, the Company may consider dupilumab (Dupixent) for the treatment of moderate to severe asthma to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for dupilumab (Dupixent) for the treatment of moderate to severe asthma will be considered when the patient selection criteria are met:

Initial

I. Patient has a diagnosis of moderate to severe asthma; AND

II. Patient is 12 years of age or older; AND

III. Patient meets one of the following (a or b):
   a) Patient has a blood eosinophil level of greater than or equal to 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any interleukin therapy (e.g., mepolizumab [Nucala®]‡, reslizumab [Cinqair®]‡, benralizumab [Fasenra®]‡); OR
   b) Patient has oral (systemic) corticosteroid dependent asthma per the prescriber; AND

IV. The requested drug is NOT used in combination with other monoclonal antibodies typically used to treat asthma (e.g., mepolizumab [Nucala], reslizumab [Cinqair], benralizumab [Fasenra], omalizumab [Xolair®]‡); AND

V. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
*(Note that the 3 month timeframe is an additional company requirement and will be denied as not medically necessary** if not met.)*
   a) Inhaled corticosteroid (ICS), (e.g., fluticasone products [Flovent® HFA, Flovent Diskus®, Arnuity™ Ellipta®, Armonair™ Respiclick®]‡, mometasone products [Asmanex® Twisthaler®, Asmanex HFA]‡, flunisolide products (Aersopan™)‡, ciclesonide products (Alvesco®)‡, budesonide products [Pulmicort Flexhaler®]‡, beclomethasone products [QVAR®]‡); AND
   b) At least ONE of the following (1, 2, 3, OR 4):
      1) Inhaled long-acting beta-agonist (LABA), (e.g., salmeterol products [Serevent® Diskus]‡, olodaterol products [Striverdi® Respimat®]‡, indacaterol products [Arcapta™ Neohaler™]‡); OR
      Note: Use of a combination inhaler containing both an ICS and a LABA would fulfill the requirement for both criteria a.) and b.) (e.g., fluticasone propionate and salmeterol inhalation powder/aerosol [Advair® Diskus/HFA, fluticasone/salmeterol generics, Wixela™ Inhub, AirDuo™ Respiclick]‡, budesonide and formoterol fumarate inhalation aerosol [Symbicort®]‡, fluticasone furoate and vilanterol inhalation powder [Breo® Ellipta®]‡, mometasone furoate and formoterol fumarate inhalation aerosol [Dulera®]‡).
      2) Inhaled long-acting muscarinic antagonist (LAMA), (e.g., tiotropium bromide inhalation spray [Spiriva® Respimat®, Spiriva Handihaler®, Stiolto® Respimat]‡, aclidinium products [Tudorza® Pressair®]‡, glycopyrrolate products [Seebri™ Neohaler, Bevespi™ Aerosphere, Utibron™ Neohaler]‡, umeclidinium products [Incruse® Ellipta, Anoro® Ellipta] ‡); OR
      3) Leukotriene receptor antagonist (LTRA), (e.g., montelukast tablets/granules [Singulair®, generics], zafirlukast tablets [Accolate®])‡; OR
      4) Theophylline (Theo-24, Uniphyl, TheoChron ER, generics); AND

VI. Patient's asthma continues to be uncontrolled as defined by ONE of the following (a, b, c, d, or e):

a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
b) Patient experienced one or more asthma exacerbations requiring hospitalization or an Emergency Department (ED) visit in the previous year; OR
c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
e) Patient's asthma worsens upon tapering of oral corticosteroid therapy.

Continuation

I. Patient has received an initial authorization; AND
II. Requested drug is NOT being used in combination with other monoclonal antibodies typically used to treat asthma (e.g., mepolizumab [Nucala], reslizumab [Cinqair], benralizumab [Fasenra], omalizumab [Xolair]); AND
III. Patient continues to receive the medications required in criterion V. in the "Initial Criteria"; AND
IV. Patient has responded to requested therapy as determined by the prescribing physician (e.g., decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, ED/urgent care, or physician visits due to asthma; decreased requirement for oral corticosteroid therapy).
*(Note that this criterion is an additional company requirement and will be denied as not medically necessary** if not met.)*

Chronic Sinusitis with Nasal Polyposis

Based on review of available data, the Company may consider dupilumab (Dupixent) for the treatment of chronic sinusitis with nasal polyposis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for dupilumab (Dupixent) for the treatment of chronic sinusitis with nasal polyposis will be considered when the patient selection criteria are met:

