dupilumab (Dupixent®)

Policy # 00567
Original Effective Date: 06/21/2017
Current Effective Date: 04/01/2019

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 18 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 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 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 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.)*

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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®]‡, 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]‡); 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]‡, 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®]‡); 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.)

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).

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 adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable AND 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. For atopic dermatitis, Dupixent can be used with or without topical corticosteroids. The recommended dose of Dupixent for atopic dermatitis 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 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. Dupixent is supplied as 200 mg (asthma only) and 300 mg (asthma or atopic dermatitis) 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. 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.

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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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Dupixent is indicated for the treatment of adult patients 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.

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.

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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.

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.

References

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Policy History

Original Effective Date:	06/21/2017
Current Effective Date:	04/01/2019
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. New policy.
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.
Next Scheduled Review Date:	01/2020

*****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:

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.

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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.