Initial

I. Patient has inadequately controlled chronic rhinosinusitis with nasal polyposis; AND
II. Patient is 18 years of age or older; AND
III. Patient has recurrent polyposis after at least TWO surgical resections (unless resection is contraindicated); AND

*(Note that this criterion is an additional company requirement and will be denied as not medically necessary** if not met.)*

IV. Patient's nasal polyposis has been confirmed as grade 3 or higher with nasal endoscopy; AND
*(Note that this criterion is an additional company requirement and will be denied as not medically necessary** if not met.)*

V. Patient's polyposis recurrence occurred within 6 months of at least one high dose oral steroid taper after the most recent resection unless there is clinical evidence or patient history that suggests the use of a high dose oral steroid taper will be ineffective or cause an adverse effect to the patient; AND
*(Note that this criterion is an additional company requirement and will be denied as not medically necessary** if not met.)*

VI. Patient has tried and failed (e.g., intolerance or inadequate response) BOTH fluticasone 50 mcg (generic OR over the counter) AND GENERIC mometasone after least 30 days with EACH product unless there is clinical evidence or patient history that suggests the use of these nasal sprays will be ineffective or cause an adverse effect to the patient; AND
*(Note that this criterion is an additional company requirement and will be denied as not medically necessary** if not met.)*

VII. Patient has tried and failed (e.g., intolerance or inadequate response) Xhance®‡ (fluticasone 93 mcg) after at least 30 days of therapy unless there is clinical evidence or patient history that suggests the use of Xhance (fluticasone 93 mcg) will be ineffective or cause an adverse effect to the patient; AND
*(Note that this criterion is an additional company requirement and will be denied as not medically necessary** if not met.)*

VIII. Patient has tried and failed (e.g., intolerance or inadequate response) GENERIC montelukast after at least 30 days of therapy unless there is clinical evidence or patient history that suggests the use of GENERIC montelukast will be ineffective or cause an adverse effect to the patient; AND
*(Note that this criterion is an additional company requirement and will be denied as not medically necessary** if not met.)*

IX. Patient will continue to use an intra-nasal corticosteroid (e.g., fluticasone, mometasone, Xhance) in combination with Dupixent (if the intra-nasal corticosteroid was tolerated).

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Continuation

I. Patient has received an initial authorization; AND
II. Patient will continue to use an intra-nasal corticosteroid (e.g., fluticasone, mometasone, Xhance) in combination with Dupixent (if the intra-nasal corticosteroid was tolerated); AND
III. Patient has responded to requested therapy as determined by the prescribing physician (e.g., decrease in nasal polyps, decreased congestion/obstruction, etc).
*(Note that this criterion is an additional company requirement and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of dupilumab (Dupixent) when ANY of the following criteria for the requested diagnosis are NOT met to be **not medically necessary**:**

- Atopic Dermatitis:
  - Patient has had chronic atopic dermatitis for at least 3 years
  - Patient has atopic dermatitis involvement estimated to be ≥ 10% of the BSA according to the prescribing physician
  - Patient has tried and failed one of the following generic systemic agents for the treatment of atopic dermatitis: oral cyclosporine, oral azathioprine, oral methotrexate, or oral mycophenolate mofetil
  - For continuation requests: Patient has had an improvement in atopic dermatitis symptoms per the prescribing physician.
- Moderate to Severe Asthma:
  - Patient has been on the listed pre-requisite asthma medications (criteria V.) for at least 3 months
  - For continuation requests: Patient has responded to requested therapy as determined by the prescribing physician (e.g., decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, ED/urgent care, or physician visits due to asthma; decreased requirement for oral corticosteroid therapy).
- Chronic Rhinosinusitis with Nasal Polyposis:
  - Patient has recurrent polyposis after at least TWO surgical resections (unless resection is contraindicated)

- Patient's nasal polyposis has been confirmed as grade 3 or higher with nasal endoscopy
- Patient's polyposis recurrence occurred within 6 months of at least one high dose oral steroid taper after the most recent resection
- Patient has tried and failed BOTH fluticasone 50 mcg (generic OR over the counter) AND GENERIC mometasone after least 30 days with EACH product
- Patient has tried and failed Xhance (fluticasone 93 mcg) after at least 30 days of therapy
- Patient has tried and failed GENERIC montelukast after at least 30 days of therapy
- For continuation requests: Patient has responded to requested therapy as determined by the prescribing physician (e.g., decrease in nasal polyps, decreased congestion/obstruction, etc.).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of dupilumab (Dupixent) when the patient selection criteria are not met (EXCEPT those denoted as **not medically necessary****) to be **investigational.***

Based on review of available data, the Company considers the use of dupilumab (Dupixent) for any non-FDA approved indication to be **investigational.***

Background/Overview

Dupixent is an interleukin-4 receptor alpha antagonist indicated for the treatment of patients aged 6 years 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. Dupixent is also approved as add-on maintenance treatment in patients with moderate to severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. Most recently, Dupixent gained an indication as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis. For atopic dermatitis, Dupixent can be used with or without topical corticosteroids. The recommended dose of Dupixent for the

treatment of atopic dermatitis in adults as well as adolescents weighing 60 kg or more is 600 mg injected subcutaneously initially (two injections in different sites), then 300 mg given subcutaneously every other week. The recommended dose of Dupixent for the treatment of atopic dermatitis in pediatric patients weighing 30 kg to less than 60 kg is 400 mg (two 200 mg injections) subcutaneously, followed by 200 mg subcutaneously given every other week. The recommended dose of Dupixent for the treatment of atopic dermatitis in pediatric patients weighing 15 kg to less than 30 kg is 600 mg (two 300 mg injections) subcutaneously, followed by 300 mg every 4 weeks. The recommended dose of Dupixent for moderate to severe asthma is either an initial dose of 400 mg (two 200 mg injections) subcutaneously, followed by 200 mg subcutaneously given every other week OR an initial dose of 600 mg subcutaneously (two 300 mg injections) followed by 300 mg subcutaneously given every other week. For asthma patients requiring concomitant oral steroids or with comorbid moderate to severe atopic dermatitis, the latter dose is recommended. The recommended dose of Dupixent for nasal polyposis is 300 mg given every other week. Dupixent is supplied as 200 mg and 300 mg prefilled syringes.

Atopic Dermatitis
There are various treatment options for atopic dermatitis, including first line agents such as topical corticosteroids (many of which are in generic form), and topical immunomodulatory agents, such as generic tacrolimus. For those that are refractory to topical therapies, systemic immunomodulatory agents are indicated (e.g., cyclosporine, azathioprine, and methotrexate) via guidelines from the American Academy of Dermatology. Dupixent has not yet been integrated into the guidelines at the time of this publication. These systemic immunosuppressants have also been studied in the pediatric population. The availability of generic products in this treatment category lends itself to be a more economical option for the treatment of atopic dermatitis versus the branded products available on the market. However, if these products have been tried and failed, then Dupixent is a reasonable approach to therapy based on the current standard of care.

Asthma
Asthma is a respiratory disorder characterized by increased responsiveness of the trachea and bronchi to various stimuli resulting in the narrowing of the airways, along with mucous secretion. Symptoms vary in severity and intensity and include wheezing, cough and dyspnea. Attacks can be triggered by exercise, allergens, irritants and viral infections. Based on symptoms, the four levels of asthma severity are:

- Mild intermittent (comes and goes)—you have episodes of asthma symptoms twice a week or less, and you are bothered by symptoms at night twice a month or less; between episodes, however, you have no symptoms and your lung function is normal.
- Mild persistent asthma—you have asthma symptoms more than twice a week, but no more than once in a single day. You are bothered by symptoms at night more than twice a month. You may have asthma attacks that affect your activity.
- Moderate persistent asthma—you have asthma symptoms every day, and you are bothered by nighttime symptoms more than once a week. Asthma attacks may affect your activity.
- Severe persistent asthma—you have symptoms throughout the day on most days, and you are bothered by nighttime symptoms often. In severe asthma, your physical activity is likely to be limited.

Treatment of asthma is based on a step up and step down approach based on the asthma severity and symptoms. Medications include short acting beta agonists for fast relief. Long term treatment centers around the use of ICSs and possible addition of medications such as long acting beta agonists, LTRAs, inhaled long acting muscarinic antagonists, or theophylline. In the past few years, biologic products have been approved for the treatment of asthma, including Xolair, Nucala, Fasenra, and Cinqair for those that are not controlled on traditional agents. Guidelines have not been updated to include Dupixent.

Chronic Rhinosinusitis with Nasal Polyposis

Chronic rhinosinusitis is an inflammatory condition involving the nasal sinuses and the lining of the nasal passages. Chronic rhinosinusitis often involves nasal drainage, nasal obstruction, facial pain and/or pressure and decreased sense of smell. Chronic rhinosinusitis with nasal polyposis is characterized by the presence of bilateral nasal polyps in the middle meatus. As imagined, these polyps lead to worsening nasal congestion, pressure, drainage, etc. Treatments for chronic rhinosinusitis with nasal polyposis includes various treatment modalities including, but not limited to, intranasal saline, intranasal steroids, oral steroids, surgery, non-sedating antihistamines, anti-leukotriene agents, and for those who have failed these more traditional therapies, Dupixent (which is the first monoclonal antibody approved for this condition).

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Dupixent is indicated for the treatment of patients aged 6 years 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. Dupixent can be used with or without topical corticosteroids. Dupixent is also indicated for add-on maintenance treatment in patients with moderate to severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. Dupixent's most recent indication is as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Atopic Dermatitis

The safety and efficacy of Dupixent was established in three randomized, double-blind, placebo controlled pivotal studies. The populations in these trials included adults that had atopic dermatitis for at least 3 years and had involvement ≥ 10% of the BSA. The study entrants were also previously uncontrolled by topical therapies. SOLO-1 (n=671) and SOLO-2 (n=708) evaluated Dupixent as monotherapy, while CHRONOS (n=740) evaluated Dupixent as combination therapy. In all studies, the primary 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. In SOLO-1, the primary endpoint was met in 38% of subjects in the Dupixent group versus 10% of subjects in the placebo group (P<0.001). In SOLO-2, the primary endpoint was achieved in 36% of subjects in the Dupixent group versus 18% in the placebo group (P<0.001). In week 16 of the CHRONOS trial, 38.7% of Dupixent subjects met the primary endpoint versus 10% of those treated with placebo (P<0.001). At week 52, similar results were reported for the CHRONOS trial.

The efficacy and safety of Dupixent monotherapy in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 251 adolescent subjects 12 to 17 years of age, with moderate-to-severe atopic dermatitis. Subjects in the Dupixent group with baseline weight of <60 kg received an initial dose of 400 mg at week 0, followed by 200 mg every two weeks for 16 weeks. Subjects with baseline weight of ≥60 kg received an initial dose of 600 mg at week 0, followed by 300 mg every two weeks for 16 weeks. The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to week 16. In the Dupixent group, 24% of subjects achieved an IGA score of 0 or 1 vs. 2% in the placebo group.

The efficacy and safety of Dupixent in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 367 subjects 6 to 11 years of age, with atopic dermatitis defined by an IGA score of 4 (scale of 0 to 4), an Eczema Area and Severity Index (EASI) score ≥21 (scale of 0 to 72), and a minimum BSA involvement of ≥15%. Subjects were given various doses of Dupixent depending on weight. Subjects were permitted to receive rescue treatment at the discretion of the investigator. The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) at week 16. The proportion of subjects with an IGA of 0 or 1 ranged from 36-39% in the Dupixent group versus 9-12% in the placebo group.

Asthma

The efficacy of Dupixent for the treatment of asthma was established in three randomized, placebo-controlled studies in patients with persistent asthma. Study 1 (n = 776) was a Phase IIb, 24-week study that included adult patients with uncontrolled asthma despite therapy with a medium-to-high dose inhaled corticosteroid and up to two additional controller medications. The annualized exacerbation rate was reduced by 70% with Dupixent 200 mg once every 2 weeks and reduced by 70.5% with Dupixent 300 mg every 2 weeks compared with placebo ($P < 0.05$ for each comparison). The relative risk reduction was greater in the subgroup of patients with a baseline blood eosinophil count ≥ 300 cells/microliter (80.7% reduction with Dupixent 300 mg every 2 weeks vs. placebo). Significant improvements in the FEV_1 were also observed with both doses of Dupixent vs. placebo. The second study, LIBERTY ASTHMA QUEST (n = 1,902), was a Phase III study that included patients ≥ 12 years of age who had uncontrolled moderate-to-severe asthma despite treatment with a medium- to high-dose inhaled corticosteroid and up to two additional controller medications. Over the 52-week treatment period, Dupixent 200 mg every 2 weeks and 300 mg every 2 weeks reduced the adjusted annualized rate of severe asthma exacerbations vs. placebo by 47.7% and 46.0%,

respectively (P < 0.001 for both comparisons). At week 12, FEV_1 was increased by 0.14 L with Dupixent 200 mg vs. placebo and 0.13 L with Dupixent 300 mg vs. placebo. Larger improvements in both asthma exacerbations and FEV_1 values were observed in patients with a baseline blood eosinophil count ≥ 300 cells/microliter as well as in patients with an elevated baseline fraction of exhaled nitric oxide (FENO) ≥ 25 parts per billion. A second Phase III study, LIBERTY ASTHMA VENTURE (n = 210), included patients ≥ 12 years of age who had severe asthma that required regular treatment with systemic corticosteroids despite treatment with a high-dose ICS and up to two additional controller medications. From baseline to week 24, the oral corticosteroid dose was reduced by 70.1% with Dupixent 300 mg every two weeks compared with 41.9% with placebo (P < 0.001), while maintaining asthma control. In total, 80% of patients receiving Dupixent achieved at least a 50% corticosteroid dose reduction vs. 50% of patients assigned to placebo (P < 0.001). Dupixent was associated with a greater oral corticosteroid dose reduction regardless of baseline blood eosinophil count; however, the magnitude of the dose reduction was larger in patients with blood eosinophils > 300 cells/microliter. In addition to reducing oral corticosteroid use, Dupixent reduced the rate of severe asthma exacerbations by 59% compared with placebo.

It should be noted that higher baseline eosinophil levels were correlated with larger asthma exacerbation reductions and greater increases in lung function parameters than were observed in the overall patient population. In patients with baseline blood eosinophil levels < 150 cells/microliter, the magnitude of the reductions in asthma exacerbations observed with Dupixent vs. placebo were non-significant.

Nasal Polyposis
The chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (CSNP Trial 1 and CSNP Trial 2) in 724 subjects aged 18 years and older on background intranasal corticosteroids. These studies included subjects with CRSwNP despite prior sino-nasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Patients with chronic rhinosinusitis without nasal polyposis were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator's discretion.

In CSNP Trial 1, a total of 276 subjects were randomized to receive either 300 mg Dupixent (n=143) or placebo (n=133) every other week for 24 weeks. In CSNP Trial 2, 448 subjects were randomized

to receive either 300 mg Dupixent (n=150) every other week for 52 weeks, 300 mg Dupixent (n=145) every other week until week 24 followed by 300 mg Dupixent every 4 weeks until week 52, or placebo (n=153). All subjects had evidence of sinus opacification on the Lund Mackay (LMK) sinus CT scan and 73% to 90% of subjects had opacification of all sinuses. Subjects were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD). A total of 63% of subjects reported previous sinus surgery, with a mean number of 2.0 prior surgeries, 74% used systemic corticosteroids in the previous 2 years with a mean number of 1.6 systemic corticosteroid courses in the previous 2 years, 59% had co-morbid asthma, and 28% had NSAID-ERD. The co-primary efficacy endpoints were change from baseline to week 24 in bilateral endoscopic nasal polyps score (NPS; 0-8 scale) as graded by central blinded readers and change from baseline to week 24 in nasal congestion/obstruction score averaged over 28 days (NC; 0-3 scale), as determined by subjects using a daily diary. For NPS, polyps on each side of the nose were graded on a categorical scale (0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity). The total score was the sum of the right and left scores. Nasal congestion was rated daily by the subjects on a 0 to 3 categorical severity scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms). In both studies, key secondary end-points at week 24 included change from baseline in: LMK sinus CT scan score, daily loss of smell, and 22-item sino-nasal outcome test (SNOT-22). The LMK sinus CT scan score evaluated the opacification of each sinus using a 0 to 2 scale (0=normal; 1=partial opacification; 2=total opacification) deriving a maximum score of 12 per side and a total maximum score of 24 (higher scores indicate more opacification). Loss of smell was scored reflectively by the patient every morning on a 0-3 scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). SNOT-22 includes 22 items assessing symptoms and symptom impact associated with CRSwNP with each item scored from 0 (no problem) to 5 (problem as bad as it can be) with a global score ranging from 0 to 110. SNOT-22 had a 2 week recall period. In the pooled efficacy results, the reduction in the proportion of subjects rescued with systemic corticosteroids and/or sino-nasal surgery (up to week 52) were evaluated.

In CSNP Trial 1, the LS mean difference vs. placebo was -2.06 for the NPS and -0.89 for the NC scores. In CNSP Trial 2, the LS mean difference vs. placebo was -1.80 for the NPS and -0.87 for the NC scores. Statistically significant efficacy was observed in CSNP Trial 2 with regard to

improvement in bilateral endoscopic NPS score at week 24 and week 52. Similar results were seen in CSNP Trial 1 at week 24. In the post-treatment period when subjects were off Dupixent, the treatment effect diminished over time.

At week 52, the LS mean difference for nasal congestion in the Dupixent group versus placebo was -0.98 (95% CI -1.17, -0.79). In both studies, significant improvements in nasal congestion were observed as early as the first assessment at week 4. The LS mean difference for nasal congestion at week 4 in the Dupixent group versus placebo was -0.41 (95% CI: -0.52, -0.30) in CSNP Trial 1 and -0.37 (95% CI: -0.46, -0.27) in CSNP Trial 2.

A significant decrease in the LMK sinus CT scan score was observed. The LS mean difference for LMK sinus CT scan score at week 24 in the Dupixent group versus placebo was -7.44 (95% CI: -8.35, -6.53) in CSNP Trial 1 and -5.13 (95% CI: -5.80, -4.46) in CSNP Trial 2. At week 52, in CSNP Trial 2 the LS mean difference for LMK sinus CT scan score in the Dupixent group versus placebo was -6.94 (95% CI: -7.87, -6.01). Dupixent significantly improved the loss of smell compared to placebo. The LS mean difference for loss of smell at week 24 in the Dupixent group versus placebo was -1.12 (95% CI: -1.31, -0.93) in CSNP Trial 1 and -0.98 (95% CI: -1.15, -0.81) in CSNP Trial 2. At week 52, the LS mean difference for loss of smell in the Dupixent group versus placebo was -1.10 (95% CI -1.31, -0.89). In both studies, significant improvements in daily loss of smell severity were observed as early as the first assessment at week 4.

Dupixent significantly decreased sino-nasal symptoms as measured by SNOT-22 compared to placebo. The LS mean difference for SNOT-22 at week 24 in the Dupixent group versus placebo was -21.12 (95% CI: -25.17, -17.06) in CSNP Trial 1 and -17.36 (95% CI: -20.87, -13.85) in CSNP Trial 2. At week 52, the LS mean difference in the Dupixent group versus placebo was -20.96 (95% CI -25.03, -16.89). In the pre-specified multiplicity-adjusted pooled analysis of two studies, treatment with Dupixent resulted in significant reduction of systemic corticosteroid use and need for sino-nasal surgery versus placebo (HR of 0.24; 95% CI: 0.17, 0.35). The proportion of subjects who required systemic corticosteroids was reduced by 74% (HR of 0.26; 95% CI: 0.18, 0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (RR of 0.25; 95% CI: 0.17, 0.37). The proportion of subjects who required surgery was reduced by 83% (HR of 0.17; 95% CI: 0.07, 0.46).

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The effects of Dupixent on the primary endpoints of NPS and nasal congestion and the key secondary endpoint of LMK sinus CT scan score were consistent in patients with prior surgery and without prior surgery.

References

1. Dupixent [package insert]. Regeneron Pharmaceuticals, Inc. Tarrytown, New York. Updated June 2020.
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Policy History

Original Effective Date: 06/21/2017
Current Effective Date: 10/12/2020
06/01/2017 Medical Policy Committee review
06/21/2017 Medical Policy Implementation Committee approval. New policy.

dupilumab (Dupixent®)

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06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/10/2019	Medical Policy Committee review
01/23/2019	Medical Policy Implementation Committee approval. Added coverage for asthma as per the new FDA approved indication. Removed systemic steroids as a pre-requisite option prior to use of Dupixent for atopic dermatitis.
05/02/2019	Medical Policy Committee review
05/15/2019	Medical Policy Implementation Committee approval. Changed age from 18 years to 12 years per the FDA package insert indication change. Updated relevant background and rationale information.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Updated with newest FDA indication for the treatment of chronic rhinosinusitis with nasal polyposis.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Updated the age for use in atopic dermatitis (from 12 years down to 6 years of age) to align with the FDA approval update. Updated background and rationale/source sections.

Next Scheduled Review Date: 09/2021

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.